Clinical trial results:
A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study To Evaluate The Efficacy And Safety Of Apremilast (Cc-10004) In The Treatment Of Active Ankylosing Spondylitis

Summary

EudraCT number	2011-001555-37
Trial protocol	GB HU DE SK NL ES PL SE CZ AT BG FR EE
Global end of trial date	25 October 2018

Results information

Result version number	v1 (current)
This version publication date	11 November 2019
First version publication date	11 November 2019

Trial information

Trial identification

Sponsor protocol code	CC-10004-AS-001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01583374
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Celgene Corporation
Sponsor organisation address	86 Morris Avenue, Summit, United States, 07901
Public contact	Clinical Trial Disclosure, Celgene Corporation, 01 888-260-1599, ClinicalTrialDisclosure@Celgene.com
Scientific contact	Sue Cheng, MD, Celgene Corporation, 01 908 887-3916, SuCheng@Celgene.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	25 October 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	25 October 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was to evaluate the efficacy of APR 30 BID, compared with placebo, in the reduction of signs and symptoms in subjects with active AS at 16 weeks of treatment.

Protection of trial subjects:

Patient Confidentiality, Informed Consent, Archiving of Essential Documents

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	02 May 2012
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	5 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 24
Country: Number of subjects enrolled	Austria: 2
Country: Number of subjects enrolled	Bulgaria: 30
Country: Number of subjects enrolled	Czech Republic: 75
Country: Number of subjects enrolled	Estonia: 25
Country: Number of subjects enrolled	France: 19
Country: Number of subjects enrolled	Germany: 15
Country: Number of subjects enrolled	Hungary: 34
Country: Number of subjects enrolled	Netherlands: 4
Country: Number of subjects enrolled	Poland: 93
Country: Number of subjects enrolled	Romania: 11
Country: Number of subjects enrolled	Russian Federation: 36
Country: Number of subjects enrolled	Slovakia: 10
Country: Number of subjects enrolled	Spain: 23
Country: Number of subjects enrolled	United Kingdom: 12
Country: Number of subjects enrolled	Canada: 24
Country: Number of subjects enrolled	Sweden: 1
Country: Number of subjects enrolled	United States: 52
Worldwide total number of subjects	490
EEA total number of subjects	354

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	458
From 65 to 84 years	32
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study enrolled participants at 88 study sites and in 18 countries (Australia, Austria, Bulgaria, Czech Republic, Estonia, France, Germany, Hungary, the Netherlands, Poland, Romania, Russia, Slovakia, Spain, the United Kingdom, Canada, Sweden, and the United States [US]).

Pre-assignment

Screening details:

Randomized participants were stratified by the following 2 parameters:
1. C-Reactive Protein (CRP) concentration (normal: ≤ 1.5 mg/dL or elevated: > 1.5 mg/dL) from screening;
2. The Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score < 6.0 or BASDAI score ≥ 6.0 from baseline.

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, Carer, Assessor

Blinding implementation details:

The blind was not to be broken during the course of the study unless, in the opinion of the Investigator, it was absolutely necessary to safely treat the subject. If it was medically imperative to know what IP the subject was receiving, the Investigator or authorized person could call the IVRS for unblinded dose information according to the procedure supplied by the IVRS vendor.

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

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

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

Dosage and administration details:

Placebo tablets (identical in appearance to apremilast) twice daily

Arm title	Apremilast 20 mg

Arm description:

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

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

Dosage and administration details:

Apremilast 20 mg tablets twice daily.

Arm title	Apremilast 30 mg

Arm description:

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

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

Dosage and administration details:

Apremilast 30 mg tablets twice daily.

Number of subjects in period 1	Placebo	Apremilast 20 mg	Apremilast 30 mg
Started	164	163	163
Received Treatment	164	163	163
Completed Week 16	150	151	144
Early Escape at Week 16	51 [1]	49 [2]	49 [3]
Completed	145	147	138
Not completed	19	16	25
Consent withdrawn by subject	8	3	5
Adverse event, non-fatal	6	7	12
Non-compliance with study drug	1	1	-
Unspecified	-	1	-
Lost to follow-up	1	2	-
Lack of efficacy	3	2	5
Protocol deviation	-	-	3

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	Extension Phase (Weeks 24 to 52)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer, Assessor

Blinding implementation details:

The blind was not to be broken during the course of the study unless, in the opinion of the Investigator, it was absolutely necessary to safely treat the subject. If it was medically imperative to know what IP the subject was receiving, the Investigator or authorized person could call the IVRS for unblinded dose information according to the procedure supplied by the IVRS vendor.

Arms

Are arms mutually exclusive?	Yes
Arm title	Apremilast 20 mg

Arm description:

Participants initially randomized to 20 mg apremilast tablets BID in the 24-week placebo-controlled phase continued to receive 20 mg apremilast tablets BID for up to 4.5 years in the long-term extension phase.

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

Dosage and administration details:

Apremilast 20 mg tablets twice daily.

Arm title	Apremilast 30 mg

Arm description:

Participants initially randomized to 30 mg apremilast tablets BID in the 24-week placebo-controlled phase, continued to receive 30 mg apremilast tablets BID for up to 4.5 years in the long-term extension phase.

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

Dosage and administration details:

Apremilast 30 mg tablets twice daily

Arm title	Placebo / Apremilast 30 mg Early Escape (EE)

Arm description:

Participants initially randomized to receive placebo tablets BID who did not have at least 20% improvement or ≥ 1 unit improvement from baseline in 2 out of 4 of the Assessment of SpondyloArthritis International Society (ASAS) domains at Week 16 were transitioned to 30 mg apremilast tablets BID and continued to receive 30 mg apremilast tablets BID for up to 4.5 years in the long-term extension phase.

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

Dosage and administration details:

Apremilast 30 mg tablets twice a day

Arm title	Placebo/Apremilast 30 mg Crossover (XO)

Arm description:

Participants initially randomized to placebo tablets BID in the 24-week placebo controlled phase were transitioned to 30 mg apremilast tablets BID at Week 24 and continued to receive 30 mg apremilast tablets BID for up to 4.5 years in the long-term extension phase.

