



## 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 Who Have Not Been Previously Treated with Disease-modifying Antirheumatic Drugs

#### Summary

EudraCT number	2010-020324-22
Trial protocol	GB HU BE CZ LT IT PL BG EE
Global end of trial date	26 September 2017

#### Results information

Result version number	v1 (current)
This version publication date	12 October 2018
First version publication date	12 October 2018

#### Trial information

##### Trial identification

Sponsor protocol code	CC-10004-PSA-005
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01307423
WHO universal trial number (UTN)	-

Notes:

#### Sponsors

Sponsor organisation name	Celgene Corporation
Sponsor organisation address	86 Morris Avenue, Summit, NJ, United States, 07901
Public contact	ClinicalTrialDisclosure, Celgene Corporation, +1 8882601599, ClinicalTrialDisclosure@celgene.com
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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	17 October 2017
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	26 September 2017
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:

This study was conducted in accordance with the guidelines of current Good Clinical Practice including the archiving of essential documents.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	09 December 2010
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy, Ethical reason, Regulatory reason, Scientific research
Long term follow-up duration	5 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	Bulgaria: 41
Country: Number of subjects enrolled	Australia: 12
Country: Number of subjects enrolled	Canada: 47
Country: Number of subjects enrolled	Czech Republic: 30
Country: Number of subjects enrolled	Estonia: 25
Country: Number of subjects enrolled	France: 1
Country: Number of subjects enrolled	Hungary: 27
Country: Number of subjects enrolled	Italy: 10
Country: Number of subjects enrolled	Lithuania: 17
Country: Number of subjects enrolled	New Zealand: 13
Country: Number of subjects enrolled	Poland: 74
Country: Number of subjects enrolled	Romania: 3
Country: Number of subjects enrolled	Russian Federation: 109
Country: Number of subjects enrolled	United Kingdom: 10
Country: Number of subjects enrolled	United States: 108
Worldwide total number of subjects	527
EEA total number of subjects	238

Notes:

<b>Subjects enrolled per age group</b>	
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)	109
From 65 to 84 years	418
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

The study was conducted in 16 countries including the United States, Canada, Europe, New Zealand, Australia and Russia.

### Pre-assignment

Screening details:

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

### Period 1

Period 1 title	Placebo-controlled Phase (Week 0 - 24)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	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
<b>Arm title</b>	Placebo

Arm description:

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

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:

Participants initially randomized to receive placebo tablets twice daily (BID) in the 24-week placebo-controlled phase.

<b>Arm title</b>	Apremilast 20mg
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Arm description:

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

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

Dosage and administration details:

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

<b>Arm title</b>	Apremilast 30mg
Arm description: Participants initially randomized to 30 mg apremilast tablets twice daily in the 24-week placebo-controlled phase.	
Arm type	Experimental
Investigational medicinal product name	CC-10004
Investigational medicinal product code	
Other name	Otezla
Pharmaceutical forms	Tablet
Routes of administration	Oral use

**Dosage and administration details:**

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

<b>Number of subjects in period 1</b>	Placebo	Apremilast 20mg	Apremilast 30mg
Started	176	175	176
Received Treatment	176	175	175
Completed Week 16	166	168	166
Early Escape at Week 16	103 <sup>[1]</sup>	73 <sup>[2]</sup>	79 <sup>[3]</sup>
Completed	156	160	155
Not completed	20	15	21
Consent withdrawn by subject	8	4	10
Non-compliance with Study Drug	-	1	1
Adverse event, non-fatal	4	4	6
Unspecified	1	2	-
Lost to follow-up	5	1	2
Lack of efficacy	1	3	2
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: For all the arms, the number of subjects starting the subsequent periods were less than or equal to the number completing the preceding period, this is because not all subjects who completed the preceding period would enter the subsequent period.

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

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

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

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

## Period 2

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

### Blinding implementation details:

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

## Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Apremilast 20mg

### Arm description:

Participants initially randomized to receive 20 mg apremilast tablets twice daily in the 24-week placebo-controlled phase continued to receive 20 mg apremilast tablets twice daily for up to 4.5 years 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:

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

<b>Arm title</b>	Apremilast 30mg
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### Arm description:

Participants initially randomized to receive 30 mg apremilast tablets twice daily in the 24-week placebo-controlled phase continued to receive 30 mg apremilast tablets twice daily for up to 4.5 years 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:

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

<b>Arm title</b>	Placebo/ 20mg Apremilast EE
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### Arm description:

Participants initially randomized to placebo twice daily were re-randomized due to early escape (EE) at Week 16 to 20 mg apremilast twice daily in 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:

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

<b>Arm title</b>	Placebo / Apremilast 20 mg XO
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Arm description:

Participants initially randomized to placebo twice daily were re-randomized at Week 24 (XO) to 20 mg apremilast twice daily in 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:

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

<b>Arm title</b>	Placebo / Apremilast 30 mg EE
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Arm description:

Participants initially randomized to placebo twice daily were re-randomized due to early escape (EE) at Week 16 to 30 mg apremilast twice daily in 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:

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

<b>Arm title</b>	Placebo / Apremilast 30 mg XO
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Arm description:

Participants initially randomized to placebo twice daily were re-randomized at Week 24 to 30 mg apremilast twice daily in 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:

Participants initially randomized to receive placebo twice daily were re-randomized at Week 24 (XO) to 30 mg apremilast tablets twice daily in the active treatment phase.

<b>Number of subjects in period 2<sup>[4]</sup></b>	Apremilast 20mg	Apremilast 30mg	Placebo/ 20mg Apremilast EE
Started	151	150	46
Completed	132	141	38
Not completed	19	9	8
Consent withdrawn by subject	11	2	-
Non-compliance with Study Drug	-	-	-
Adverse event, non-fatal	3	2	2
Unspecified	-	-	1
Lost to follow-up	-	-	2
Lack of efficacy	5	5	3
Protocol deviation	-	-	-

<b>Number of subjects in period 2<sup>[4]</sup></b>	Placebo / Apremilast 20 mg XO	Placebo / Apremilast 30 mg EE	Placebo / Apremilast 30 mg XO
Started	26	46	26
Completed	23	43	25
Not completed	3	3	1
Consent withdrawn by subject	-	1	1
Non-compliance with Study Drug	-	1	-
Adverse event, non-fatal	2	-	-
Unspecified	-	-	-
Lost to follow-up	-	-	-
Lack of efficacy	1	-	-
Protocol deviation	-	1	-

Notes:

[4] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

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

### Period 3

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

### Arms

Are arms mutually exclusive?	Yes
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<b>Arm title</b>	Apremilast 20mg
Arm description: Participants initially randomized to receive 20 mg apremilast tablets twice daily in the 24-week placebo-controlled phase and continued to receive 20 mg apremilast tablets twice daily for up to 4.5 years 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:**

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

<b>Arm title</b>	Apremilast 30mg
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**Arm description:**

Participants initially randomized to receive 30 mg apremilast tablets twice daily in the 24-week placebo-controlled phase and continued to receive 30 mg apremilast tablets twice daily for up to 4.5 years 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:**

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

<b>Arm title</b>	Placebo/Apremilast 20 mg [Long-Term Safety Phase (LTSP)]
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**Arm description:**

Participants initially randomized to placebo tablets twice daily during the 24-week placebo-controlled phase were re-randomized to 20 mg apremilast tablets twice daily at Week 16 or Week 24 and continued receiving apremilast 20 mg tablets twice daily in 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:**

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

<b>Arm title</b>	Placebo/Apremilast 30 mg (Long-Term Safety Phase)
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**Arm description:**

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

Arm type	Experimental
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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:

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

Number of subjects in period 3 <sup>[5]</sup>	Apremilast 20mg	Apremilast 30mg	Placebo/Apremilast 20 mg [Long-Term Safety Phase (LTSP)]
Started	122	134	57
Completed	99	109	48
Not completed	23	25	9
Noncompliance with Study Drug	-	1	-
Consent withdrawn by subject	13	12	3
Adverse event, non-fatal	2	7	1
Miscellaneous	1	-	1
Lack of efficacy	7	5	4

Number of subjects in period 3 <sup>[5]</sup>	Placebo/Apremilast 30 mg (Long-Term Safety Phase)
Started	67
Completed	60
Not completed	7
Noncompliance with Study Drug	-
Consent withdrawn by subject	2
Adverse event, non-fatal	1
Miscellaneous	1
Lack of efficacy	3

Notes:

[5] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

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

**Period 4**

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

## Arms

Are arms mutually exclusive?	Yes
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<b>Arm title</b>	Apremilast 20mg
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### Arm description:

Participants initially randomized to receive 20 mg apremilast tablets twice daily in the 24-week placebo-controlled phase continued to receive 20 mg apremilast tablets twice daily for up to 4.5 years 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:

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

<b>Arm title</b>	Apremilast 30mg
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### Arm description:

Participants initially randomized to receive 30 mg apremilast tablets twice daily in the 24-week placebo-controlled phase continued to receive 30 mg apremilast tablets twice daily for up to 4.5 years 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:

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

<b>Arm title</b>	Placebo/Apremilast 20 mg [Long-Term Safety Phase (LTSP)]
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### Arm description:

Participants initially randomized to placebo tablets twice daily during the 24-week placebo-controlled phase were re-randomized to 20 mg apremilast tablets twice daily at Week 16 or Week 24 and continued receiving apremilast 20 mg tablets twice daily in 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:

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

<b>Arm title</b>	Placebo/Apremilast 30 mg (Long-Term Safety Phase)
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### Arm description:

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

Arm type	Experimental
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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:

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

Number of subjects in period 4	Apremilast 20mg	Apremilast 30mg	Placebo/Apremilast 20 mg [Long-Term Safety Phase (LTSP)]
Started	99	109	48
Completed	90	91	40
Not completed	9	18	8
Noncompliance with Study Drug	1	1	-
Consent withdrawn by subject	2	8	2
Adverse event, non-fatal	1	2	3
Miscellaneous	1	-	1
Lost to follow-up	2	3	1
Lack of efficacy	2	4	1

Number of subjects in period 4	Placebo/Apremilast 30 mg (Long-Term Safety Phase)
Started	60
Completed	49
Not completed	11
Noncompliance with Study Drug	-
Consent withdrawn by subject	4
Adverse event, non-fatal	4
Miscellaneous	-
Lost to follow-up	1
Lack of efficacy	2

## Period 5

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

## Arms

Are arms mutually exclusive?	Yes
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<b>Arm title</b>	Apremilast 20mg
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### Arm description:

Participants initially randomized to receive 20 mg apremilast tablets twice daily in the 24-week placebo-controlled phase continued to receive 20 mg apremilast tablets twice daily for up to 4.5 years 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:

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

<b>Arm title</b>	Apremilast 30mg
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### Arm description:

Participants initially randomized to receive 30 mg apremilast tablets twice daily in the 24-week placebo-controlled phase continued to receive 30 mg apremilast tablets twice daily for up to 4.5 years 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:

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

<b>Arm title</b>	Placebo/Apremilast 20 mg (LTSP)
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### Arm description:

Participants initially randomized to placebo tablets twice daily during the 24-week placebo-controlled phase were re-randomized to 20 mg apremilast tablets twice daily at Week 16 or Week 24 and continued receiving apremilast 20 mg tablets twice daily in 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:

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

<b>Arm title</b>	Placebo/Apremilast 30 mg (Long-Term Safety Phase)
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### Arm description:

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

Arm type	Experimental
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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:

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

<b>Number of subjects in period 5<sup>[6]</sup></b>	Apremilast 20mg	Apremilast 30mg	Placebo/Apremilast 20 mg (LTSP)
Started	89	91	40
Completed	81	86	38
Not completed	8	5	2
Consent withdrawn by subject	5	4	1
Adverse event, non-fatal	2	-	-
Miscellaneous	-	-	1
Lost to follow-up	-	1	-
Lack of efficacy	1	-	-

<b>Number of subjects in period 5<sup>[6]</sup></b>	Placebo/Apremilast 30 mg (Long-Term Safety Phase)
Started	49
Completed	44
Not completed	5
Consent withdrawn by subject	4
Adverse event, non-fatal	-
Miscellaneous	-
Lost to follow-up	-
Lack of efficacy	1

Notes:

[6] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

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

**Period 6**

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

**Arms**

Are arms mutually exclusive?	Yes
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<b>Arm title</b>	Apremilast 20mg
Arm description: Participants initially randomized to receive 20 mg apremilast tablets twice daily in the 24-week placebo-controlled phase continued to receive 20 mg apremilast tablets twice daily for up to 4.5 years in the active treatment / long-term safety phase. (After 30 mg apremilast BID was identified as the optimal dose, all participants receiving 20 mg apremilast BID were switched to the 30 mg apremilast BID dose).	
Arm type	Experimental
Investigational medicinal product name	CC-10004
Investigational medicinal product code	
Other name	Otezla
Pharmaceutical forms	Tablet
Routes of administration	Oral use

**Dosage and administration details:**

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

<b>Arm title</b>	Apremilast 30mg
Arm description: Participants initially randomized to receive 30 mg apremilast tablets twice daily in the 24-week placebo-controlled phase continued to receive 30 mg apremilast tablets twice daily for up to 4.5 years 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:**

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

<b>Arm title</b>	Placebo/Apremilast 20 mg [Long-Term Safety Phase (LTSP)]
Arm description: Participants initially randomized to placebo tablets twice daily during the 24-week placebo-controlled phase were re-randomized to 20 mg apremilast tablets twice daily at Week 16 or Week 24 and continued receiving apremilast 20 mg tablets twice daily in active treatment / long-term safety phase. (After 30 mg apremilast BID was identified as the optimal dose, all participants receiving 20 mg apremilast BID were switched to the 30 mg apremilast BID dose).	
Arm type	Experimental
Investigational medicinal product name	CC-10004
Investigational medicinal product code	
Other name	Otezla
Pharmaceutical forms	Tablet
Routes of administration	Oral use

**Dosage and administration details:**

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

<b>Arm title</b>	Placebo/Apremilast 30 mg (Long-Term Safety Phase)
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**Arm description:**

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

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

**Dosage and administration details:**

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

Number of subjects in period 6	Apremilast 20mg	Apremilast 30mg	Placebo/Apremilast 20 mg [Long-Term Safety Phase (LTSP)]
Started	81	86	38
Completed	71	80	37
Not completed	10	6	1
Consent withdrawn by subject	6	2	-
Adverse event, non-fatal	1	1	-
Miscellaneous	-	2	1
Lost to follow-up	1	-	-
Lack of efficacy	2	1	-

Number of subjects in period 6	Placebo/Apremilast 30 mg (Long-Term Safety Phase)
Started	44
Completed	41
Not completed	3
Consent withdrawn by subject	1
Adverse event, non-fatal	1
Miscellaneous	1
Lost to follow-up	-
Lack of efficacy	-



## Baseline characteristics

### Reporting groups

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

Reporting group values	Placebo	Apremilast 20mg	Apremilast 30mg
Number of subjects	176	175	176
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)	160	159	161
From 65-84 years	16	16	15
85 years and over	0	0	0
Age Continuous			
Units: years			
arithmetic mean	50.5	49.2	48.4
standard deviation	± 11.58	± 12.00	± 12.52
Gender, Male/Female			
Units: Subjects			
Female	86	95	96
Male	90	80	80
Duration of Psoriatic Arthritis			
Psoriatic arthritis (PsA) is a chronic and progressive inflammatory arthritis that, depending on the method of ascertainment, occurs in 6% to 39% of patients with psoriasis. Disease onset typically occurs between the ages of 30 and 55 years and affects both sexes equally. In the majority of patients, psoriasis precedes PsA by several years. The diagnosis of PsA is made on clinical grounds in patients with psoriasis having skin, scalp or nail changes.			
Units: years			
arithmetic mean	3.42	3.19	3.62
standard deviation	± 5.103	± 4.706	± 5.041

Reporting group values	Total		
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Number of subjects	527		
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)	480		
From 65-84 years	47		
85 years and over	0		
Age Continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender, Male/Female			
Units: Subjects			
Female	277		
Male	250		
Duration of Psoriatic Arthritis			
<p>Psoriatic arthritis (PsA) is a chronic and progressive inflammatory arthritis that, depending on the method of ascertainment, occurs in 6% to 39% of patients with psoriasis. Disease onset typically occurs between the ages of 30 and 55 years and affects both sexes equally. In the majority of patients, psoriasis precedes PsA by several years. The diagnosis of PsA is made on clinical grounds in patients with psoriasis having skin, scalp or nail changes.</p>			
Units: years			
arithmetic mean			
standard deviation	-		

## End points

### End points reporting groups

Reporting group title	Placebo
Reporting group description: Participants initially randomized to receive placebo tablets twice daily (BID) in the 24-week placebo-controlled phase. Participants who did not have at least 20% improvement in swollen and tender joint counts at Week (Wk) 16 were re-randomized to either 20 mg or 30 mg apremilast twice daily (early escape).	
Reporting group title	Apremilast 20mg
Reporting group description: Participants initially randomized to 20 mg apremilast tablets twice daily in the 24-week placebo-controlled phase.	
Reporting group title	Apremilast 30mg
Reporting group description: Participants initially randomized to 30 mg apremilast tablets twice daily in the 24-week placebo-controlled phase.	
Reporting group title	Apremilast 20mg
Reporting group description: Participants initially randomized to receive 20 mg apremilast tablets twice daily in the 24-week placebo-controlled phase continued to receive 20 mg apremilast tablets twice daily for up to 4.5 years in the active treatment / long-term safety phase.	
Reporting group title	Apremilast 30mg
Reporting group description: Participants initially randomized to receive 30 mg apremilast tablets twice daily in the 24-week placebo-controlled phase continued to receive 30 mg apremilast tablets twice daily for up to 4.5 years in the active treatment / long-term safety phase.	
Reporting group title	Placebo/ 20mg Apremilast EE
Reporting group description: Participants initially randomized to placebo twice daily were re-randomized due to early escape (EE) at Week 16 to 20 mg apremilast twice daily in the active treatment phase.	
Reporting group title	Placebo / Apremilast 20 mg XO
Reporting group description: Participants initially randomized to placebo twice daily were re-randomized at Week 24 (XO) to 20 mg apremilast twice daily in the active treatment phase.	
Reporting group title	Placebo / Apremilast 30 mg EE
Reporting group description: Participants initially randomized to placebo twice daily were re-randomized due to early escape (EE) at Week 16 to 30 mg apremilast twice daily in the active treatment phase.	
Reporting group title	Placebo / Apremilast 30 mg XO
Reporting group description: Participants initially randomized to placebo twice daily were re-randomized at Week 24 to 30 mg apremilast twice daily in the active treatment phase.	
Reporting group title	Apremilast 20mg
Reporting group description: Participants initially randomized to receive 20 mg apremilast tablets twice daily in the 24-week placebo-controlled phase and continued to receive 20 mg apremilast tablets twice daily for up to 4.5 years in the active treatment / long-term safety phase.	
Reporting group title	Apremilast 30mg
Reporting group description: Participants initially randomized to receive 30 mg apremilast tablets twice daily in the 24-week placebo-controlled phase and continued to receive 30 mg apremilast tablets twice daily for up to 4.5 years in the active treatment / long-term safety phase.	
Reporting group title	Placebo/Apremilast 20 mg [Long-Term Safety Phase (LTSP)]
Reporting group description: Participants initially randomized to placebo tablets twice daily during the 24-week placebo-controlled	

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

Reporting group title	Placebo/Apremilast 30 mg (Long-Term Safety Phase)
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Reporting group description:

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

Reporting group title	Apremilast 20mg
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Reporting group description:

Participants initially randomized to receive 20 mg apremilast tablets twice daily in the 24-week placebo-controlled phase continued to receive 20 mg apremilast tablets twice daily for up to 4.5 years in the active treatment / long-term safety phase.

Reporting group title	Apremilast 30mg
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Reporting group description:

Participants initially randomized to receive 30 mg apremilast tablets twice daily in the 24-week placebo-controlled phase continued to receive 30 mg apremilast tablets twice daily for up to 4.5 years in the active treatment / long-term safety phase.

Reporting group title	Placebo/Apremilast 20 mg [Long-Term Safety Phase (LTSP)]
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Reporting group description:

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

Reporting group title	Placebo/Apremilast 30 mg (Long-Term Safety Phase)
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Reporting group description:

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

Reporting group title	Apremilast 20mg
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Reporting group description:

Participants initially randomized to receive 20 mg apremilast tablets twice daily in the 24-week placebo-controlled phase continued to receive 20 mg apremilast tablets twice daily for up to 4.5 years in the active treatment / long-term safety phase.

Reporting group title	Apremilast 30mg
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Reporting group description:

Participants initially randomized to receive 30 mg apremilast tablets twice daily in the 24-week placebo-controlled phase continued to receive 30 mg apremilast tablets twice daily for up to 4.5 years in the active treatment / long-term safety phase.

Reporting group title	Placebo/Apremilast 20 mg (LTSP)
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Reporting group description:

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

Reporting group title	Placebo/Apremilast 30 mg (Long-Term Safety Phase)
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Reporting group description:

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

Reporting group title	Apremilast 20mg
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Reporting group description:

Participants initially randomized to receive 20 mg apremilast tablets twice daily in the 24-week placebo-controlled phase continued to receive 20 mg apremilast tablets twice daily for up to 4.5 years in the active treatment / long-term safety phase. (After 30 mg apremilast BID was identified as the optimal dose, all participants receiving 20 mg apremilast BID were switched to the 30 mg apremilast BID dose).

Reporting group title	Apremilast 30mg
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Reporting group description:

Participants initially randomized to receive 30 mg apremilast tablets twice daily in the 24-week placebo-controlled phase continued to receive 30 mg apremilast tablets twice daily for up to 4.5 years in the active treatment / long-term safety phase.

Reporting group title	Placebo/Apremilast 20 mg [Long-Term Safety Phase (LTSP)]
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Reporting group description:

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

Reporting group title	Placebo/Apremilast 30 mg (Long-Term Safety Phase)
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Reporting group description:

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

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

Subject analysis set description:

Participants 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	Full analysis

Subject analysis set description:

Participants 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	Full analysis

Subject analysis set description:

Participants initially randomized to receive apremilast 20 mg tablets twice daily.

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

Subject analysis set description:

Participants initially randomized to receive apremilast 30 mg tablets twice daily.

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

Subject analysis set description:

Participants who received 20 mg apremilast tablets twice daily, regardless of when the apremilast exposure started (at Week 0, 16 or 24). Only the TEAEs that occurred during apremilast 20 mg BID were counted.

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

Subject analysis set description:

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

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

Subject analysis set description:

Participants who received apremilast 30 mg twice daily regardless of when the apremilast-exposure started (at Week 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
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End point description:

A participant was a responder if the following 3 criteria for improvement from Baseline were met: •  $\geq 20\%$  improvement in 78 tender joint count; •  $\geq 20\%$  improvement in 76 swollen joint count; and •  $\geq 20\%$  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 consisting of all subjects randomized as specified in the protocol; one participant randomized in error and did not receive any dose of investigational product (IP) was excluded. Participants who withdrew early or 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 20mg	Apremilast 30mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	176	175	176	
Units: percentage of participants				
number (not applicable)	15.9	28.0	30.7	

## Statistical analyses

<b>Statistical analysis title</b>	Statistical Analysis 1
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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 20mg
Number of subjects included in analysis	351
Analysis specification	Pre-specified
Analysis type	superiority <sup>[1]</sup>
P-value	= 0.0062
Method	Chi-squared
Parameter estimate	Risk difference (RD)
Point estimate	12.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.5
upper limit	20.7

Notes:

[1] - Two-sided 95% CI of the proportion difference is based on the normal approximation to the binomial distribution

<b>Statistical analysis title</b>	Statistical Analysis 2
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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 30mg
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Number of subjects included in analysis	352
Analysis specification	Pre-specified
Analysis type	superiority <sup>[2]</sup>
P-value	= 0.001
Method	Chi-squared
Parameter estimate	Risk difference (RD)
Point estimate	14.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	6.1
upper limit	23.5

Notes:

[2] - Two-sided 95% CI of the proportion difference is based on the normal approximation to the binomial distribution.

## 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
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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 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
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End point timeframe:

Baseline and Week 16

End point values	Placebo	Apremilast 20mg	Apremilast 30mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	167	168	167	
Units: units on a scale				
least squares mean (standard error)	0.012 (± 0.0350)	-0.156 (± 0.0349)	-0.205 (± 0.0350)	

## Statistical analyses

Statistical analysis title	Statistical Analysis 1
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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 20mg
Number of subjects included in analysis	335
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0008 <sup>[3]</sup>
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.168
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.265
upper limit	-0.071

Notes:

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

<b>Statistical analysis title</b>	Statistical Analysis 2
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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 30mg
Number of subjects included in analysis	334
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 <sup>[4]</sup>
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.217
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.314
upper limit	-0.12

Notes:

[4] - Based on an analysis of covariance (ANCOVA) model with treatment group as a factor, 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
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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: •  $\geq 20\%$  improvement in 78 tender joint count; •  $\geq 20\%$  improvement in 76 swollen joint count; and •  $\geq 20\%$  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); Full analysis set; Participants who discontinued early, escaped 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
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End point timeframe:

Baseline and Week 24



<b>End point values</b>	Placebo	Apremilast 20mg	Apremilast 30mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	176	175	176	
Units: percentage of participants				
number (not applicable)	13.1	29.1	24.4	

## Statistical analyses

<b>Statistical analysis title</b>	Statistical Analysis 1
Comparison groups	Placebo v Apremilast 20mg
Number of subjects included in analysis	351
Analysis specification	Pre-specified
Analysis type	superiority <sup>[5]</sup>
P-value	= 0.0002 <sup>[6]</sup>
Method	Chi-squared
Parameter estimate	Risk difference (RD)
Point estimate	16.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	7.7
upper limit	24.4

Notes:

[5] - Two-sided 95% CI of the proportion difference is based on the normal approximation to the binomial distribution.

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

<b>Statistical analysis title</b>	Statistical Analysis 2
Comparison groups	Placebo v Apremilast 30mg
Number of subjects included in analysis	352
Analysis specification	Pre-specified
Analysis type	superiority <sup>[7]</sup>
P-value	= 0.0063 <sup>[8]</sup>
Method	Chi-squared
Parameter estimate	Risk difference (RD)
Point estimate	11.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.3
upper limit	19.4

Notes:

[7] - Two-sided 95% CI of the proportion difference is based on the normal approximation to the binomial distribution.

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

## 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
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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 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 20mg	Apremilast 30mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	167	169	167	
Units: units on a scale				
least squares mean (standard error)	0.012 (± 0.0370)	-0.156 (± 0.0368)	-0.207 (± 0.0369)	

## Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Apremilast 20mg
Number of subjects included in analysis	336
Analysis specification	Pre-specified
Analysis type	superiority <sup>[9]</sup>
P-value	= 0.0014 <sup>[10]</sup>
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.168
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.271
upper limit	-0.065

Notes:

[9] - Based on an analysis of covariance model for the change from baseline at Week 24, with treatment group as a factor and baseline value as a covariate.

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

<b>Statistical analysis title</b>	Statistical Analysis 1
Comparison groups	Placebo v Apremilast 30mg
Number of subjects included in analysis	334
Analysis specification	Pre-specified
Analysis type	superiority <sup>[11]</sup>
P-value	< 0.0001 <sup>[12]</sup>
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.219
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.322
upper limit	-0.117

Notes:

[11] - Based on an analysis of covariance model for the change from baseline at Week 24, with treatment group as a factor and baseline value as a covariate.

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

### **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
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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). SF-36 domain scores were first calculated to range from 0 to 100 and then transformed to norm-based scores (the norm-based scores in the US general population have an average of 50 and a standard deviation of 10). Norm-based scores were used in analyses, with higher scores indicating 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
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End point timeframe:

Baseline and Week 16

<b>End point values</b>	Placebo	Apremilast 20mg	Apremilast 30mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	176	175	176	
Units: units on a scale				
least squares mean (standard error)	0.01 (± 0.588)	2.39 (± 0.586)	3.19 (± 0.590)	

## Statistical analyses

<b>Statistical analysis title</b>	Statistical Analysis 1
Comparison groups	Placebo v Apremilast 20mg
Number of subjects included in analysis	351
Analysis specification	Pre-specified
Analysis type	superiority <sup>[13]</sup>
P-value	= 0.0043 <sup>[14]</sup>
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	2.38
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.75
upper limit	4.01

Notes:

[13] - Based on an analysis of covariance model for the change from baseline at Week 16, with treatment group as a factor and baseline value as a covariate

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

<b>Statistical analysis title</b>	Statistical Analysis 2
Comparison groups	Placebo v Apremilast 30mg
Number of subjects included in analysis	352
Analysis specification	Pre-specified
Analysis type	superiority <sup>[15]</sup>
P-value	= 0.0002 <sup>[16]</sup>
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	3.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.55
upper limit	4.82

Notes:

[15] - Based on an analysis of covariance model for the change from baseline at Week 16, with treatment group as a factor and baseline value as a covariate

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

## 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=lowest disease activity and 100=highest; • Physician global assessment of disease activity, measured on a 100 mm VAS, where 0=lowest disease activity and 100=highest. Improvement or worsening in joint counts is defined as decrease or increase, respectively, from baseline by  $\geq 30\%$ , and improvement or worsening in global assessments is defined as decrease or increase, respectively, from baseline by  $\geq 20$  mm VAS. Full analysis set; Participants who discontinued early, or who did not have sufficient data for a definitive determination of response status at Week 16 were counted as non-responders.