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

Dosage and administration details:

Apremilast 30 mg tablets twice a day

Arm title	Apremilast 30 mg /Apremilast 30 mg EE

Arm description:

Participants initially randomized to 30 mg apremilast tablets BID in the 24-week placebo-controlled phase who did not have at least 20% improvement or a ≥ 1-unit improvement from baseline in 2 of the 4 ASAS domains at Week 16 continued to receive 30 mg apremilast tablets BID for up to 4.5 years in the long-term extension phase.

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

Dosage and administration details:

Apremilast 30 mg tablets twice a day.

Arm title	Apremilast 20 mg /Apremilast 30 mg EE

Arm description:

Participants initially randomized to 20 mg apremilast tablets BID who did not have at least 20% improvement or ≥ 1 unit improvement from baseline in 2 out of 4 of the ASAS domains at Week 16 were transitioned to 30 mg apremilast tablets BID and continued to receive 30 mg apremilast tablets BID for up to 4.5 years in the long-term extension phase.

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

Dosage and administration details:

Apremilast 30 mg tablets twice a day.

Arm title	Apremilast 30 mg /Apremilast 30 mg Second Escape (SE)

Arm description:

Participants initially randomized to 30 mg apremilast tablets BID who did not have at least 20% improvement or ≥ 1 unit improvement from baseline in 2 out of 4 of the ASAS domains from baseline at Week 24 continued to receive 30 mg apremilast tablets BID (second escape) for up to 4.5 years in the long-term extension phase.

Arm type	Experimental

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

Dosage and administration details:

Apremilast 30 mg tablets twice a day.

Arm title	Apremilast 20 mg/Apremilast 30 mg SE

Arm description:

Participants initially randomized to 20 mg apremilast tablets BID who did not have at least 20% improvement or ≥ 1 unit improvement from baseline in 2 out of 4 of the ASAS domains at Week 24 were transitioned to 30 mg apremilast tablets BID (second escape) and continued to receive 30 mg apremilast tablets BID for up to 4.5 years in the long-term extension phase.

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

Dosage and administration details:

Apremilast 30 mg tablets twice a day.

Number of subjects in period 2[4]	Apremilast 20 mg	Apremilast 30 mg	Placebo / Apremilast 30 mg Early Escape (EE)
Started	74	65	47
Completed	69	61	41
Not completed	5	4	6
Non-compliance study drug	2	1	-
Consent withdrawn by subject	-	1	-
Adverse event, non-fatal	1	2	-
Lost to follow-up	-	-	-
Lack of efficacy	2	-	6

Number of subjects in period 2[4]	Placebo/Apremilast 30 mg Crossover (XO)	Apremilast 30 mg /Apremilast 30 mg EE	Apremilast 20 mg /Apremilast 30 mg EE
Started	91	48	48
Completed	85	43	43
Not completed	6	5	5
Non-compliance study drug	1	-	-
Consent withdrawn by subject	1	2	-
Adverse event, non-fatal	1	1	-
Lost to follow-up	-	-	-
Lack of efficacy	3	2	5

Number of subjects in period 2	Apremilast 30 mg	Apremilast 20

[4]	/Apremilast 30 mg Second Escape (SE)	mg/Apremilast 30 mg SE
Started	25	23
Completed	22	21
Not completed	3	2
Non-compliance study drug	-	-
Consent withdrawn by subject	-	-
Adverse event, non-fatal	1	-
Lost to follow-up	1	-
Lack of efficacy	1	2

Notes:

[4] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: For all the arms, the number of subjects starting the subsequent periods were less than or equal to the number completing the preceding period, this is because not all subjects who completed the preceding period would enter the subsequent period.

Period 3

Period 3 title	Long-Term Extension Phase (Weeks 52-260)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Apremilast 20 mg

Arm description:

Participants initially randomized to 20 mg apremilast tablets BID in the 24-week placebo-controlled phase continued to receive 20 mg apremilast tablets BID for up to 4.5 years in the long-term extension phase.

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

Dosage and administration details:

Apremilast 20 mg tablets twice daily.

Arm title	Apremilast 30 mg

Arm description:

Participants initially randomized to 30 mg apremilast tablets BID in the 24-week placebo-controlled phase, continued to receive 30 mg apremilast tablets BID for up to 4.5 years in the long-term extension phase.

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

Dosage and administration details:

Apremilast 30 mg tablets twice daily

Arm title	Placebo / Apremilast 30 mg Early Escape (EE)

Arm description:

Participants initially randomized to receive placebo tablets BID who did not have at least 20% improvement or ≥ 1 unit improvement from baseline in 2 out of 4 of the Assessment of SpondyloArthritis International Society (ASAS) domains at Week 16 were transitioned to 30 mg apremilast tablets BID and continued to receive 30 mg apremilast tablets BID for up to 4.5 years in the long-term extension phase.

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

Dosage and administration details:

Apremilast 30 mg tablets twice a day

Arm title	Placebo/Apremilast 30 mg Crossover (XO)

Arm description:

Participants initially randomized to placebo tablets BID in the 24-week placebo controlled phase were transitioned to 30 mg apremilast tablets BID at Week 24 and continued to receive 30 mg apremilast tablets BID for up to 4.5 years in the long-term extension phase.

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

Dosage and administration details:

Apremilast 30 mg tablets twice a day

Arm title	Apremilast 30 mg /Apremilast 30 mg EE

Arm description:

Participants initially randomized to 30 mg apremilast tablets BID in the 24-week placebo-controlled phase who did not have at least 20% improvement or a ≥ 1-unit improvement from baseline in 2 of the 4 ASAS domains at Week 16 continued to receive 30 mg apremilast tablets BID for up to 4.5 years in the long-term extension phase.

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

Dosage and administration details:

Apremilast 30 mg tablets twice a day.