End point type	Secondary
End point timeframe:	
Baseline and Week 16	

End point values	Placebo	Apremilast 20mg	Apremilast 30mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	176	175	176	
Units: percentage of participants				
number (not applicable)	24.4	38.9	45.5	

### Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Apremilast 20mg
Number of subjects included in analysis	351
Analysis specification	Pre-specified
Analysis type	superiority <sup>[17]</sup>
P-value	= 0.0037 <sup>[18]</sup>
Method	Chi-squared
Parameter estimate	Risk difference (RD)
Point estimate	14.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.8
upper limit	24

Notes:

[17] - Two-sided 95% CI of the proportion difference is based on the normal approximation to the binomial distribution.

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

Statistical analysis title	Statistical Analysis 2
Comparison groups	Placebo v Apremilast 30mg
Number of subjects included in analysis	352
Analysis specification	Pre-specified
Analysis type	superiority <sup>[19]</sup>
P-value	< 0.0001 <sup>[20]</sup>
Method	Chi-squared
Parameter estimate	Risk difference (RD)
Point estimate	21
Confidence interval	
level	95 %
sides	2-sided
lower limit	11.3
upper limit	30.7

Notes:

[19] - Two-sided 95% CI of the proportion difference is based on the normal approximation to the binomial distribution.

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

## 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
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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
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End point timeframe:

Baseline and Week 16

End point values	Placebo	Apremilast 20mg	Apremilast 30mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	176	175	176	
Units: mm				
least squares mean (standard error)	-2.6 ( $\pm$ 1.81)	-7.7 ( $\pm$ 1.79)	-10.5 ( $\pm$ 1.80)	

## Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Apremilast 20mg
Number of subjects included in analysis	351
Analysis specification	Pre-specified
Analysis type	superiority <sup>[21]</sup>
P-value	= 0.0485 <sup>[22]</sup>
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10
upper limit	0

Notes:

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

[22] - 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

Statistical analysis title	Statistical Analysis 2
Comparison groups	Placebo v Apremilast 30mg

Number of subjects included in analysis	352
Analysis specification	Pre-specified
Analysis type	superiority <sup>[23]</sup>
P-value	= 0.0022 <sup>[24]</sup>
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-7.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.8
upper limit	-2.8

Notes:

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

[24] - 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

### 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
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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 Achilles 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
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End point timeframe:

Baseline and Week 16

End point values	Placebo	Apremilast 20mg	Apremilast 30mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	115	117	111	
Units: units on a scale				
least squares mean (standard error)	-0.5 (± 0.24)	-0.5 (± 0.24)	-1.5 (± 0.25)	

### Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Apremilast 20mg

Number of subjects included in analysis	232
Analysis specification	Pre-specified
Analysis type	superiority <sup>[25]</sup>
P-value	= 0.7696
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.8
upper limit	0.6

Notes:

[25] - Based on an analysis of covariance model for the change from baseline at Week 16, with treatment group as a factor and the baseline value as a covariate

<b>Statistical analysis title</b>	Statistical Analysis 2
Comparison groups	Placebo v Apremilast 30mg
Number of subjects included in analysis	226
Analysis specification	Pre-specified
Analysis type	superiority <sup>[26]</sup>
P-value	= 0.0038 <sup>[27]</sup>
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.7
upper limit	-0.3

Notes:

[26] - Based on an analysis of covariance model for the change from baseline at Week 16, with treatment group as a factor and the baseline value as a covariate

[27] - 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

## 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 to Week 16	



End point values	Placebo	Apremilast 20mg	Apremilast 30mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	90	89	84	
Units: units on a scale				
least squares mean (standard error)	-1.0 ( $\pm$ 0.25)	-1.9 ( $\pm$ 0.25)	-1.7 ( $\pm$ 0.26)	

## Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Apremilast 20mg
Number of subjects included in analysis	179
Analysis specification	Pre-specified
Analysis type	superiority <sup>[28]</sup>
Parameter estimate	LS Mean Difference
Point estimate	-0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.6
upper limit	-0.2

Notes:

[28] - Based on analysis of covariance model for the change from baseline at Week 16, with treatment group as a factor and the baseline value as a covariate.

Statistical analysis title	Statistical Analysis 2
Comparison groups	Placebo v Apremilast 30mg
Number of subjects included in analysis	174
Analysis specification	Pre-specified
Analysis type	superiority <sup>[29]</sup>
Parameter estimate	LS Mean Difference
Point estimate	-0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.4
upper limit	0

Notes:

[29] - Based on analysis of covariance model for the change from baseline at Week 16, with treatment group as a factor and the baseline value as a covariate

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

End point title	Change from Baseline in Clinical Disease Activity Index (CDAI) at Week 16
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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:  $\leq 2.8$  Low Disease Activity:  $> 2.8$  and  $\leq 10$  Moderate Disease Activity:  $> 10$  and  $\leq 22$  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 20mg	Apremilast 30mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	163	166	164	
Units: units on a scale				
least squares mean (standard error)	-1.98 ( $\pm$ 0.770)	-6.89 ( $\pm$ 0.763)	-7.63 ( $\pm$ 0.768)	

## Statistical analyses

<b>Statistical analysis title</b>	Statistical Analysis 1
Comparison groups	Placebo v Apremilast 20mg
Number of subjects included in analysis	329
Analysis specification	Pre-specified
Analysis type	superiority <sup>[30]</sup>
Parameter estimate	LS Mean Difference
Point estimate	-4.91
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.04
upper limit	-2.78

Notes:

[30] - Based on analysis of covariance model for the change from baseline at Week 16, with treatment group as a factor and the baseline value as a covariate

<b>Statistical analysis title</b>	Statistical Analysis 2
Comparison groups	Placebo v Apremilast 30mg
Number of subjects included in analysis	327
Analysis specification	Pre-specified
Analysis type	superiority <sup>[31]</sup>
Parameter estimate	LS Mean Difference
Point estimate	-5.65
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.78
upper limit	-3.51

Notes:

[31] - Based on analysis of covariance model for the change from baseline at Week 16, with treatment group as a factor and the baseline value as a covariate

## Secondary: Change in Baseline in the Disease Activity Score (DAS28) after 16 Weeks of Treatment

End point title	Change in Baseline in the Disease Activity Score (DAS28) after 16 Weeks of Treatment
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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 16 are included. LOCF was used.

End point type	Secondary
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End point timeframe:

Baseline and Week 16

End point values	Placebo	Apremilast 20mg	Apremilast 30mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	164	164	167	
Units: units on a scale				
least squares mean (standard error)	-0.15 ( $\pm$ 0.076)	-0.61 ( $\pm$ 0.076)	-0.68 ( $\pm$ 0.075)	

## Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Apremilast 20mg
Number of subjects included in analysis	328
Analysis specification	Pre-specified
Analysis type	superiority <sup>[32]</sup>
Parameter estimate	LS Mean Difference
Point estimate	-0.46
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.67
upper limit	-0.25

Notes:

[32] - Based on analysis of covariance model for the change from baseline at Week 16, with treatment group as a factor and the baseline value as a covariate

Statistical analysis title	Statistical Analysis 2
Comparison groups	Placebo v Apremilast 30mg

Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	LS Mean Difference
Point estimate	-0.53
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.74
upper limit	-0.32

### 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
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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
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End point timeframe:

Baseline and Week 16

End point values	Placebo	Apremilast 20mg	Apremilast 30mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	167	168	166	
Units: units on a scale				
least squares mean (standard error)	0.07 (± 0.631)	1.19 (± 0.629)	2.62 (± .0633)	

### Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Apremilast 20mg
Number of subjects included in analysis	335
Analysis specification	Pre-specified
Analysis type	superiority <sup>[33]</sup>
Parameter estimate	Difference in LS Means
Point estimate	1.12

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.63
upper limit	2.87

Notes:

[33] - Based on an analysis of covariance model for the change from baseline at Week 16, with treatment group as a factor and the baseline value as a covariate

<b>Statistical analysis title</b>	Statistical Analysis 2
Comparison groups	Placebo v Apremilast 30mg
Number of subjects included in analysis	333
Analysis specification	Pre-specified
Analysis type	superiority <sup>[34]</sup>
Parameter estimate	Difference in LS Means
Point estimate	2.55
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.8
upper limit	4.31

Notes:

[34] - Based on an analysis of covariance model for the change from baseline at Week 16, with treatment group as a factor and the baseline value as a covariate.

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

End point title	Change From Baseline in 36-item Short Form Health Survey (SF-36) Physical Functioning Domain at Week 24
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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 QOL and consists of 36 questions in 8 domains (physical function, pain, general and mental health, vitality, social function, physical and emotional health). SF-36 domain scores were first calculated to range from 0 to 100 and then transformed to norm-based scores (the norm-based scores in the US population have an average of 50 and a standard deviation of 10). Norm-based scores were used in analyses, with higher scores indicating 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. FAS; subjects 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 those who EE at Week 16.

End point type	Secondary
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End point timeframe:

Baseline and Week 24

End point values	Placebo	Apremilast 20mg	Apremilast 30mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	176	175	176	
Units: units on a scale				
least squares mean (standard error)	0.16 (± 0.609)	2.13 (± 0.605)	3.88 (± 0.611)	

## Statistical analyses

<b>Statistical analysis title</b>	Statistical Analysis 1
Comparison groups	Placebo v Apremilast 20mg
Number of subjects included in analysis	351
Analysis specification	Pre-specified
Analysis type	superiority <sup>[35]</sup>
Parameter estimate	LS Means Difference
Point estimate	1.97
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.28
upper limit	3.65

Notes:

[35] - Based on an analysis of covariance model for the change from baseline at Week 24, with treatment group as a factor and the baseline value as a covariate

<b>Statistical analysis title</b>	Statistical Analysis 2
Comparison groups	Placebo v Apremilast 30mg
Number of subjects included in analysis	352
Analysis specification	Pre-specified
Analysis type	superiority <sup>[36]</sup>
Parameter estimate	LS Mean Difference
Point estimate	3.72
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.02
upper limit	5.41

Notes:

[36] - Based on an analysis of covariance model for the change from baseline at Week 24, with treatment group as a factor and the baseline value as a covariate

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

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

End point description:

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

End point type	Secondary
End point timeframe:	
Baseline and Week 24	

End point values	Placebo	Apremilast 20mg	Apremilast 30mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	176	175	176	
Units: percentage of participants				
number (not applicable)	17.0	36.6	35.2	

### Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Apremilast 20mg
Number of subjects included in analysis	351
Analysis specification	Pre-specified
Analysis type	superiority <sup>[37]</sup>
Parameter estimate	Risk difference (RD)
Point estimate	19.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	10.5
upper limit	28.6

Notes:

[37] - Two-sided 95% CI of the proportion difference is based on the normal approximation to the binomial distribution

Statistical analysis title	Statistical Analysis 2
Comparison groups	Placebo v Apremilast 30mg
Number of subjects included in analysis	352
Analysis specification	Pre-specified
Analysis type	superiority <sup>[38]</sup>
Parameter estimate	Risk difference (RD)
Point estimate	18.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	9.2
upper limit	27.2

Notes:

[38] - Two-sided 95% CI of the proportion difference is based on the normal approximation to the binomial distribution

### Secondary: Change from Baseline in Participants Assessment of Pain at Week 24

End point title	Change from Baseline in Participants Assessment of Pain at Week 24
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**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	

<b>End point values</b>	Placebo	Apremilast 20mg	Apremilast 30mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	167	169	167	
Units: mm				
least squares mean (standard error)	-3.8 ( $\pm$ 1.83)	-9.4 ( $\pm$ 1.82)	-9.6 ( $\pm$ 1.83)	

**Statistical analyses**

<b>Statistical analysis title</b>	Statistical Analysis 1
Comparison groups	Placebo v Apremilast 20mg
Number of subjects included in analysis	336
Analysis specification	Pre-specified
Analysis type	superiority <sup>[39]</sup>
Parameter estimate	LS Mean Difference
Point estimate	-5.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.6
upper limit	-0.5

**Notes:**

[39] - Based on an analysis of covariance (Ancova) model for the change from baseline at Week 24, with treatment group as a factor and the baseline value as a covariate

<b>Statistical analysis title</b>	Statistical Analysis 2
Comparison groups	Placebo v Apremilast 30mg
Number of subjects included in analysis	334
Analysis specification	Pre-specified
Analysis type	superiority <sup>[40]</sup>
Parameter estimate	LS Mean Difference
Point estimate	-5.7



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

Notes:

[40] - Based on an analysis of covariance (Ancova) model for the change from baseline at Week 24, with treatment group as a factor and the baseline value as a covariate

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

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

End point description:

The Maastricht Ankylosing Spondylitis Enthesitis Score quantitates inflammation of the entheses (enthesitis) by assessing pain at the following entheses (sites where tendons or ligaments insert into the bone): 1st costochondral joints left/right; 7th costochondral joints left/right; posterior superior iliac spine left/right; anterior superior iliac spine left/right; iliac crest left/right; 5th lumbar spinous process; and the proximal insertion of the Achilles 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
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End point timeframe:

Baseline and Week 24

End point values	Placebo	Apremilast 20mg	Apremilast 30mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	111	113	106	
Units: units on a scale				
least squares mean (standard error)	-0.6 (± 0.25)	-0.9 (± 0.25)	-1.5 (± 0.26)	

## Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Apremilast 20mg
Number of subjects included in analysis	224
Analysis specification	Pre-specified
Analysis type	superiority <sup>[41]</sup>
Parameter estimate	LS Mean Difference
Point estimate	-0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1
upper limit	0.4

Notes:

[41] - Based on an analysis of covariance (Ancova) model for the change from baseline at Week 24, with treatment group as a factor and the baseline value as a covariate.