Arm title	Apremilast 20 mg /Apremilast 30 mg EE

Arm description:

Participants initially randomized to 20 mg apremilast tablets BID who did not have at least 20% improvement or ≥ 1 unit improvement from baseline in 2 out of 4 of the ASAS domains at Week 16 were transitioned to 30 mg apremilast tablets BID and continued to receive 30 mg apremilast tablets BID for up to 4.5 years in the long-term extension phase.

Arm type	Experimental

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

Dosage and administration details:

Apremilast 30 mg tablets twice a day.

Arm title	Apremilast 30 mg /Apremilast 30 mg Second Escape (SE)

Arm description:

Participants initially randomized to 30 mg apremilast tablets BID who did not have at least 20% improvement or ≥ 1 unit improvement from baseline in 2 out of 4 of the ASAS domains from baseline at Week 24 continued to receive 30 mg apremilast tablets BID (second escape) for up to 4.5 years in the long-term extension phase.

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

Dosage and administration details:

Apremilast 30 mg tablets twice a day.

Arm title	Apremilast 20 mg/Apremilast 30 mg SE

Arm description:

Participants initially randomized to 20 mg apremilast tablets BID who did not have at least 20% improvement or ≥ 1 unit improvement from baseline in 2 out of 4 of the ASAS domains at Week 24 were transitioned to 30 mg apremilast tablets BID (second escape) and continued to receive 30 mg apremilast tablets BID for up to 4.5 years in the long-term extension phase.

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

Dosage and administration details:

Apremilast 30 mg tablets twice a day.

Number of subjects in period 3[5]	Apremilast 20 mg	Apremilast 30 mg	Placebo / Apremilast 30 mg Early Escape (EE)
Started	66	61	35
Completed	40	41	22
Not completed	26	20	13
Noncomplinace with IP	-	-	-
Adverse event, serious fatal	-	-	-
Consent withdrawn by subject	11	11	1
Adverse event, non-fatal	5	2	2
Miscellaneous	5	1	2
Lost to follow-up	1	-	1

Lack of efficacy	4	6	7

Number of subjects in period 3[5]	Placebo/Apremilast 30 mg Crossover (XO)	Apremilast 30 mg /Apremilast 30 mg EE	Apremilast 20 mg /Apremilast 30 mg EE
Started	81	39	38
Completed	50	22	20
Not completed	31	17	18
Noncomplinace with IP	1	-	-
Adverse event, serious fatal	1	-	1
Consent withdrawn by subject	12	7	5
Adverse event, non-fatal	6	2	2
Miscellaneous	-	1	5
Lost to follow-up	1	-	1
Lack of efficacy	10	7	4

Number of subjects in period 3[5]	Apremilast 30 mg /Apremilast 30 mg Second Escape (SE)	Apremilast 20 mg/Apremilast 30 mg SE
Started	21	20
Completed	12	10
Not completed	9	10
Noncomplinace with IP	1	1
Adverse event, serious fatal	-	-
Consent withdrawn by subject	3	3
Adverse event, non-fatal	3	1
Miscellaneous	-	1
Lost to follow-up	-	-
Lack of efficacy	2	4

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.

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Participants initially randomized to receive placebo tablets BID in the 24-week placebo-controlled phase.	
Reporting group title	Apremilast 20 mg
Reporting group description:	
Participants initially randomized to 20 mg apremilast tablets BID in the 24-week placebo-controlled phase.	
Reporting group title	Apremilast 30 mg
Reporting group description:	
Participants initially randomized to 30 mg apremilast tablets BID in the 24-week placebo-controlled phase.	

Reporting group values	Placebo	Apremilast 20 mg	Apremilast 30 mg
Number of subjects	164	163	163
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	147	156	155
From 65-84 years	17	7	8
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	44.0	45.2	44.8
standard deviation	± 12.89	± 11.90	± 11.75
Sex: Female, Male Units: Subjects			
Female	40	42	56
Male	124	121	107
Duration of Ankylosing Spondylitis Units: Subjects			
≤ 2 years	41	48	40
> 2 to ≤ 5 years	29	23	26
> 5 to ≤ 10 years	33	29	33
> 10 years	61	63	64
Race/Ethnicity, Customized Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	2	2	0
Black or African American	1	2	2

Native Hawaiian or Other Pacific Islander	1	0	0
White	158	154	158
Other	1	2	3
Missing	1	3	0
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	5	1	1
Not Hispanic or Latino	158	159	162
Unknown or Not Reported	1	3	0
Duration of Ankylosing Spondylitis (Lower Back Pain and Stiffness) Units: years			
arithmetic mean	10.40	11.06	10.32
standard deviation	± 10.375	± 11.302	± 9.887
Baseline Bath Ankylosing Spondylitis Functional Index (BASFI) Score (0 - 10 NRS)			
The BASFI was a composite score based on a participant self-administered survey of ten questions using a 0 to 10 unit numerical rating scale (NRS) that BASFI is a composite score based on a self-administered survey of 10 questions using a 0 to 10 unit numerical rating scale (NRS) that assesses the degree of mobility and functional ability. The survey consists of 8 questions regarding function in AS and the last 2 reflect the ability to manage everyday life. The patient marks a box with an X on a 0 to 10 unit NRS for 10 questions; the left-hand box of 0 = easy; the right-hand box = impossible.			
Units: Units on a Scale			
arithmetic mean	5.76	5.75	5.65
standard deviation	± 2.194	± 2.061	± 2.100
Baseline Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) Score (0 - 10 NRS)			
The BASDAI is a composite score based on a self-administered survey of 6 questions using a 0 to 10 unit NRS that assesses for 5 major symptoms of AS: fatigue; spinal pain; peripheral joint pain/swelling; areas of localized tenderness; morning stiffness severity upon wakening; morning stiffness duration upon wakening. To give each of the 5 symptoms equal weighting, the mean of the 2 scores relating to morning stiffness is taken. The resulting 0 to 50 score is divided by 5 to give a final 0 to 10 BASDAI score. A score of ≥4 is considered to be indicative of active			
Units: Units on a Scale			
arithmetic mean	6.45	6.46	6.37
standard deviation	± 1.319	± 1.352	± 1.357
Baseline Bath Ankylosing Spondylitis Metrology Index (BASMI)-Linear Score (0 - 10 NRS)			
The BASMI-Linear was designed to assess axial status (ie, cervical, dorsal and lumbar spine, hips, and pelvic soft tissue) and to define clinically significant changes in spinal movement. Five dimensions of movement (lateral lumbar flexion, tragus to wall, forward lumbar flexion, maximal intermalleolar distance, and cervical rotation) were measured and normalized on 0 to 10 unit NRS. The average of these scores is the total BASMI score, with a higher value indicating more severe limitation in spinal mobility.			
Units: Units on a Scale			
arithmetic mean	4.36	4.63	4.41
standard deviation	± 1.608	± 1.721	± 1.700
Baseline Ankylosing Spondylitis Quality of Life (ASQoL) Summary Score (0-18)			
The ASQoL is a validated disease specific patient reported outcomes instrument to assess the impact of ankylosing spondylitis on the QoL of individuals with emphasis on the ability of the person to fulfill his or her needs. It consisted of 18 items requesting a yes (score=1) or no (score=0) response to questions related to the impact of pain on sleep, mood, motivation, ability to cope, activities of daily living, independence, relationships, and social life. The summary score ranges 0–18 with higher scores indicating worse quality of life.			

Units: Units on a Scale			
arithmetic mean	9.10	8.38	8.62
standard deviation	± 4.639	± 4.548	± 4.935
Baseline Physical Component Summary Score of Medical Outcome Study Short Form 36-Item Survey			
The SF- 36 is a self-administered instrument that measures the impact of disease and consists of 36 questions in 8 domains (physical function, pain, general and mental health, vitality, social function, physical and emotional health). Two overall summary scores can also be obtained—a Physical Component Summary score (PCS) and a Mental Component Summary score (MCS). The PCS and MCS scores are transformed to have a mean of 50 and standard deviation of 10, with higher scores indicating better health. Scale scores range from 0 to 100, with higher scores indicating better health.			
Units: Units on a Scale			
arithmetic mean	32.57	31.89	32.16
standard deviation	± 7.821	± 8.561	± 8.846

Reporting group values	Total		
Number of subjects	490		
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)	458		
From 65-84 years	32		
85 years and over	0		
Age Continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Sex: Female, Male			
Units: Subjects			
Female	138		
Male	352		
Duration of Ankylosing Spondylitis			
Units: Subjects			
≤ 2 years	129		
> 2 to ≤ 5 years	78		
> 5 to ≤ 10 years	95		
> 10 years	188		
Race/Ethnicity, Customized			
Units: Subjects			
American Indian or Alaska Native	0		
Asian	4		
Black or African American	5		
Native Hawaiian or Other Pacific Islander	1		
White	470		

Other	6		
Missing	4		
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	7		
Not Hispanic or Latino	479		
Unknown or Not Reported	4		
Duration of Ankylosing Spondylitis (Lower Back Pain and Stiffness) Units: years arithmetic mean standard deviation	 -		
Baseline Bath Ankylosing Spondylitis Functional Index (BASFI) Score (0 - 10 NRS)			
The BASFI was a composite score based on a participant self-administered survey of ten questions using a 0 to 10 unit numerical rating scale (NRS) that BASFI is a composite score based on a self-administered survey of 10 questions using a 0 to 10 unit numerical rating scale (NRS) that assesses the degree of mobility and functional ability. The survey consists of 8 questions regarding function in AS and the last 2 reflect the ability to manage everyday life. The patient marks a box with an X on a 0 to 10 unit NRS for 10 questions; the left-hand box of 0 = easy; the right-hand box = impossible.			
Units: Units on a Scale arithmetic mean standard deviation	 -		
Baseline Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) Score (0 - 10 NRS)			
The BASDAI is a composite score based on a self-administered survey of 6 questions using a 0 to 10 unit NRS that assesses for 5 major symptoms of AS: fatigue; spinal pain; peripheral joint pain/swelling; areas of localized tenderness; morning stiffness severity upon wakening; morning stiffness duration upon wakening. To give each of the 5 symptoms equal weighting, the mean of the 2 scores relating to morning stiffness is taken. The resulting 0 to 50 score is divided by 5 to give a final 0 to 10 BASDAI score. A score of ≥4 is considered to be indicative of active			
Units: Units on a Scale arithmetic mean standard deviation	 -		
Baseline Bath Ankylosing Spondylitis Metrology Index (BASMI)-Linear Score (0 - 10 NRS)			
The BASMI-Linear was designed to assess axial status (ie, cervical, dorsal and lumbar spine, hips, and pelvic soft tissue) and to define clinically significant changes in spinal movement. Five dimensions of movement (lateral lumbar flexion, tragus to wall, forward lumbar flexion, maximal intermalleolar distance, and cervical rotation) were measured and normalized on 0 to 10 unit NRS. The average of these scores is the total BASMI score, with a higher value indicating more severe limitation in spinal mobility.			
Units: Units on a Scale arithmetic mean standard deviation	 -		
Baseline Ankylosing Spondylitis Quality of Life (ASQoL) Summary Score (0-18)			
The ASQoL is a validated disease specific patient reported outcomes instrument to assess the impact of ankylosing spondylitis on the QoL of individuals with emphasis on the ability of the person to fulfill his or her needs. It consisted of 18 items requesting a yes (score=1) or no (score=0) response to questions related to the impact of pain on sleep, mood, motivation, ability to cope, activities of daily living, independence, relationships, and social life. The summary score ranges 0–18 with higher scores indicating worse quality of life.			
Units: Units on a Scale arithmetic mean			

standard deviation	-		
Baseline Physical Component Summary Score of Medical Outcome Study Short Form 36-Item Survey			
The SF- 36 is a self-administered instrument that measures the impact of disease and consists of 36 questions in 8 domains (physical function, pain, general and mental health, vitality, social function, physical and emotional health). Two overall summary scores can also be obtained—a Physical Component Summary score (PCS) and a Mental Component Summary score (MCS). The PCS and MCS scores are transformed to have a mean of 50 and standard deviation of 10, with higher scores indicating better health. Scale scores range from 0 to 100, with higher scores indicating better health.			
Units: Units on a Scale			
arithmetic mean			
standard deviation	-		