<b>Statistical analysis title</b>	Statistical Analysis 2
Comparison groups	Placebo v Apremilast 30mg
Number of subjects included in analysis	217
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	LS Mean Difference
Point estimate	-0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.6
upper limit	-0.2

### 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	

<b>End point values</b>	Placebo	Apremilast 20mg	Apremilast 30mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	87	85	79	
Units: units on a scale				
least squares mean (standard error)	-1.0 (± 0.26)	-2.0 (± 0.26)	-1.7 (± 0.27)	

### Statistical analyses

<b>Statistical analysis title</b>	Statistical Analysis 1
Comparison groups	Placebo v Apremilast 20mg

Number of subjects included in analysis	172
Analysis specification	Pre-specified
Analysis type	superiority <sup>[42]</sup>
Parameter estimate	LS Mean Difference
Point estimate	-1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.7
upper limit	-0.3

Notes:

[42] - Based on an analysis of covariance (Ancova) model for the change from baseline at Week 24, with treatment group as a factor and the baseline value as a covariate.

<b>Statistical analysis title</b>	Statistical Analysis 2
Comparison groups	Placebo v Apremilast 30mg
Number of subjects included in analysis	166
Analysis specification	Pre-specified
Analysis type	superiority <sup>[43]</sup>
Parameter estimate	LS Mean Difference
Point estimate	-0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.4
upper limit	0.1

Notes:

[43] - Based on an analysis of covariance (Ancova) model for the change from baseline at Week 24, with treatment group as a factor and the baseline value as a covariate.

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

End point title	Change From Baseline in Clinical Disease Activity Index (CDAI) at Week 24
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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:  $\leq 2.8$ ; Low Disease Activity:  $> 2.8$  and  $\leq 10$ ; Moderate Disease Activity:  $> 10$  and  $\leq 22$ ; 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
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End point timeframe:

Baseline and Week 24

End point values	Placebo	Apremilast 20mg	Apremilast 30mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	176	175	176	
Units: units on a scale				
least squares mean (standard error)	-2.23 ( $\pm$ 0.807)	-7.30 ( $\pm$ 0.803)	-7.36 ( $\pm$ 0.810)	

## Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Apremilast 20mg
Number of subjects included in analysis	351
Analysis specification	Pre-specified
Analysis type	superiority <sup>[44]</sup>
Parameter estimate	LS Mean Difference
Point estimate	-5.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.31
upper limit	-2.84

Notes:

[44] - Based on an analysis of covariance (Ancova) model for the change from baseline at Week 24, with treatment group as a factor and the baseline value as a covariate.

Statistical analysis title	Statistical Analysis 2
Comparison groups	Placebo v Apremilast 30mg
Number of subjects included in analysis	352
Analysis specification	Pre-specified
Analysis type	superiority <sup>[45]</sup>
Parameter estimate	LS Mean Difference
Point estimate	-5.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.38
upper limit	-2.89

Notes:

[45] - Based on an analysis of covariance (Ancova) model for the change from baseline at Week 24, with treatment group as a factor and the baseline value as a covariate.

## Secondary: Change in Disease Activity Score (DAS 28) at Week 24

End point title	Change in Disease Activity Score (DAS 28) at Week 24
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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 20mg	Apremilast 30mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	167	167	167	
Units: units on a scale				
least squares mean (standard error)	-0.22 ( $\pm$ 0.084)	-0.69 ( $\pm$ 0.084)	0.68 ( $\pm$ 0.084)	

### Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Apremilast 20mg
Number of subjects included in analysis	334
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	-0.23

Statistical analysis title	Statistical Analysis 2
Comparison groups	Placebo v Apremilast 30mg
Number of subjects included in analysis	334
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0001 <sup>[46]</sup>
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.46
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.69
upper limit	-0.22

Notes:

[46] - Based on an analysis of covariance (Ancova) model for the change from baseline at Week 24, with treatment group as a factor and the baseline value as a covariate.

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

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

Baseline and Week 24

End point values	Placebo	Apremilast 20mg	Apremilast 30mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	167	169	166	
Units: units on a scale				
least squares mean (standard error)	0.25 (± 0.652)	1.37 (± 0.648)	2.58 (± 0.655)	

## Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Apremilast 20mg
Number of subjects included in analysis	336
Analysis specification	Pre-specified
Analysis type	superiority <sup>[47]</sup>
Parameter estimate	LS Mean Difference
Point estimate	1.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.68
upper limit	2.93

Notes:

[47] - Based on an analysis of covariance model (Ancova) for the change from baseline at Week 24, with treatment group as a factor and the baseline value as a covariate.

Statistical analysis title	Statistical Analysis 2
Comparison groups	Placebo v Apremilast 30mg

Number of subjects included in analysis	333
Analysis specification	Pre-specified
Analysis type	superiority <sup>[48]</sup>
Parameter estimate	LS Mean difference
Point estimate	2.33
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.52
upper limit	4.15

Notes:

[48] - Based on an analysis of covariance model (Ancova) for the change from baseline at Week 24, with treatment group as a factor and the baseline value as a covariate.

### **Secondary: Percentage of Participants with $\geq 20\%$ Improvement in Maastricht Ankylosing Spondylitis Entheses Score at Week 16**

End point title	Percentage of Participants with $\geq 20\%$ Improvement in Maastricht Ankylosing Spondylitis Entheses Score at Week 16
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End point description:

Percentage of participants with pre-existing enthesopathy whose MASES improved by  $\geq 20\%$  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 Achilles 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
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End point timeframe:

Baseline and Week 16

<b>End point values</b>	Placebo	Apremilast 20mg	Apremilast 30mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	115	117	111	
Units: percentage of participants				
number (not applicable)	46.1	48.7	63.1	

### **Statistical analyses**

<b>Statistical analysis title</b>	Statistical Analysis 1
Comparison groups	Placebo v Apremilast 20mg

Number of subjects included in analysis	232
Analysis specification	Pre-specified
Analysis type	superiority <sup>[49]</sup>
Parameter estimate	Risk difference (RD)
Point estimate	2.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.2
upper limit	15.5

Notes:

[49] - Two-sided 95% CI of the proportion difference is based on the normal approximation to the binomial distribution

<b>Statistical analysis title</b>	Statistical Analysis 2
Comparison groups	Placebo v Apremilast 30mg
Number of subjects included in analysis	226
Analysis specification	Pre-specified
Analysis type	superiority <sup>[50]</sup>
Parameter estimate	Risk difference (RD)
Point estimate	17
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.2
upper limit	29.8

Notes:

[50] - Two-sided 95% CI of the proportion difference is based on the normal approximation to the binomial distribution

## Secondary: Percentage of Participants with Dactylitis Improvement $\geq 1$ point at Week 16

End point title	Percentage of Participants with Dactylitis Improvement $\geq 1$ point at Week 16
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End point description:

Percentage of participants with pre-existing dactylitis whose dactylitis severity score improved by  $\geq 1$  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 20mg	Apremilast 30mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	90	89	84	
Units: percentage of participants				
number (not applicable)	60.0	66.3	61.9	

## Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Apremilast 20mg
Number of subjects included in analysis	179
Analysis specification	Pre-specified
Analysis type	superiority <sup>[51]</sup>
Parameter estimate	Risk difference (RD)
Point estimate	6.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.8
upper limit	20.4

Notes:

[51] - Two-sided 95% CI of the proportion difference is based on the normal approximation to the binomial distribution.

Statistical analysis title	Statistical Analysis 2
Comparison groups	Placebo v Apremilast 30mg
Number of subjects included in analysis	174
Analysis specification	Pre-specified
Analysis type	superiority <sup>[52]</sup>
Parameter estimate	Risk difference (RD)
Point estimate	1.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.6
upper limit	16.4

Notes:

[52] - Two-sided 95% CI of the proportion difference is based on the normal approximation to the binomial distribution

## 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
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End point description:

The EULAR response criteria classify each subject as a good, moderate or non-responder to treatment based on the degree of improvement from baseline and the level of disease activity at the endpoint. EULAR response is derived using the individual subject's DAS28 as the measure of severity of disease. Good or moderate response is defined as follows: Good response: DAS28 at the time point  $\leq 3.2$  and improvement from baseline  $> 1.2$  Moderate response: DAS28 at the time point  $> 3.2$  and improvement from baseline  $> 1.2$ , or DAS28 at the time point  $\leq 5.1$  and improvement from baseline  $> 0.6$  and  $\leq 1.2$ .

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 20mg	Apremilast 30mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	176	175	176	
Units: percentage of participants				
number (not applicable)	25.0	41.1	44.3	

## Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Apremilast 20mg
Number of subjects included in analysis	351
Analysis specification	Pre-specified
Analysis type	superiority <sup>[53]</sup>
Parameter estimate	Risk difference (RD)
Point estimate	16.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	6.4
upper limit	25.8

Notes:

[53] - Two-sided 95% CI of the proportion difference is based on the normal approximation to the binomial distribution

Statistical analysis title	Statistical Analysis 2
Comparison groups	Placebo v Apremilast 30mg
Number of subjects included in analysis	352
Analysis specification	Pre-specified
Analysis type	superiority <sup>[54]</sup>
Parameter estimate	Risk difference (RD)
Point estimate	19.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	9.6
upper limit	29.1

Notes:

[54] - Two-sided 95% CI of the proportion difference is based on the normal approximation to the binomial distribution.

## Secondary: Percentage of Participants with MASES Improvement $\geq$ 20% at Week 24

End point title	Percentage of Participants with MASES Improvement $\geq$ 20% at Week 24
End point description: Percentage of participants with pre-existing enthesopathy whose MASES improved by $\geq$ 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 Achilles 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 24	

End point values	Placebo	Apremilast 20mg	Apremilast 30mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	115	117	111	
Units: percentage of participants				
number (not applicable)	48.7	54.7	66.7	

## Statistical analyses

<b>Statistical analysis title</b>	Statistical Analysis 1
Comparison groups	Placebo v Apremilast 20mg
Number of subjects included in analysis	232
Analysis specification	Pre-specified
Analysis type	superiority <sup>[55]</sup>
Parameter estimate	Risk difference (RD)
Point estimate	6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.8
upper limit	18.8

Notes:

[55] - Two-sided 95% CI of the proportion difference is based on the normal approximation to the binomial distribution.

<b>Statistical analysis title</b>	Statistical Analysis 2
Comparison groups	Placebo v Apremilast 30mg
Number of subjects included in analysis	226
Analysis specification	Pre-specified
Analysis type	superiority <sup>[56]</sup>
Parameter estimate	Risk difference (RD)
Point estimate	18

Confidence interval	
level	95 %
sides	2-sided
lower limit	5.3
upper limit	30.6

Notes:

[56] - Two-sided 95% CI of the proportion difference is based on the normal approximation to the binomial distribution

## Secondary: Percentage of Participants with Dactylitis improvement $\geq 1$ point at Week 24

End point title	Percentage of Participants with Dactylitis improvement $\geq 1$ point at Week 24
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End point description:

Percentage of participants with pre-existing dactylitis whose dactylitis severity score improved by  $\geq 1$  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
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End point timeframe:

Baseline and Week 24

End point values	Placebo	Apremilast 20mg	Apremilast 30mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	90	89	84	
Units: percentage of participants				
number (not applicable)	57.8	69.7	63.1	

## Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Apremilast 20mg
Number of subjects included in analysis	179
Analysis specification	Pre-specified
Analysis type	superiority <sup>[57]</sup>
Parameter estimate	Risk difference (RD)
Point estimate	11.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.1
upper limit	25.9

Notes:

[57] - Two-sided 95% CI of the proportion difference is based on the normal approximation to the binomial distribution.

<b>Statistical analysis title</b>	Statistical Analysis 2
Comparison groups	Placebo v Apremilast 30mg
Number of subjects included in analysis	174
Analysis specification	Pre-specified
Analysis type	superiority <sup>[58]</sup>
Parameter estimate	Risk difference (RD)
Point estimate	5.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.2
upper limit	19.8

Notes:

[58] - Two-sided 95% CI of the proportion difference is based on the normal approximation to the binomial distribution.

### 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
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End point description:

The EULAR response reflects an improvement in disease activity and an attainment of a lower degree of disease activity based on the DAS-28. Good or moderate response is defined as follows: Good response: DAS28 at the time point  $\leq 3.2$  and improvement from baseline  $> 1.2$  Moderate response: DAS28 at the time point  $> 3.2$  and improvement from baseline  $> 1.2$ , or DAS28 at the time point  $\leq 5.1$  and improvement from baseline  $> 0.6$  and  $\leq 1.2$  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
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End point timeframe:

Baseline and Week 24

End point values	Placebo	Apremilast 20mg	Apremilast 30mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	176	175	176	
Units: percentage of participants				
number (not applicable)	17.0	34.9	28.4	

### Statistical analyses

<b>Statistical analysis title</b>	Statistical Analysis 1
Comparison groups	Placebo v Apremilast 20mg

Number of subjects included in analysis	351
Analysis specification	Pre-specified
Analysis type	superiority <sup>[59]</sup>
Parameter estimate	Risk difference (RD)
Point estimate	17.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	8.8
upper limit	26.8

Notes:

[59] - Two-sided 95% CI of the proportion difference is based on the normal approximation to the binomial distribution.

<b>Statistical analysis title</b>	Statistical Analysis 2
Comparison groups	Placebo v Apremilast 30mg
Number of subjects included in analysis	352
Analysis specification	Pre-specified
Analysis type	superiority <sup>[60]</sup>
Parameter estimate	Risk difference (RD)
Point estimate	11.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.7
upper limit	20

Notes:

[60] - Two-sided 95% CI of the proportion difference is based on the normal approximation to the binomial distribution.

## 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
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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: •  $\geq 50\%$  improvement in 78 tender joint count; •  $\geq 50\%$  improvement in 76 swollen joint count; and •  $\geq 50\%$  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
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End point timeframe:

Baseline and Week 16

End point values	Placebo	Apremilast 20mg	Apremilast 30mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	176	175	176	
Units: Percentage of participants				
number (not applicable)	4.5	11.4	11.4	

## Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Apremilast 20mg
Number of subjects included in analysis	351
Analysis specification	Pre-specified
Analysis type	superiority <sup>[61]</sup>
Parameter estimate	Risk difference (RD)
Point estimate	6.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.3
upper limit	12.5

Notes:

[61] - Two-sided 95% CI of the proportion difference is based on the normal approximation to the binomial distribution.

Statistical analysis title	Statistical Analysis 2
Comparison groups	Placebo v Apremilast 30mg
Number of subjects included in analysis	352
Analysis specification	Pre-specified
Analysis type	superiority <sup>[62]</sup>
Parameter estimate	Risk difference (RD)
Point estimate	6.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.2
upper limit	12.4

Notes:

[62] - Two-sided 95% CI of the proportion difference is based on the normal approximation to the binomial distribution.

## Secondary: Percentage of Participants with a ACR 70 response at Week 16

End point title	Percentage of Participants with a ACR 70 response at Week 16
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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: •  $\geq 70\%$  improvement in 78 tender joint count; •  $\geq 70\%$  improvement in 76 swollen joint count; and •  $\geq 70\%$  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 20mg	Apremilast 30mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	176	175	176	
Units: percentage of participants				
number (not applicable)	1.1	4.0	4.0	

### Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Apremilast 20mg
Number of subjects included in analysis	351
Analysis specification	Pre-specified
Analysis type	superiority <sup>[63]</sup>
Parameter estimate	Risk difference (RD)
Point estimate	2.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4
upper limit	6.2

Notes:

[63] - Two-sided 95% CI of the proportion difference is based on the normal approximation to the binomial distribution.

Statistical analysis title	Statistical Analysis 2
Comparison groups	Placebo v Apremilast 30mg
Number of subjects included in analysis	352
Analysis specification	Pre-specified
Analysis type	superiority <sup>[64]</sup>
Parameter estimate	Risk difference (RD)
Point estimate	2.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4
upper limit	6.1

Notes:

[64] - Two-sided 95% CI of the proportion difference is based on the normal approximation to the binomial distribution

### Secondary: Percentage of Participants with a ACR 50 response at Week 24



End point title	Percentage of Participants with a 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: • $\geq 50\%$ improvement in 78 tender joint count; • $\geq 50\%$ improvement in 76 swollen joint count; and • $\geq 50\%$ 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 20mg	Apremilast 30mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	176	175	176	
Units: percentage of participants				
number (not applicable)	6.3	16.0	12.5	

## Statistical analyses

<b>Statistical analysis title</b>	Statistical Analysis 1
Comparison groups	Placebo v Apremilast 20mg
Number of subjects included in analysis	351
Analysis specification	Pre-specified
Analysis type	superiority <sup>[65]</sup>
Parameter estimate	Risk difference (RD)
Point estimate	9.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.2
upper limit	16.3

Notes:

[65] - Two-sided 95% CI of the proportion difference is based on the normal approximation to the binomial distribution

<b>Statistical analysis title</b>	Statistical Analysis 2
Comparison groups	Placebo v Apremilast 30mg
Number of subjects included in analysis	352
Analysis specification	Pre-specified
Analysis type	superiority <sup>[66]</sup>
Parameter estimate	Risk difference (RD)
Point estimate	6.3

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.2
upper limit	12.3

Notes:

[66] - Two-sided 95% CI of the proportion difference is based on the normal approximation to the binomial distribution

## 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
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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: •  $\geq 70\%$  improvement in 78 tender joint count; •  $\geq 70\%$  improvement in 76 swollen joint count; and •  $\geq 70\%$  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
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End point timeframe:

Baseline and Week 24

End point values	Placebo	Apremilast 20mg	Apremilast 30mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	176	175	176	
Units: percentage of participants				
number (not applicable)	4.0	4.0	4.5	

## Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Apremilast 20mg
Number of subjects included in analysis	351
Analysis specification	Pre-specified
Analysis type	superiority <sup>[67]</sup>
Parameter estimate	Risk difference (RD)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.1
upper limit	4.1

Notes:

[67] - Two-sided 95% CI of the proportion difference is based on the normal approximation to the binomial distribution.

<b>Statistical analysis title</b>	Statistical Analysis 2
Comparison groups	Placebo v Apremilast 30mg
Number of subjects included in analysis	352
Analysis specification	Pre-specified
Analysis type	superiority <sup>[68]</sup>
Parameter estimate	Risk difference (RD)
Point estimate	0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.7
upper limit	4.8

Notes:

[68] - Two-sided 95% CI of the proportion difference is based on the normal approximation to the binomial distribution.

### **Secondary: Percentage of Participants with Pre-existing Enthesopathy whose Maastricht Ankylosing Spondylitis Entheses Score Improves to 0 at Week 16**

End point title	Percentage of Participants with Pre-existing Enthesopathy whose Maastricht Ankylosing Spondylitis Entheses Score Improves to 0 at Week 16
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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 Achilles 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
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End point timeframe:

Baseline and Week 16

<b>End point values</b>	Placebo	Apremilast 20mg	Apremilast 30mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	115	117	111	
Units: percentage of participants				
number (not applicable)	19.1	21.4	36.9	

## **Statistical analyses**

<b>Statistical analysis title</b>	Statistical Analysis 1
Comparison groups	Placebo v Apremilast 20mg
Number of subjects included in analysis	232
Analysis specification	Pre-specified
Analysis type	superiority <sup>[69]</sup>
Parameter estimate	Risk difference (RD)
Point estimate	2.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.1
upper limit	12.6

Notes:

[69] - Two-sided 95% CI of the proportion difference is based on the normal approximation to the binomial distribution.

<b>Statistical analysis title</b>	Statistical Analysis 2
Comparison groups	Placebo v Apremilast 30mg
Number of subjects included in analysis	226
Analysis specification	Pre-specified
Analysis type	superiority <sup>[70]</sup>
Parameter estimate	Risk difference (RD)
Point estimate	17.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	6.3
upper limit	29.3

Notes:

[70] - Two-sided 95% CI of the proportion difference is based on the normal approximation to the binomial distribution.

### **Secondary: Percentage of Participants with Pre-existing Dactylitis whose Dactylitis Severity Score Improves to 0 at Week 16**

End point title	Percentage of Participants with Pre-existing Dactylitis whose Dactylitis Severity Score Improves to 0 at Week 16
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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
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End point timeframe:

Baseline and Week 16

End point values	Placebo	Apremilast 20mg	Apremilast 30mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	90	89	84	
Units: percentage of participants				
number (not applicable)	33.3	42.7	40.5	

## Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Apremilast 20mg
Number of subjects included in analysis	179
Analysis specification	Pre-specified
Analysis type	superiority <sup>[71]</sup>
Parameter estimate	Risk difference (RD)
Point estimate	9.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.8
upper limit	23.5

Notes:

[71] - Two-sided 95% CI of the proportion difference is based on the normal approximation to the binomial distribution.

Statistical analysis title	Statistical Analysis 2
Comparison groups	Placebo v Apremilast 30mg
Number of subjects included in analysis	174
Analysis specification	Pre-specified
Analysis type	superiority <sup>[72]</sup>
Parameter estimate	Risk difference (RD)
Point estimate	7.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.2
upper limit	21.5

Notes:

[72] - Two-sided 95% CI of the proportion difference is based on the normal approximation to the binomial distribution

## 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
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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 Achilles tendon left/right. The MASES, ranging from 0 to 13, is the number of painful entheses out of 13 entheses. Full analysis set; participants with a baseline MASES > 0 are included; LOCF was used. The Week 16 value was carried over to Week 24 for participants who escaped early at Week 16. Participants who did not have sufficient data (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 20mg	Apremilast 30mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	115	117	111	
Units: percentage of participants				
number (not applicable)	22.6	29.1	37.8	

## Statistical analyses

<b>Statistical analysis title</b>	Statistical Analysis 1
Statistical analysis description:	
Two-sided 95% CI of the proportion difference is based on the normal approximation to the binomial distribution.	
Comparison groups	Placebo v Apremilast 20mg
Number of subjects included in analysis	232
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Risk difference (RD)
Point estimate	6.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.8
upper limit	17.7

<b>Statistical analysis title</b>	Statistical Analysis 2
Comparison groups	Placebo v Apremilast 30mg
Number of subjects included in analysis	226
Analysis specification	Pre-specified
Analysis type	superiority <sup>[73]</sup>
Parameter estimate	Risk difference (RD)
Point estimate	15.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.4
upper limit	27.1

Notes:

[73] - Two-sided 95% CI of the proportion difference is based on the normal approximation to the binomial distribution.

## 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
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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:	
Baseline and Week 24	

End point values	Placebo	Apremilast 20mg	Apremilast 30mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	90	89	84	
Units: percentage of participants				
number (not applicable)	35.6	46.1	40.5	

## Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Apremilast 20mg
Number of subjects included in analysis	179
Analysis specification	Pre-specified
Analysis type	superiority <sup>[74]</sup>
Parameter estimate	Risk difference (RD)
Point estimate	10.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.8
upper limit	24.8

Notes:

[74] - Two-sided 95% CI of the proportion difference is based on the normal approximation to the binomial distribution.

Statistical analysis title	Statistical Analysis 2
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Comparison groups	Placebo v Apremilast 30mg
Number of subjects included in analysis	174
Analysis specification	Pre-specified
Analysis type	superiority <sup>[75]</sup>
Parameter estimate	Risk difference (RD)
Point estimate	4.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.5
upper limit	19.3

Notes:

[75] - Two-sided 95% CI of the proportion difference is based on the normal approximation to the binomial distribution.

## 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
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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:  $\geq 20\%$  improvement in 78 tender joint count;  $\geq 20\%$  improvement in 76 swollen joint count; and  $\geq 20\%$  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 consists of all participants who were randomized or re-randomized to apremilast at any time during the study. Participants who had sufficient data for a definitive determination of response status at Week 52 are included.

End point type	Secondary
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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	67	131	138
Units: Percentage of Participants				
number (confidence interval 95%)	59.7 (46.4 to 71.9)	56.7 (44.0 to 68.8)	53.4 (44.5 to 62.2)	58.7 (50.0 to 67.0)

## 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
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**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 changes from Baseline in the overall score indicate improvement in functional ability. Apremilast Subjects as Randomized/Re-randomized (AAR) Population; participants with a Baseline value and a Week 52 value are included.

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End point type	Secondary
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End point timeframe:

Baseline and Week 52

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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	68	132	139
Units: units on a scale				
arithmetic mean (standard deviation)	-0.21 (± 0.450)	-0.25 (± 0.533)	-0.32 (± 0.559)	-0.39 (± 0.567)

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**Statistical analyses**

No statistical analyses for this end point

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**Secondary: Change From Baseline in the SF-36v2 Physical Functioning Scale Score at Week 52**

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End point title	Change From Baseline in the SF-36v2 Physical Functioning Scale Score at Week 52
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**End point description:**

The Medical Outcome Study Short Form 36-Item Health Survey, Version 2 (SF-36) is a self-administered instrument that measures the impact of disease on overall quality of life and consists of 36 questions in eight domains (physical function, pain, general and mental health, vitality, social function, physical and emotional health). Norm-based scores were used in analyses, calibrated so that 50 is the average score and the standard deviation equals 10. Higher scores indicate a higher level of functioning. The physical functioning domain assesses limitations in physical activities because of health problems. A positive change from Baseline score indicates an improvement.

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

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End point type	Secondary
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End point timeframe:

Baseline and Week 52

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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	68	132	139
Units: units on a scale				
arithmetic mean (standard deviation)	7.76 (± 8.236)	6.87 (± 7.241)	5.68 (± 8.467)	5.87 (± 8.008)

## 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:	
Measure 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=lowest disease activity and 100=highest; • Physician global assessment of disease activity, measured on a 100 mm VAS, where 0=lowest disease activity and 100=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. The Apremilast Subjects as Randomized/Re-randomized (AAR) Population; only those participants who had sufficient data for a definitive determination of response status at Week 52 are included.	
End point type	Secondary
End point timeframe:	
Baseline and Week 52	

End point values	Placebo / Apremilast 20 mg	Placebo / Apremilast 30 mg	Apremilast 20 mg	Apremilast 30 mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	61	67	131	137
Units: Percentage of Participants				
number (confidence interval 95%)	73.8 (60.9 to 84.2)	79.1 (67.4 to 88.1)	75.6 (67.3 to 82.7)	75.9 (67.9 to 82.8)

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change from Baseline in the Participants Assessment of Pain using the Visual Analog Scale at Week 52

End point title	Change from Baseline in the Participants Assessment of Pain using the Visual Analog Scale 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	62	68	132	139
Units: mm				
arithmetic mean (standard deviation)	-13.1 (± 25.57)	-18.9 (± 24.28)	-15.6 (± 27.29)	-14.2 (± 28.14)

## 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
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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 Achilles tendon left/right. The MASES, ranging from 0 to 13, is the number of painful entheses out of 13 entheses. The Apremilast Subjects as Randomized/Re-randomized (AAR) Population; participants with a baseline value > 0 (i.e., pre-existing enthesopathy) and a Week 52 value are included.

End point type	Secondary
End point timeframe:	
Baseline and Week 52	

End point values	Placebo / Apremilast 20 mg	Placebo / Apremilast 30 mg	Apremilast 20 mg	Apremilast 30 mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	41	42	91	85
Units: units on a scale				
arithmetic mean (standard deviation)	-1.7 (± 2.38)	-1.8 (± 2.34)	-1.5 (± 2.62)	-1.8 (± 3.03)

## 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
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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. The Apremilast Subjects as Randomized/Re-randomized (AAR) Population; participants with a baseline value > 0 (i.e., pre-existing dactylitis) and a Week 52 value are included.

End point type	Secondary
End point timeframe:	
Baseline and Week 52	

End point values	Placebo / Apremilast 20 mg	Placebo / Apremilast 30 mg	Apremilast 20 mg	Apremilast 30 mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	32	38	70	64
Units: units on a scale				
arithmetic mean (standard deviation)	-2.2 (± 1.89)	2.9 (± 2.47)	-2.2 (± 4.09)	-2.9 (± 3.55)

## 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
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End point description:

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

End point type	Secondary
End point timeframe:	
Baseline and Week 52	

End point values	Placebo / Apremilast 20 mg	Placebo / Apremilast 30 mg	Apremilast 20 mg	Apremilast 30 mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	61	67	131	137
Units: units on a scale				
arithmetic mean (standard deviation)	-11.0 (± 10.288)	-14.67 (± 11.943)	-14.32 (± 11.128)	-13.98 (± 10.541)

### 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
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End point description:

The DAS28 measures the severity of disease at a specific time and is derived from the following variables: • 28 tender joint count • 28 swollen joint count, which do not include the DIP joints, the hip joint, or the joints below the knee; • C-reactive protein (CRP) • Patient's global assessment of disease activity. DAS28(CRP) scores range from 0 to approximately 10, with the upper bound dependent on the highest possible level of CRP. A DAS28 score higher than 5.1 indicates high disease activity, a DAS28 score less than 3.2 indicates low disease activity, and a DAS28 score less than 2.6 indicates clinical remission. The Apremilast Subjects as Randomized/Re-randomized (AAR) Population; participants with a Baseline value and a Week 52 value are included.