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Participants initially randomized to receive placebo tablets BID in the 24-week placebo-controlled phase.	
Reporting group title	Apremilast 20 mg
Reporting group description:	
Participants initially randomized to 20 mg apremilast tablets BID in the 24-week placebo-controlled phase.	
Reporting group title	Apremilast 30 mg
Reporting group description:	
Participants initially randomized to 30 mg apremilast tablets BID in the 24-week placebo-controlled phase.	
Reporting group title	Apremilast 20 mg
Reporting group description:	
Participants initially randomized to 20 mg apremilast tablets BID in the 24-week placebo-controlled phase continued to receive 20 mg apremilast tablets BID for up to 4.5 years in the long-term extension phase.	
Reporting group title	Apremilast 30 mg
Reporting group description:	
Participants initially randomized to 30 mg apremilast tablets BID in the 24-week placebo-controlled phase, continued to receive 30 mg apremilast tablets BID for up to 4.5 years in the long-term extension phase.	
Reporting group title	Placebo / Apremilast 30 mg Early Escape (EE)
Reporting group description:	
Participants initially randomized to receive placebo tablets BID who did not have at least 20% improvement or ≥ 1 unit improvement from baseline in 2 out of 4 of the Assessment of SpondyloArthritis International Society (ASAS) domains at Week 16 were transitioned to 30 mg apremilast tablets BID and continued to receive 30 mg apremilast tablets BID for up to 4.5 years in the long-term extension phase.	
Reporting group title	Placebo/Apremilast 30 mg Crossover (XO)
Reporting group description:	
Participants initially randomized to placebo tablets BID in the 24-week placebo controlled phase were transitioned to 30 mg apremilast tablets BID at Week 24 and continued to receive 30 mg apremilast tablets BID for up to 4.5 years in the long-term extension phase.	
Reporting group title	Apremilast 30 mg /Apremilast 30 mg EE
Reporting group description:	
Participants initially randomized to 30 mg apremilast tablets BID in the 24-week placebo-controlled phase who did not have at least 20% improvement or a ≥ 1-unit improvement from baseline in 2 of the 4 ASAS domains at Week 16 continued to receive 30 mg apremilast tablets BID for up to 4.5 years in the long-term extension phase.	
Reporting group title	Apremilast 20 mg /Apremilast 30 mg EE
Reporting group description:	
Participants initially randomized to 20 mg apremilast tablets BID who did not have at least 20% improvement or ≥ 1 unit improvement from baseline in 2 out of 4 of the ASAS domains at Week 16 were transitioned to 30 mg apremilast tablets BID and continued to receive 30 mg apremilast tablets BID for up to 4.5 years in the long-term extension phase.	
Reporting group title	Apremilast 30 mg /Apremilast 30 mg Second Escape (SE)
Reporting group description:	
Participants initially randomized to 30 mg apremilast tablets BID who did not have at least 20% improvement or ≥ 1 unit improvement from baseline in 2 out of 4 of the ASAS domains from baseline at Week 24 continued to receive 30 mg apremilast tablets BID (second escape) for up to 4.5 years in the long-term extension phase.	
Reporting group title	Apremilast 20 mg/Apremilast 30 mg SE
Reporting group description:	
Participants initially randomized to 20 mg apremilast tablets BID who did not have at least 20%	

improvement or ≥ 1 unit improvement from baseline in 2 out of 4 of the ASAS domains at Week 24 were transitioned to 30 mg apremilast tablets BID (second escape) and continued to receive 30 mg apremilast tablets BID for up to 4.5 years in the long-term extension phase.

Reporting group title	Apremilast 20 mg

Reporting group description:

Participants initially randomized to 20 mg apremilast tablets BID in the 24-week placebo-controlled phase continued to receive 20 mg apremilast tablets BID for up to 4.5 years in the long-term extension phase.

Reporting group title	Apremilast 30 mg

Reporting group description:

Participants initially randomized to 30 mg apremilast tablets BID in the 24-week placebo-controlled phase, continued to receive 30 mg apremilast tablets BID for up to 4.5 years in the long-term extension phase.

Reporting group title	Placebo / Apremilast 30 mg Early Escape (EE)

Reporting group description:

Participants initially randomized to receive placebo tablets BID who did not have at least 20% improvement or ≥ 1 unit improvement from baseline in 2 out of 4 of the Assessment of SpondyloArthritis International Society (ASAS) domains at Week 16 were transitioned to 30 mg apremilast tablets BID and continued to receive 30 mg apremilast tablets BID for up to 4.5 years in the long-term extension phase.

Reporting group title	Placebo/Apremilast 30 mg Crossover (XO)

Reporting group description:

Participants initially randomized to placebo tablets BID in the 24-week placebo controlled phase were transitioned to 30 mg apremilast tablets BID at Week 24 and continued to receive 30 mg apremilast tablets BID for up to 4.5 years in the long-term extension phase.

Reporting group title	Apremilast 30 mg /Apremilast 30 mg EE

Reporting group description:

Participants initially randomized to 30 mg apremilast tablets BID in the 24-week placebo-controlled phase who did not have at least 20% improvement or a ≥ 1-unit improvement from baseline in 2 of the 4 ASAS domains at Week 16 continued to receive 30 mg apremilast tablets BID for up to 4.5 years in the long-term extension phase.

Reporting group title	Apremilast 20 mg /Apremilast 30 mg EE

Reporting group description:

Participants initially randomized to 20 mg apremilast tablets BID who did not have at least 20% improvement or ≥ 1 unit improvement from baseline in 2 out of 4 of the ASAS domains at Week 16 were transitioned to 30 mg apremilast tablets BID and continued to receive 30 mg apremilast tablets BID for up to 4.5 years in the long-term extension phase.