End point type	Secondary
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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	68	130	138
Units: units on a scale				
arithmetic mean (standard deviation)	-1.08 (± 1.113)	-1.28 (± 1.044)	-1.37 (± 1.128)	-1.39 (± 0.970)

### 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
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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	62	67	131	139
Units: units on a scale				
arithmetic mean (standard deviation)	6.03 (± 8.787)	4.27 (± 9.461)	2.39 (± 10.197)	5.89 (± 10.471)

## 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
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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 Achilles tendon left/right. The MASES, ranging from 0 to 13, is the number of painful entheses out of 13 entheses. The Apremilast Subjects as Randomized/Re-randomized (AAR) Population; participants with a baseline MASES > 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:	
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	41	42	91	85
Units: Percentage of Participants				
number (confidence interval 95%)	70.0 (54.5 to 83.9)	81.0 (65.9 to 91.4)	65.9 (55.3 to 75.5)	69.4 (58.5 to 79.0)

## Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Participants with Pre-existing Dactylitis whose Dactylitis Severity Score Improves from Baseline by $\geq 1$ at Week 52

End point title	Percentage of Participants with Pre-existing Dactylitis whose Dactylitis Severity Score Improves from Baseline by $\geq 1$ at Week 52
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End point description:

Percentage of participants with pre-existing dactylitis whose dactylitis severity score improved by  $\geq 1$  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. The Apremilast Subjects as Randomized/Re-randomized (AAR) Population; Participants with a baseline dactylitis severity score  $> 0$  (i.e., pre-existing dactylitis) and who had sufficient data for a definitive determination of response status at Week 52 are included.

End point type	Secondary
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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	32	38	70	64
Units: Percentage of Participants				
number (confidence interval 95%)	93.8 (79.2 to 99.2)	94.7 (82.3 to 99.4)	87.1 (77.0 to 93.9)	85.9 (75.0 to 93.4)

## 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
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End point description:

The EULAR response criteria classify each subject as a good, moderate or non-responder to treatment based on the degree of improvement from baseline and the level of disease activity at the endpoint. EULAR response is derived using the individual subject's DAS28 as the measure of severity of disease. A Good response is defined as follows: Good response: DAS28 at the time point  $\leq 3.2$  and improvement from baseline  $> 1.2$  A Moderate Response is defined as either: an improvement (decrease) in the DAS28 of greater than 0.6 and less than or equal to 1.2 and attainment of a DAS28 score of less than or equal to 5.1 or, an improvement (decrease) in the DAS28 of more than 1.2 and attainment of a DAS28 score of greater than 3.2. The Apremilast Subjects as Randomized/Re-randomized (AAR) Population; only those participants who had sufficient data for a definitive determination of response status at Week 52 are included.

End point type	Secondary
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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	68	130	138
Units: Percentage of Participants				
number (not applicable)	64.5	73.5	75.4	79.0

## 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
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End point description:

A participant was a responder if the following 3 criteria for improvement from Baseline were met:  $\geq 50\%$  improvement in 78 tender joint count;  $\geq 50\%$  improvement in 76 swollen joint count; and  $\geq 50\%$  improvement in at least 3 of the 5 following parameters: o Patient's assessment of pain (measured on a 100 mm visual analog scale [VAS]); 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 consists of all participants who were randomized or re-randomized to apremilast at any time during the study. Only those participants who had sufficient data for a definitive determination of response status at Week 52 are included.

End point type	Secondary
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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	67	129	138
Units: Percentage of Participants				
number (confidence interval 95%)	30.6 (19.6 to 43.7)	25.4 (15.5 to 37.5)	27.1 (19.7 to 35.7)	31.9 (24.2 to 40.4)

## 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: A participant was a responder if the following 3 criteria for improvement from Baseline were met: $\geq 70\%$ improvement in 78 tender joint count; $\geq 70\%$ improvement in 76 swollen joint count; and $\geq 70\%$ 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. The Apremilast Subjects as Randomized/Re-randomized (AAR) Population; only those participants who had sufficient data for a definitive determination of response status at Week 52 are included.	
End point type	Secondary
End point timeframe: Baseline and Week 52	

End point values	Placebo / Apremilast 20 mg	Placebo / Apremilast 30 mg	Apremilast 20 mg	Apremilast 30 mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	61	68	131	138
Units: Percentage of Participants				
number (confidence interval 95%)	8.2 (2.7 to 18.1)	10.3 (4.2 to 20.1)	13.7 (8.4 to 20.8)	18.1 (12.1 to 25.6)

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Participants with Pre-existing Enthesopathy whose MASES Improves from Baseline to 0 at Week 52

End point title	Percentage of Participants with Pre-existing Enthesopathy whose MASES Improves from Baseline to 0 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 Achilles tendon left/right. The MASES, ranging from 0 to 13, is the number of painful entheses out of 13 entheses. The Apremilast Subjects as Randomized/Re-randomized (AAR) Population; 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: 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	41	42	91	85
Units: percentage of participants				
number (confidence interval 95%)	39.0 (24.2 to 55.5)	61.9 (45.6 to 76.4)	39.6 (29.5 to 50.4)	45.9 (35.0 to 57.0)

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Participants with Pre-existing Dactylitis whose Dactylitis Severity Score Improves from Baseline to 0 at Week 52

End point title	Percentage of Participants with Pre-existing Dactylitis whose Dactylitis Severity Score Improves from Baseline to 0 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. The Apremilast Subjects as Randomized/Re-randomized (AAR) Population; Participants with a baseline dactylitis severity score > 0 (i.e., pre-existing dactylitis) and who had sufficient data for a definitive determination of response status at Week 52 are included.	
End point type	Secondary
End point timeframe:	
Baseline and Week 52	

End point values	Placebo / Apremilast 20 mg	Placebo / Apremilast 30 mg	Apremilast 20 mg	Apremilast 30 mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	32	38	70	64
Units: Percentage of Participants				
number (confidence interval 95%)	75.0 (56.6 to 88.5)	78.9 (62.7 to 90.4)	68.6 (56.4 to 79.1)	68.8 (55.9 to 79.8)

## Statistical analyses

No statistical analyses for this end point

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

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

A TEAE is an adverse event (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 subject during the course of a study. A serious AE is any AE that results in death; is life-threatening; requires inpatient hospitalization or prolongation of existing hospitalization; results in persistent or significant disability/incapacity; is a congenital anomaly/birth defect; or constitutes an important medical event. For both AEs and SAEs the investigator assessed the severity of the event according to the grading scale: Mild: asymptomatic or with mild symptoms, Moderate: symptoms causing moderate discomfort or Severe: symptoms causing severe discomfort or pain. Safety population included participants who were randomized and received at least one dose of IP.

End point type	Secondary
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**End point timeframe:**

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

End point values	Placebo	Apremilast 20mg	Apremilast 30mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	176	175	175	
Units: Participants				
Any TEAE	73	87	99	
Any Drug-Related TEAE	25	40	58	
Any Severe TEAE	6	4	2	
Any Serious TEAE (SAE)	5	3	1	
Drug-Related (SAE)	0	0	1	
Any TEAE Leading to Drug Interruption	8	11	0	
Any TEAE Leading to Drug Withdrawal	4	4	6	
Any TEAE Leading to Death	0	0	0	

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Number of Participants with Treatment Emergent Adverse Events During the Apremilast Exposure Period**

End point title	Number of Participants with Treatment Emergent Adverse Events During the Apremilast Exposure Period
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**End point description:**

A TEAE is an AE with a start date on or after the date of the first dose of IP and no later than 28 days after the last dose. An AE is any noxious, unintended, or untoward medical occurrence that may appear or worsen in a subject during the course of a study. A SAE = AE that results in death; is life-threatening; requires inpatient hospitalization; results in persistent or significant disability/incapacity; is a congenital anomaly/birth defect; or constitutes an important medical event. For both AEs and SAEs the severity of the event was applied to the grading scale: Mild: asymptomatic or with mild symptoms, Moderate: symptoms causing moderate discomfort or Severe: symptoms causing severe discomfort. Apremilast Subjects as Treated (AAT) received at least 1 dose of APR at any time during the study. Subjects were included in the treatment group corresponding to the APR dosing regimen they received, irrespective of the treatment group to which they were randomized or re-randomized.

End point type	Secondary
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**End point timeframe:**

Week 0 to Week 260; median duration of exposure to apremilast 20 mg BID was 168.93 weeks and

<b>End point values</b>	Apremilast 20 mg (Pre-Switch)	Apremilast 20/30 mg (Post-Switch)	Apremilast 30 mg	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	252	122	252	
Units: Participants				
Any TEAE	188	60	204	
Any Drug-Related TEAE	89	16	113	
Any Severe TEAE	24	3	23	
Any Serious TEAE (SAE)	35	5	36	
Drug-Related (SAE)	6	1	6	
Any TEAE Leading to Drug Interruption	41	5	36	
Any TEAE Leading to Drug Withdrawal	22	2	26	
Any TEAE Leading to Death	0	0	0	

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

AEs are reported for the placebo-controlled phase from Week 0 to Week 16 for placebo subjects who entered EE at Week 16 and up to Week 24 for all others and reported for the Apremilast Exposure Period from Week 0 to Week 260

Adverse event reporting additional description:

Median duration of APR 20 mg BID was 168.93 weeks and 229.36 weeks for apremilast 30 mg twice daily

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	V14.0
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### Reporting groups

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

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

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

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

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

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

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

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

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

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

Reporting group title	APR Exposure Period Up to 5 Years: Apremilast 30 mg
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Reporting group description:

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

Serious adverse events	Weeks 0-24: Placebo (Placebo- Controlled Phase)	Weeks 0-24: Apremilast 20 mg (Placebo-Controlled Phase)	Weeks 0-24: Apremilast 30 mg (Placebo-Controlled Phase)
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 176 (2.84%)	3 / 175 (1.71%)	1 / 175 (0.57%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	0 / 176 (0.00%)	0 / 175 (0.00%)	0 / 175 (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
Cervix carcinoma stage 0			
subjects affected / exposed	0 / 176 (0.00%)	0 / 175 (0.00%)	0 / 175 (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
Lung squamous cell carcinoma stage unspecified			
subjects affected / exposed	0 / 176 (0.00%)	0 / 175 (0.00%)	0 / 175 (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
Papilloma			
subjects affected / exposed	0 / 176 (0.00%)	1 / 175 (0.57%)	0 / 175 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostate cancer			
subjects affected / exposed	0 / 176 (0.00%)	0 / 175 (0.00%)	0 / 175 (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			
Femoral artery occlusion			
subjects affected / exposed	0 / 176 (0.00%)	0 / 175 (0.00%)	0 / 175 (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 / 176 (0.00%)	0 / 175 (0.00%)	0 / 175 (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			
Non-cardiac chest pain			

subjects affected / exposed	0 / 176 (0.00%)	0 / 175 (0.00%)	0 / 175 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	0 / 176 (0.00%)	0 / 175 (0.00%)	0 / 175 (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			
Cystocele			
subjects affected / exposed	0 / 176 (0.00%)	0 / 175 (0.00%)	0 / 175 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endometrial atrophy			
subjects affected / exposed	0 / 176 (0.00%)	0 / 175 (0.00%)	0 / 175 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endometrial hyperplasia			
subjects affected / exposed	1 / 176 (0.57%)	0 / 175 (0.00%)	0 / 175 (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
Metrorrhagia			
subjects affected / exposed	0 / 176 (0.00%)	0 / 175 (0.00%)	0 / 175 (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
Postmenopausal haemorrhage			
subjects affected / exposed	0 / 176 (0.00%)	0 / 175 (0.00%)	0 / 175 (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
Rectocele			
subjects affected / exposed	0 / 176 (0.00%)	0 / 175 (0.00%)	0 / 175 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 176 (0.00%)	0 / 175 (0.00%)	0 / 175 (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	1 / 176 (0.57%)	0 / 175 (0.00%)	0 / 175 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nasal polyps			
subjects affected / exposed	0 / 176 (0.00%)	0 / 175 (0.00%)	0 / 175 (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 / 176 (0.00%)	0 / 175 (0.00%)	0 / 175 (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			
Confusional state			
subjects affected / exposed	0 / 176 (0.00%)	1 / 175 (0.57%)	0 / 175 (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
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 176 (0.00%)	0 / 175 (0.00%)	0 / 175 (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
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 176 (0.00%)	0 / 175 (0.00%)	0 / 175 (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			
Contusion			



subjects affected / exposed	0 / 176 (0.00%)	0 / 175 (0.00%)	0 / 175 (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
Incisional hernia			
subjects affected / exposed	1 / 176 (0.57%)	0 / 175 (0.00%)	0 / 175 (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
Multiple fractures			
subjects affected / exposed	0 / 176 (0.00%)	0 / 175 (0.00%)	0 / 175 (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
Multiple injuries			
subjects affected / exposed	0 / 176 (0.00%)	1 / 175 (0.57%)	0 / 175 (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
Post procedural fistula			
subjects affected / exposed	0 / 176 (0.00%)	0 / 175 (0.00%)	0 / 175 (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
Radius fracture			
subjects affected / exposed	0 / 176 (0.00%)	0 / 175 (0.00%)	0 / 175 (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 / 176 (0.00%)	1 / 175 (0.57%)	0 / 175 (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
Tibia fracture			
subjects affected / exposed	0 / 176 (0.00%)	0 / 175 (0.00%)	0 / 175 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute myocardial infarction			

subjects affected / exposed	0 / 176 (0.00%)	0 / 175 (0.00%)	0 / 175 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina pectoris			
subjects affected / exposed	0 / 176 (0.00%)	0 / 175 (0.00%)	0 / 175 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina unstable			
subjects affected / exposed	0 / 176 (0.00%)	0 / 175 (0.00%)	0 / 175 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	0 / 176 (0.00%)	0 / 175 (0.00%)	0 / 175 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial flutter			
subjects affected / exposed	0 / 176 (0.00%)	0 / 175 (0.00%)	0 / 175 (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
Atrioventricular block			
subjects affected / exposed	0 / 176 (0.00%)	0 / 175 (0.00%)	0 / 175 (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
Atrioventricular block second degree			
subjects affected / exposed	0 / 176 (0.00%)	0 / 175 (0.00%)	0 / 175 (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
Coronary artery disease			
subjects affected / exposed	0 / 176 (0.00%)	0 / 175 (0.00%)	0 / 175 (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
Coronary artery occlusion			

subjects affected / exposed	0 / 176 (0.00%)	0 / 175 (0.00%)	0 / 175 (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
Palpitations			
subjects affected / exposed	0 / 176 (0.00%)	0 / 175 (0.00%)	0 / 175 (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
Pericarditis			
subjects affected / exposed	0 / 176 (0.00%)	0 / 175 (0.00%)	0 / 175 (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
Stress cardiomyopathy			
subjects affected / exposed	0 / 176 (0.00%)	0 / 175 (0.00%)	0 / 175 (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 / 176 (0.00%)	0 / 175 (0.00%)	0 / 175 (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
Epilepsy			
subjects affected / exposed	0 / 176 (0.00%)	1 / 175 (0.57%)	0 / 175 (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
Sciatica			
subjects affected / exposed	0 / 176 (0.00%)	1 / 175 (0.57%)	0 / 175 (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
Spinal cord compression			
subjects affected / exposed	0 / 176 (0.00%)	0 / 175 (0.00%)	0 / 175 (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
Transient ischaemic attack			

subjects affected / exposed	0 / 176 (0.00%)	0 / 175 (0.00%)	0 / 175 (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
Vertigo CNS origin			
subjects affected / exposed	0 / 176 (0.00%)	0 / 175 (0.00%)	0 / 175 (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			
Lymphadenopathy mediastinal			
subjects affected / exposed	0 / 176 (0.00%)	0 / 175 (0.00%)	0 / 175 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 176 (0.00%)	0 / 175 (0.00%)	0 / 175 (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			
Retinal vein thrombosis			
subjects affected / exposed	0 / 176 (0.00%)	0 / 175 (0.00%)	0 / 175 (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 lower			
subjects affected / exposed	0 / 176 (0.00%)	0 / 175 (0.00%)	0 / 175 (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 / 176 (0.00%)	0 / 175 (0.00%)	0 / 175 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			

subjects affected / exposed	0 / 176 (0.00%)	0 / 175 (0.00%)	0 / 175 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	0 / 176 (0.00%)	0 / 175 (0.00%)	0 / 175 (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
Enterocoele			
subjects affected / exposed	0 / 176 (0.00%)	0 / 175 (0.00%)	0 / 175 (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 / 176 (0.00%)	0 / 175 (0.00%)	0 / 175 (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
Irritable bowel syndrome			
subjects affected / exposed	0 / 176 (0.00%)	0 / 175 (0.00%)	0 / 175 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis acute			
subjects affected / exposed	0 / 176 (0.00%)	0 / 175 (0.00%)	0 / 175 (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
Rectal haemorrhage			
subjects affected / exposed	0 / 176 (0.00%)	0 / 175 (0.00%)	0 / 175 (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
Umbilical hernia			
subjects affected / exposed	0 / 176 (0.00%)	0 / 175 (0.00%)	0 / 175 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis			

subjects affected / exposed	0 / 176 (0.00%)	0 / 175 (0.00%)	0 / 175 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	0 / 176 (0.00%)	0 / 175 (0.00%)	0 / 175 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Psoriasis			
subjects affected / exposed	0 / 176 (0.00%)	0 / 175 (0.00%)	0 / 175 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Calculus ureteric			
subjects affected / exposed	0 / 176 (0.00%)	0 / 175 (0.00%)	0 / 175 (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
Hydronephrosis			
subjects affected / exposed	0 / 176 (0.00%)	0 / 175 (0.00%)	0 / 175 (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
Nephrolithiasis			
subjects affected / exposed	0 / 176 (0.00%)	0 / 175 (0.00%)	0 / 175 (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
Pyuria			
subjects affected / exposed	0 / 176 (0.00%)	0 / 175 (0.00%)	0 / 175 (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 / 176 (0.00%)	0 / 175 (0.00%)	0 / 175 (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 / 176 (0.00%)	1 / 175 (0.57%)	0 / 175 (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
Back pain			
subjects affected / exposed	0 / 176 (0.00%)	1 / 175 (0.57%)	0 / 175 (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
Intervertebral disc disorder			
subjects affected / exposed	0 / 176 (0.00%)	0 / 175 (0.00%)	0 / 175 (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 pain			
subjects affected / exposed	0 / 176 (0.00%)	0 / 175 (0.00%)	0 / 175 (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 stiffness			
subjects affected / exposed	0 / 176 (0.00%)	0 / 175 (0.00%)	0 / 175 (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	1 / 176 (0.57%)	0 / 175 (0.00%)	0 / 175 (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
Spinal osteoarthritis			
subjects affected / exposed	0 / 176 (0.00%)	0 / 175 (0.00%)	0 / 175 (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			
Chronic sinusitis			
subjects affected / exposed	0 / 176 (0.00%)	0 / 175 (0.00%)	0 / 175 (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 / 176 (0.00%)	1 / 175 (0.57%)	0 / 175 (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	
Clostridium difficile colitis				
subjects affected / exposed	0 / 176 (0.00%)	0 / 175 (0.00%)	0 / 175 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0	
Diabetic gangrene				
subjects affected / exposed	1 / 176 (0.57%)	0 / 175 (0.00%)	0 / 175 (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	
Gallbladder empyema				
subjects affected / exposed	0 / 176 (0.00%)	0 / 175 (0.00%)	0 / 175 (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	
Infective exacerbation of chronic obstructive airways disease				
subjects affected / exposed	0 / 176 (0.00%)	0 / 175 (0.00%)	0 / 175 (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				
subjects affected / exposed	0 / 176 (0.00%)	0 / 175 (0.00%)	0 / 175 (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	
Meningitis bacterial				
subjects affected / exposed	0 / 176 (0.00%)	0 / 175 (0.00%)	0 / 175 (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	
Pelvic abscess				
subjects affected / exposed	0 / 176 (0.00%)	0 / 175 (0.00%)	0 / 175 (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	
Pneumococcal bacteraemia				



subjects affected / exposed	0 / 176 (0.00%)	0 / 175 (0.00%)	0 / 175 (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 / 176 (0.00%)	0 / 175 (0.00%)	0 / 175 (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
Pyelonephritis			
subjects affected / exposed	0 / 176 (0.00%)	0 / 175 (0.00%)	0 / 175 (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
Pyelonephritis acute			
subjects affected / exposed	0 / 176 (0.00%)	0 / 175 (0.00%)	1 / 175 (0.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection bacterial			
subjects affected / exposed	0 / 176 (0.00%)	0 / 175 (0.00%)	0 / 175 (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			
Hypocalcaemia			
subjects affected / exposed	0 / 176 (0.00%)	0 / 175 (0.00%)	0 / 175 (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 / 176 (0.00%)	0 / 175 (0.00%)	0 / 175 (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

<b>Serious adverse events</b>	APR Exposure Period Up to 5 Years: Apremilast 20 mg	APR Exposure Period Up to 5 Years: Apremilast 20mg/30 mg	APR Exposure Period Up to 5 Years: Apremilast 30 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	35 / 252 (13.89%)	5 / 122 (4.10%)	36 / 252 (14.29%)
number of deaths (all causes)	0	0	0

number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	0 / 252 (0.00%)	0 / 122 (0.00%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cervix carcinoma stage 0			
subjects affected / exposed	0 / 252 (0.00%)	0 / 122 (0.00%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung squamous cell carcinoma stage unspecified			
subjects affected / exposed	1 / 252 (0.40%)	0 / 122 (0.00%)	0 / 252 (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
Papilloma			
subjects affected / exposed	1 / 252 (0.40%)	0 / 122 (0.00%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostate cancer			
subjects affected / exposed	1 / 252 (0.40%)	0 / 122 (0.00%)	0 / 252 (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			
Femoral artery occlusion			
subjects affected / exposed	0 / 252 (0.00%)	0 / 122 (0.00%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Varicose vein			
subjects affected / exposed	1 / 252 (0.40%)	0 / 122 (0.00%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Non-cardiac chest pain			

subjects affected / exposed	1 / 252 (0.40%)	0 / 122 (0.00%)	0 / 252 (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
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	1 / 252 (0.40%)	0 / 122 (0.00%)	0 / 252 (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
Reproductive system and breast disorders			
Cystocele			
subjects affected / exposed	0 / 252 (0.00%)	0 / 122 (0.00%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endometrial atrophy			
subjects affected / exposed	1 / 252 (0.40%)	0 / 122 (0.00%)	0 / 252 (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
Endometrial hyperplasia			
subjects affected / exposed	0 / 252 (0.00%)	0 / 122 (0.00%)	0 / 252 (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
Metrorrhagia			
subjects affected / exposed	1 / 252 (0.40%)	0 / 122 (0.00%)	0 / 252 (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
Postmenopausal haemorrhage			
subjects affected / exposed	1 / 252 (0.40%)	0 / 122 (0.00%)	0 / 252 (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
Rectocele			
subjects affected / exposed	0 / 252 (0.00%)	0 / 122 (0.00%)	1 / 252 (0.40%)
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			
Asthma			
subjects affected / exposed	1 / 252 (0.40%)	0 / 122 (0.00%)	0 / 252 (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
Haemoptysis			
subjects affected / exposed	0 / 252 (0.00%)	0 / 122 (0.00%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nasal polyps			
subjects affected / exposed	1 / 252 (0.40%)	0 / 122 (0.00%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	0 / 252 (0.00%)	0 / 122 (0.00%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Confusional state			
subjects affected / exposed	1 / 252 (0.40%)	0 / 122 (0.00%)	0 / 252 (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
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 252 (0.40%)	0 / 122 (0.00%)	0 / 252 (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
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 252 (0.40%)	0 / 122 (0.00%)	0 / 252 (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
Injury, poisoning and procedural complications			
Contusion			

subjects affected / exposed	0 / 252 (0.00%)	0 / 122 (0.00%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Incisional hernia			
subjects affected / exposed	1 / 252 (0.40%)	1 / 122 (0.82%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple fractures			
subjects affected / exposed	0 / 252 (0.00%)	0 / 122 (0.00%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple injuries			
subjects affected / exposed	1 / 252 (0.40%)	0 / 122 (0.00%)	0 / 252 (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
Post procedural fistula			
subjects affected / exposed	0 / 252 (0.00%)	0 / 122 (0.00%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Radius fracture			
subjects affected / exposed	0 / 252 (0.00%)	0 / 122 (0.00%)	1 / 252 (0.40%)
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	1 / 252 (0.40%)	0 / 122 (0.00%)	0 / 252 (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
Tibia fracture			
subjects affected / exposed	1 / 252 (0.40%)	0 / 122 (0.00%)	0 / 252 (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	1 / 252 (0.40%)	0 / 122 (0.00%)	0 / 252 (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
Angina pectoris			
subjects affected / exposed	1 / 252 (0.40%)	0 / 122 (0.00%)	2 / 252 (0.79%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina unstable			
subjects affected / exposed	1 / 252 (0.40%)	0 / 122 (0.00%)	0 / 252 (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 / 252 (0.00%)	0 / 122 (0.00%)	1 / 252 (0.40%)
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 flutter			
subjects affected / exposed	0 / 252 (0.00%)	0 / 122 (0.00%)	2 / 252 (0.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrioventricular block			
subjects affected / exposed	1 / 252 (0.40%)	0 / 122 (0.00%)	0 / 252 (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
Atrioventricular block second degree			
subjects affected / exposed	0 / 252 (0.00%)	0 / 122 (0.00%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery disease			
subjects affected / exposed	1 / 252 (0.40%)	0 / 122 (0.00%)	2 / 252 (0.79%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery occlusion			

subjects affected / exposed	1 / 252 (0.40%)	0 / 122 (0.00%)	0 / 252 (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
Palpitations			
subjects affected / exposed	1 / 252 (0.40%)	0 / 122 (0.00%)	0 / 252 (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
Pericarditis			
subjects affected / exposed	1 / 252 (0.40%)	0 / 122 (0.00%)	0 / 252 (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
Stress cardiomyopathy			
subjects affected / exposed	1 / 252 (0.40%)	0 / 122 (0.00%)	0 / 252 (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
Nervous system disorders			
Carpal tunnel syndrome			
subjects affected / exposed	0 / 252 (0.00%)	0 / 122 (0.00%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epilepsy			
subjects affected / exposed	1 / 252 (0.40%)	0 / 122 (0.00%)	0 / 252 (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	1 / 252 (0.40%)	0 / 122 (0.00%)	0 / 252 (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
Spinal cord compression			
subjects affected / exposed	1 / 252 (0.40%)	0 / 122 (0.00%)	0 / 252 (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
Transient ischaemic attack			

subjects affected / exposed	2 / 252 (0.79%)	0 / 122 (0.00%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vertigo CNS origin			
subjects affected / exposed	1 / 252 (0.40%)	0 / 122 (0.00%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Lymphadenopathy mediastinal			
subjects affected / exposed	0 / 252 (0.00%)	0 / 122 (0.00%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 252 (0.40%)	0 / 122 (0.00%)	0 / 252 (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
Eye disorders			
Retinal vein thrombosis			
subjects affected / exposed	1 / 252 (0.40%)	0 / 122 (0.00%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain lower			
subjects affected / exposed	0 / 252 (0.00%)	0 / 122 (0.00%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anal fissure			
subjects affected / exposed	0 / 252 (0.00%)	0 / 122 (0.00%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			



subjects affected / exposed	1 / 252 (0.40%)	0 / 122 (0.00%)	0 / 252 (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
Diarrhoea			
subjects affected / exposed	1 / 252 (0.40%)	0 / 122 (0.00%)	0 / 252 (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
Enterocoele			
subjects affected / exposed	0 / 252 (0.00%)	0 / 122 (0.00%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inguinal hernia			
subjects affected / exposed	1 / 252 (0.40%)	1 / 122 (0.82%)	3 / 252 (1.19%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Irritable bowel syndrome			
subjects affected / exposed	0 / 252 (0.00%)	0 / 122 (0.00%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis acute			
subjects affected / exposed	0 / 252 (0.00%)	0 / 122 (0.00%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal haemorrhage			
subjects affected / exposed	0 / 252 (0.00%)	0 / 122 (0.00%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Umbilical hernia			
subjects affected / exposed	0 / 252 (0.00%)	0 / 122 (0.00%)	2 / 252 (0.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis			

subjects affected / exposed	0 / 252 (0.00%)	0 / 122 (0.00%)	1 / 252 (0.40%)
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	2 / 252 (0.79%)	0 / 122 (0.00%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Psoriasis			
subjects affected / exposed	0 / 252 (0.00%)	0 / 122 (0.00%)	2 / 252 (0.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Calculus ureteric			
subjects affected / exposed	1 / 252 (0.40%)	0 / 122 (0.00%)	0 / 252 (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
Hydronephrosis			
subjects affected / exposed	1 / 252 (0.40%)	0 / 122 (0.00%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephrolithiasis			
subjects affected / exposed	1 / 252 (0.40%)	0 / 122 (0.00%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyuria			
subjects affected / exposed	0 / 252 (0.00%)	0 / 122 (0.00%)	1 / 252 (0.40%)
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 / 252 (0.00%)	0 / 122 (0.00%)	1 / 252 (0.40%)
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	1 / 252 (0.40%)	0 / 122 (0.00%)	0 / 252 (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
Back pain			
subjects affected / exposed	2 / 252 (0.79%)	0 / 122 (0.00%)	0 / 252 (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
Intervertebral disc disorder			
subjects affected / exposed	1 / 252 (0.40%)	0 / 122 (0.00%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal pain			
subjects affected / exposed	0 / 252 (0.00%)	0 / 122 (0.00%)	1 / 252 (0.40%)
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 stiffness			
subjects affected / exposed	0 / 252 (0.00%)	0 / 122 (0.00%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psoriatic arthropathy			
subjects affected / exposed	0 / 252 (0.00%)	0 / 122 (0.00%)	2 / 252 (0.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal osteoarthritis			
subjects affected / exposed	1 / 252 (0.40%)	0 / 122 (0.00%)	0 / 252 (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			
Chronic sinusitis			
subjects affected / exposed	1 / 252 (0.40%)	0 / 122 (0.00%)	0 / 252 (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