Reporting group title	Apremilast 30 mg /Apremilast 30 mg Second Escape (SE)

Reporting group description:

Participants initially randomized to 30 mg apremilast tablets BID who did not have at least 20% improvement or ≥ 1 unit improvement from baseline in 2 out of 4 of the ASAS domains from baseline at Week 24 continued to receive 30 mg apremilast tablets BID (second escape) for up to 4.5 years in the long-term extension phase.

Reporting group title	Apremilast 20 mg/Apremilast 30 mg SE

Reporting group description:

Participants initially randomized to 20 mg apremilast tablets BID who did not have at least 20% improvement or ≥ 1 unit improvement from baseline in 2 out of 4 of the ASAS domains at Week 24 were transitioned to 30 mg apremilast tablets BID (second escape) and continued to receive 30 mg apremilast tablets BID for up to 4.5 years in the long-term extension phase.

Subject analysis set title	Placebo/Apremilast 30 mg
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

Participants who initially received placebo tablets BID during the placebo controlled phase were transitioned to 30 mg apremilast tablets BID either at Week 16 or Week 24.

Subject analysis set title	Apremilast 20 mg/ Apremilast 30 mg
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

Participants who were initially randomized to 20 mg apremilast tablets BID at Week 0 and transitioned to 30 mg apremilast tablets BID at either Week 16 or Week 24.

Subject analysis set title	Apremilast 20 mg/Apremilast 20 mg
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

Participants who were initially randomized to receive 20 mg apremilast PO BID at Week 0 and continued to receive 20 mg apremilast PO BID without the transition to 30 mg apremilast PO BID.

Subject analysis set title	Apremilast 20/30 mg
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

Participants who initially received 20 mg apremilast tablets BID at Week 0 who escaped to 30 mg apremilast BID. Only the TEAEs that occurred during the apremilast 30 mg BID dose were included.

Subject analysis set title	Apremilast 20 mg (APR Exposure Period)
Subject analysis set type	Safety analysis

Subject analysis set description:

Participants who received 20 mg apremilast tablets BID only in the study. This also includes participants who initially received APR 20 BID and switched to APR 30 BID treatment. Only the TEAEs that occurred during the 20 mg apremilast BID dose were included.

Subject analysis set title	Apremilast 20 mg/30 mg (APR Exposure Period)
Subject analysis set type	Safety analysis

Subject analysis set description:

Participants who initially received 20 mg apremilast tablets BID at Week 0 who escaped to 30 mg apremilast BID. Only the TEAEs that occurred during the apremilast 30 mg BID dose were included.

Subject analysis set title	Apremilast 30 mg (APR Exposure Period)
Subject analysis set type	Safety analysis

Subject analysis set description:

Participants initially randomized to 30 mg apremilast tablets BID at Week 0 and participants who received placebo at Week 0 who escaped to 30 mg apremilast BID. Only the TEAEs that occurred during the APR 30 BID dose were included.

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

Subject analysis set description:

Participants initially randomized to 20 mg apremilast tablets BID in the 24-week placebo-controlled phase, and continued to receive apremilast 20 mg or 30 mg during weeks 24 to 260. The radiograph subset analysis population included randomized participants who received at least one dose of IP and had at least a baseline radiograph available. Includes apremilast participants as treated who had a baseline and at least one post-baseline score. Missing scores were imputed using the LOCF.

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

Subject analysis set description:

Participants initially randomized at Week 0 to 30 mg apremilast tablets BID in the 24-week placebo-controlled phase and continued to receive apremilast 30 mg during weeks 24 to 260. The radiograph subset analysis population included randomized participants who received at least one dose of IP and had at least a baseline radiograph available. Includes apremilast participants as treated who had a baseline and at least one post-baseline score. Missing scores were imputed using the LOCF.

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

Subject analysis set description:

Participants who initially received placebo tablets BID during the placebo controlled phase were transitioned to 30 mg apremilast tablets BID either at Week 16 or Week 24 through to Week 260. The radiograph subset analysis population included randomized participants who received at least one dose of IP and had at least a baseline radiograph available. Includes apremilast participants as treated who had a baseline and at least one post-baseline score. Missing scores were imputed using the LOCF.

Subject analysis set title	Apremilast 20 mg/ Apremilast 30 mg
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants who were initially randomized to 20 mg apremilast tablets BID at Week 0 and transitioned to 30 mg apremilast tablets BID at either Week 16 or Week 24 through to Week 260. The radiograph subset analysis population included randomized participants who received at least one dose of IP and had at least a baseline radiograph available. Includes apremilast participants as treated who had a

baseline and at least one post-baseline score. Missing scores were imputed using the LOCF.

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

Subject analysis set description:

Participants who were initially randomized to receive 20 mg apremilast PO BID at Week 0 and continued to receive 20 mg apremilast PO BID through to Week 260 without the transition to 30 mg apremilast PO BID. The radiograph subset analysis population included randomized participants who received at least one dose of IP and had at least a baseline radiograph available. Includes apremilast participants as treated who had a baseline and at least one post-baseline score. Missing scores were imputed using the LOCF.

Primary: Percentage of Participants Who Achieved an Assessment of SpondyloArthritis International Society 20 (ASAS 20) at Week 16

End point title	Percentage of Participants Who Achieved an Assessment of SpondyloArthritis International Society 20 (ASAS 20) at Week 16

End point description:

ASAS 20 = achieving an improvement from baseline (BL) of ≥ 20% and ≥ 1 unit in at least 3 of 4 ASAS domains on a scale of 0 to 10 units and no worsening from BL of ≥ 20% and ≥ 1 unit in the remaining ASAS domain on a scale of 0 to 10 units. The 4 ASAS domains:
1. Patient Global Assessment of Disease (0 - 10 unit Numerical Rating Scale [NRS]); subject marks an X on a 0 - 10 unit NRS; the left-hand box of 0 = not active, right-hand box = very active
2. Total Back Pain (0 - 10 unit NRS); subject marks an X on a 0 - 10 unit NRS; the left-hand box of 0 = no pain, right-hand box = most severe pain
3. Function (Bath AS Functional Index [BASFI] NRS 0 - 10 unit); subjects provide a self-administered survey assessing for mobility and functional ability
4. Inflammation domain is determined by the mean of 2 Bath AS Disease Activity Index NRS Questions #5 and #6 for morning stiffness) (0 - 10 unit). The mITT population = subjects who were randomized and received at least one dose of study drug

End point type	Primary

End point timeframe:

Baseline and Week 16

End point values	Placebo	Apremilast 20 mg	Apremilast 30 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	164	163	163	
Units: Percentage of Participants				
number (not applicable)	36.6	35.0	32.5	

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Adjusted difference is the weighted average of the treatment differences across the 4 strata of screening CRP category and baseline BASDAI score category with the Cochran-Mantel-Haenszel weights.

Comparison groups	Placebo v Apremilast 30 mg

Number of subjects included in analysis	327
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4383 [1]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Risk difference (RD)
Point estimate	-4.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-14.3
upper limit	6.2

Notes:

[1] - 2 sided p-value was based on CMH test adjusting for C-reactive protein (CRP) category and baseline BASDAI score category

Statistical analysis title	Statistical Analysis 2
Comparison groups	Placebo v Apremilast 20 mg
Number of subjects included in analysis	327
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	= 0.7427 [3]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Risk difference (RD)
Point estimate	-1.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12
upper limit	8.5

Notes:

[2] - Adjusted difference is the weighted average of the treatment differences across the 4 strata of screening CRP category and baseline BASDAI score category with the Cochran-Mantel-Haenszel weights.
[3] - 2 sided p-value was based on CMH test adjusting for C-reactive protein (CRP) category and baseline BASDAI score category.

Secondary: Change from Baseline in Bath Ankylosing Spondylitis Functional Index (BASFI) at Week 24

End point title	Change from Baseline in Bath Ankylosing Spondylitis Functional Index (BASFI) at Week 24

End point description:

The BASFI is a composite score based on a self-administered survey of 10 questions using a 0 to 10 unit numerical rating scale (NRS) that assesses the degree of mobility and functional ability. The survey consists of 8 questions regarding function in AS and the last 2 reflect the ability to manage everyday life. The patient marks a box with an X on a 0 to 10 unit NRS for 10 questions; the left-hand box of 0 = easy; the right-hand box = impossible. The resulting 0 to 100 score is divided by 10 to give a final 0 to 10 BASFI score. The overall score is the mean of the 10 items and ranges from 0 to 10. A higher score correlates to reduced functional ability. The mITT population = those who were randomized and received at least one dose of study drug. Missing data were imputed as baseline carried forward for subjects who escaped early or discontinued early (prior to Week 24) due to lack of efficacy and LOCF for other early discontinuations.

End point type	Secondary

End point timeframe:

Baseline and Week 24

End point values	Placebo	Apremilast 20 mg	Apremilast 30 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	164	163	163	
Units: Units on a Scale				
least squares mean (standard error)	-0.94 (± 0.136)	-1.11 (± 0.137)	-0.99 (± 0.138)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Apremilast 30 mg
Number of subjects included in analysis	327
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8032 [4]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.41
upper limit	0.32

Notes:

[4] - Based on ANCOVA model for change from baseline with treatment group, CRP and baseline BASDAI score as factors and baseline value as covariate.

Statistical analysis title	Statistical Analysis 2
Comparison groups	Placebo v Apremilast 20 mg
Number of subjects included in analysis	327
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3624 [5]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.53
upper limit	0.19

Notes:

[5] - Based on ANCOVA model for change from baseline with treatment group, CRP and baseline BASDAI score as factors and baseline value as covariate.

Secondary: Change from Baseline in Bath Ankylosing Spondylitis Disease Activity

Index (BASDAI) at Week 24	
End point title	Change from Baseline in Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) at Week 24

End point description:

The BASDAI is a composite score based on a subjects self-administered survey of six questions using a 0 - 10 unit NRS that assesses the subjects' 5major symptoms of AS: 1) fatigue; 2) spinal pain; 3) peripheral joint pain/swelling; 4) areas of localized tenderness; 5a) morning stiffness severity upon wakening; 5b) morning stiffness duration upon wakening. The subject was asked to mark the box with a X on a 0 - 10 unit NRS for each of the 6 questions. To give each of the 5 symptoms equal weighting, the mean of the 2 scores relating to morning stiffness is taken. The resulting 0 - 50 score was divided by 5 to give a final 0 to 10 BASDAI score. A BASDAI score of ≥4 is considered to be indicative of active AS disease. The mITT population = those who were randomized and received at least one dose of study drug. Missing data were imputed as baseline carried forward for subjects who EE or discontinued early (prior to Week 24) due to lack of efficacy and LOCF for other early discontinuations

End point type	Secondary

End point timeframe:

Baseline and Week 24

End point values	Placebo	Apremilast 20 mg	Apremilast 30 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	164	162	160	
Units: Units on a Scale				
least squares mean (standard error)	-1.21 (± 0.136)	-1.30 (± 0.136)	-1.18 (± 0.137)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Apremilast 30 mg
Number of subjects included in analysis	324
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8618 [6]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	0.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.33
upper limit	0.4

Notes:

[6] - Based on an ANCOVA model for change from baseline with treatment group, CRP and baseline BASDAI score as factors and baseline value as covariate.

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

Number of subjects included in analysis	326
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6262 [7]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.45
upper limit	0.27

Notes:

[7] - Based on an ANCOVA model for change from baseline with treatment group, CRP and baseline BASDAI score as factors and baseline value as covariate.

Secondary: Percentage of Participants who Achieved an Assessment of SpondyloArthritis International Society 20 (ASAS) at Week 24

End point title	Percentage of Participants who Achieved an Assessment of SpondyloArthritis International Society 20 (ASAS) at Week 24

End point description:

ASAS 20 = achieving an improvement from baseline (BL) of ≥ 20% and ≥ 1 unit in at least 3 of 4 ASAS domains on a scale of 0 to 10 units and no worsening from BL of ≥ 20% and ≥ 1 unit in the remaining ASAS domain on a scale of 0 to 10 units. The 4 ASAS domains:
1. Patient Global Assessment of Disease (0 - 10 unit Numerical Rating Scale [NRS]); subject marks an X on a 0 - 10 unit NRS; the left-hand box of 0 = not active, right-hand box = very active
2. Total Back Pain (0 to 10 unit NRS); subject marks an X on a 0 - 10 unit NRS; the lefthand box of 0 = no pain, right-hand box = most severe pain
3. Function (Bath AS Functional Index [BASFI] NRS 0 - 10 unit); subjects provides a self-administered survey assessing for mobility and functional ability
4. Inflammation domain is determined by the mean of 2 Bath AS Disease Activity Index NRS Questions #5 and #6 for morning stiffness) (0 - 10 unit). The mITT population = subjects who were randomized and received at least one dose of study dru

End point type	Secondary

End point timeframe:

Baseline and Week 24

End point values	Placebo	Apremilast 20 mg	Apremilast 30 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	164	163	163	
Units: Percentage of Participants				
number (not applicable)	31.7	36.2	33.7	

Statistical analyses

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

Number of subjects included in analysis	327
Analysis specification	Pre-specified
Analysis type	superiority[8]
P-value	= 0.6958 [9]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Risk difference (RD)
Point estimate	2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.1
upper limit	12.2

Notes:

[8] - Adjusted difference is the weighted average of the treatment differences across the 4 strata of screening CRP category and baseline BASDAI score category with the Cochran-Mantel-Haenszel (CMH) weights

[9] - 2 sided p-value was based on CMH test adjusting for C-reactive protein (CRP) category and baseline BASDAI score category

Statistical analysis title	Statistical Analysis 2
Comparison groups	Placebo v Apremilast 20 mg
Number of subjects included in analysis	327
Analysis specification	Pre-specified
Analysis type	superiority[10]
P-value	= 0.4051 [11]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Risk difference (RD)
Point estimate	4.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.8
upper limit	14.5

Notes:

[10] - Adjusted difference is the weighted average of the treatment differences across the 4 strata of screening CRP category and baseline BASDAI score category with the Cochran-Mantel-Haenszel (CMH) weights

[11] - 2 sided p-value was based on CMH test adjusting for C-reactive protein category and baseline BASDAI score category.

Secondary: Change from Baseline in the Ankylosing Spondylitis Quality of Life (ASQoL) Summary Score at Week 24

End point title	Change from Baseline in the Ankylosing Spondylitis Quality of Life (ASQoL) Summary Score at Week 24

End point description:

The ASQoL is a validated disease specific patient reported outcomes instrument to assess the impact of ankylosing spondylitis on the quality of life of individuals with emphasis on the ability of the person to fulfill his or her needs. It consisted of 18 items requesting a yes (score=1) or no (score=0) response to questions related to the impact of pain on sleep, mood, motivation, ability to cope, activities of daily living, independence, relationships, and social life. The summary score ranges 0–18 with higher scores indicating worse quality of life. The mITT population included those who were randomized and received at least one dose of study drug. Missing data were imputed as baseline carried forward for participants who escaped early or discontinued early (prior to Week 24) due to lack of efficacy and LOCF for other early discontinuations.

End point type	Secondary

End point timeframe:
Baseline and Week 24

End point values	Placebo	Apremilast 20 mg	Apremilast 30 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	160	161	156	
Units: Units on a Scale				
least squares mean (standard error)	-1.77 (± 0.278)	-1.50 (± 0.278)	-1.52 (± 0.281)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Apremilast 30 mg
Number of subjects included in analysis	316
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5126 [12]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	0.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.49
upper limit	0.99

Notes:

[12] - Based on an ANCOVA model for change from baseline with treatment group, CRP and baseline BASDAI score as factors and baseline value as covariate.

Statistical analysis title	Statistical Analysis 2
Comparison groups	Placebo v Apremilast 20 mg
Number of subjects included in analysis	321
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4624 [13]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	0.28
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.46
upper limit	1.01

Notes:

[13] - Based on an ANCOVA model for change from baseline with treatment group, CRP and baseline BASDAI score as factors and baseline value as covariate.

Secondary: Change from Baseline in the Physical Component Summary Score (PCS) of Medical Outcome Study Short Form 36-Item Health Survey, Version 2 (SF-36) at Week 24

End point title	Change from Baseline in the Physical Component Summary Score (PCS) of Medical Outcome Study Short Form 36-Item Health Survey, Version 2 (SF-36) at Week 24

End point description:

The Medical Outcome Study Short Form 36-Item Health Survey, Version 2 (SF-36) was 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 (based on US general population with mean of 50 and standard deviation of 10) were used in analyses. Higher scores indicate a higher level of functioning. The PCS encompasses physical functioning, role-physical, and bodily pain, as well as general health and vitality. A positive change from baseline score indicates an improvement.The mITT included those who were randomized and received at least one dose of IP. Missing data were imputed as baseline carried forward for participants who escaped early or discontinued early (prior to Week 24) due to lack of efficacy and LOCF for other early discontinuations.

End point type	Secondary

End point timeframe:

Baseline and Week 24

End point values	Placebo	Apremilast 20 mg	Apremilast 30 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	160	161	155	
Units: Units on a Scale				
least squares mean (standard error)	3.50 (± 0.553)	3.46 (± 0.551)	3.79 (± 0.559)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Apremilast 30 mg
Number of subjects included in analysis	315
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6997 [14]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	0.29
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.18
upper limit	1.76

Notes:

[14] - Based on an ANCOVA model for change from baseline with treatment group, CRP and baseline BASDAI score as factors and baseline value as covariate.

Statistical analysis title	Statistical Analysis 2
Comparison groups	Placebo v Apremilast 20 mg
Number of subjects included in analysis	321
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9587 [15]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.5
upper limit	1.42

Notes:

[15] - Based on an ANCOVA model for change from baseline with treatment group, CRP and baseline BASDAI score as factors and