Chronic tonsillitis			
subjects affected / exposed	1 / 252 (0.40%)	0 / 122 (0.00%)	0 / 252 (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
Clostridium difficile colitis			
subjects affected / exposed	0 / 252 (0.00%)	1 / 122 (0.82%)	0 / 252 (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
Diabetic gangrene			
subjects affected / exposed	0 / 252 (0.00%)	0 / 122 (0.00%)	0 / 252 (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
Gallbladder empyema			
subjects affected / exposed	0 / 252 (0.00%)	0 / 122 (0.00%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infective exacerbation of chronic obstructive airways disease			
subjects affected / exposed	1 / 252 (0.40%)	0 / 122 (0.00%)	0 / 252 (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			
subjects affected / exposed	1 / 252 (0.40%)	0 / 122 (0.00%)	0 / 252 (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
Meningitis bacterial			
subjects affected / exposed	0 / 252 (0.00%)	1 / 122 (0.82%)	0 / 252 (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
Pelvic abscess			
subjects affected / exposed	0 / 252 (0.00%)	0 / 122 (0.00%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumococcal bacteraemia			

subjects affected / exposed	0 / 252 (0.00%)	1 / 122 (0.82%)	0 / 252 (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
Pneumonia			
subjects affected / exposed	0 / 252 (0.00%)	1 / 122 (0.82%)	0 / 252 (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
Pyelonephritis			
subjects affected / exposed	0 / 252 (0.00%)	0 / 122 (0.00%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis acute			
subjects affected / exposed	0 / 252 (0.00%)	0 / 122 (0.00%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection bacterial			
subjects affected / exposed	0 / 252 (0.00%)	0 / 122 (0.00%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hypocalcaemia			
subjects affected / exposed	1 / 252 (0.40%)	0 / 122 (0.00%)	0 / 252 (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
Obesity			
subjects affected / exposed	0 / 252 (0.00%)	0 / 122 (0.00%)	1 / 252 (0.40%)
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 %

<b>Non-serious adverse events</b>	Weeks 0-24: Placebo (Placebo- Controlled Phase)	Weeks 0-24: Apremilast 20 mg (Placebo-Controlled Phase)	Weeks 0-24: Apremilast 30 mg (Placebo-Controlled Phase)
Total subjects affected by non-serious adverse events subjects affected / exposed	30 / 176 (17.05%)	51 / 175 (29.14%)	65 / 175 (37.14%)
Vascular disorders Hypertension subjects affected / exposed occurrences (all)	1 / 176 (0.57%) 1	4 / 175 (2.29%) 4	4 / 175 (2.29%) 4
Nervous system disorders Headache subjects affected / exposed occurrences (all)	4 / 176 (2.27%) 4	6 / 175 (3.43%) 6	15 / 175 (8.57%) 16
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all)  Dyspepsia subjects affected / exposed occurrences (all)  Nausea subjects affected / exposed occurrences (all)	3 / 176 (1.70%) 3  2 / 176 (1.14%) 2  5 / 176 (2.84%) 5	12 / 175 (6.86%) 13  8 / 175 (4.57%) 11  16 / 175 (9.14%) 17	21 / 175 (12.00%) 24  0 / 175 (0.00%) 0  28 / 175 (16.00%) 30
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	2 / 176 (1.14%) 2	6 / 175 (3.43%) 6	4 / 175 (2.29%) 4
Skin and subcutaneous tissue disorders Psoriasis subjects affected / exposed occurrences (all)	6 / 176 (3.41%) 6	1 / 175 (0.57%) 1	2 / 175 (1.14%) 2
Psychiatric disorders Depression subjects affected / exposed occurrences (all)	1 / 176 (0.57%) 1	1 / 175 (0.57%) 1	2 / 175 (1.14%) 2
Musculoskeletal and connective tissue disorders Back pain			

subjects affected / exposed occurrences (all)	0 / 176 (0.00%) 0	1 / 175 (0.57%) 1	3 / 175 (1.71%) 3
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	3 / 176 (1.70%)	3 / 175 (1.71%)	3 / 175 (1.71%)
occurrences (all)	3	3	3
Sinusitis			
subjects affected / exposed	1 / 176 (0.57%)	6 / 175 (3.43%)	4 / 175 (2.29%)
occurrences (all)	1	6	4
Upper respiratory tract infection			
subjects affected / exposed	4 / 176 (2.27%)	6 / 175 (3.43%)	7 / 175 (4.00%)
occurrences (all)	4	6	8
Urinary tract infection			
subjects affected / exposed	1 / 176 (0.57%)	2 / 175 (1.14%)	2 / 175 (1.14%)
occurrences (all)	1	2	2

<b>Non-serious adverse events</b>	APR Exposure Period Up to 5 Years: Apremilast 20 mg	APR Exposure Period Up to 5 Years: Apremilast 20mg/30 mg	APR Exposure Period Up to 5 Years: Apremilast 30 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	121 / 252 (48.02%)	24 / 122 (19.67%)	141 / 252 (55.95%)
Vascular disorders			
Hypertension			
subjects affected / exposed	15 / 252 (5.95%)	0 / 122 (0.00%)	16 / 252 (6.35%)
occurrences (all)	15	0	19
Nervous system disorders			
Headache			
subjects affected / exposed	15 / 252 (5.95%)	0 / 122 (0.00%)	26 / 252 (10.32%)
occurrences (all)	15	0	32
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	30 / 252 (11.90%)	2 / 122 (1.64%)	31 / 252 (12.30%)
occurrences (all)	34	4	48
Dyspepsia			
subjects affected / exposed	14 / 252 (5.56%)	0 / 122 (0.00%)	4 / 252 (1.59%)
occurrences (all)	19	0	4
Nausea			

subjects affected / exposed occurrences (all)	24 / 252 (9.52%) 27	2 / 122 (1.64%) 2	39 / 252 (15.48%) 51
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	11 / 252 (4.37%) 13	1 / 122 (0.82%) 1	13 / 252 (5.16%) 14
Skin and subcutaneous tissue disorders Psoriasis subjects affected / exposed occurrences (all)	6 / 252 (2.38%) 8	1 / 122 (0.82%) 1	13 / 252 (5.16%) 16
Psychiatric disorders Depression subjects affected / exposed occurrences (all)	5 / 252 (1.98%) 5	2 / 122 (1.64%) 2	13 / 252 (5.16%) 14
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all)	14 / 252 (5.56%) 15	0 / 122 (0.00%) 0	10 / 252 (3.97%) 11
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	20 / 252 (7.94%) 26	5 / 122 (4.10%) 6	23 / 252 (9.13%) 50
Sinusitis subjects affected / exposed occurrences (all)	16 / 252 (6.35%) 18	6 / 122 (4.92%) 7	12 / 252 (4.76%) 15
Upper respiratory tract infection subjects affected / exposed occurrences (all)	26 / 252 (10.32%) 31	5 / 122 (4.10%) 5	31 / 252 (12.30%) 41
Urinary tract infection subjects affected / exposed occurrences (all)	10 / 252 (3.97%) 15	3 / 122 (2.46%) 3	18 / 252 (7.14%) 27



## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 January 2011	<ol style="list-style-type: none"><li>1. Clarified that the modified ACR 20 (primary endpoint) is one of the tools that is listed as acceptable by the European Medicines Agency Guideline on Clinical Investigation of Medicinal Products Indicated for the Treatment of Psoriatic Arthritis.</li><li>2. Added BSA involved by psoriasis as a study assessment.</li><li>3. Clarified the language related to contraception methods in several protocol sections to ensure that the acceptable methods of contraception were precisely described and added a statement to ensure that the investigator provided appropriate education regarding acceptable contraceptive methods to the subjects.</li><li>4. Deleted the requirement for annual chest radiographs to allow local treatment guidelines to dictate when chest radiographs would be performed.</li><li>5. Modified the reasons for discontinuation of the IP (apremilast or placebo) or from the study to include "noncompliance with study drug" and "study terminated by sponsor" for alignment with the reasons that were actually displayed in the InForm database.</li><li>6. Clarified that informed consent must be obtained from the study subject or from a legal representative before any study-related procedures were performed.</li><li>7. Clarified the exclusion criteria related to psoriasis (Exclusion Criterion 16) and added fibromyalgia as an exclusion criterion (to Exclusion Criterion 18).</li><li>8. Modified the exclusion criterion related to prior malignancy.</li><li>9. Provided further clarification of prohibited concomitant medications</li></ol>
10 June 2011	<ol style="list-style-type: none"><li>1. Added a serum pregnancy test for FCBP at baseline.</li><li>2. Clarified that microscopic evaluation must be performed on all urine specimens.</li><li>3. Clarified the inclusion criteria (Inclusion Criterion 14) to indicate that the chosen form of birth contraception must be fully effective by the time the FCBP receive the first dose of IP at randomization.</li><li>4. Clarified the inclusion criterion (Inclusion Criterion 13) to indicate that male subjects must use a "male" latex or nonlatex (not made of natural membrane) condom.</li><li>5. Added "at randomization" to the text of exclusion criterion.</li><li>6. Deleted text related to the manner in which the onset and end dates of SAEs were to be recorded on the SAE Report Form (no longer applicable).</li><li>7. Corrected the name of the Celgene Therapeutic Area Head.</li><li>8. Corrected the timing of Visit 6 from Week 32 to Week 28 in the Table of Events.</li></ol>

20 April 2012	<ol style="list-style-type: none"> <li>1. Modified the treatment and administration schedule to state that the site personnel and subjects would remain blinded to the treatment assignments until all of the subjects had completed the 52-week double-blind phase of the study.</li> <li>2. Replaced the SRP with an independent external DMC.</li> <li>3. Revised the protocol to permit subjects who experienced worsening of skin psoriasis to receive topical therapy or phototherapy after completion of the 52-week double blind study period.</li> <li>4. Added an assessment of vasculitis and a psychiatric evaluation as part of the AE assessments and provided guidance related to the medical management of these conditions to the investigators.</li> <li>5. Added radiographic evaluations of symptomatic joints, as medically indicated, during the long-term extension phase of the study.</li> <li>6. Revised inclusion criteria 13 and 14 and the section on contraception education to reflect the change in the protocol requirements for contraception.</li> <li>7. Provided information on the manner in which apremilast would be supplied during the open-label extension phase of the study (ie, after Week 52).</li> <li>8. Specified that the AE tables would only summarize TEAEs.</li> <li>9. Changed "CRF" to "eCRF" to reflect that the study data were to be captured on electronic CRFs.</li> <li>10. Incorporated several administrative changes to the Table of Events to reflect changes that were made in other sections of the protocol.</li> <li>11. Updated the name and contact information of the PPD Medical Monitor.</li> </ol>
03 July 2012	<ol style="list-style-type: none"> <li>1. Changed the assessment of the primary endpoint (modified ACR 20) from Week 24 to Week 16.</li> <li>2. Elevated assessments of enthesitis and dactylitis (in subjects who presented with these manifestations of PsA at baseline) from exploratory endpoints to secondary endpoints.</li> <li>3. Added an assessment of the secondary endpoints at Week 16 (in addition to Weeks 24 and 52).</li> <li>4. Changed the order of secondary endpoints at Weeks 16, 24, and 52 to coincide with the planned sequence of statistical testing.</li> <li>5. Added the modified PsARC response and EULAR response as secondary endpoints.</li> <li>6. Added the ACR-N as an exploratory endpoint.</li> <li>7. Added an assessment of the health-related quality of life endpoints at Week 16 (in addition to Weeks 24 and 52).</li> <li>8. Modified the permitted concomitant medications to allow use of systemic corticosteroids and DMARDs for the treatment of worsening arthritic symptoms of PsA after the Week 52 visit.</li> <li>9. Revised the statistical approaches for the secondary endpoints and for the subgroup analyses.</li> </ol>
20 December 2012	<ol style="list-style-type: none"> <li>1. Extended the maximum duration of treatment from 2 years to 5 years to allow evaluation of the efficacy, safety, and tolerability of apremilast for up to 5 years in subjects with active PsA.</li> <li>2. Changed the last visit from Visit 13 to Visit 25 as a result of the study extension.</li> <li>3. Added references for the modified PsARC and EULAR response (added as secondary efficacy outcome measures).</li> </ol> <p>An administrative letter (dated 22 Feb 2012) was issued to correct the timing of the PASI in the Table of Events (removed from Visit 7).</p>

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported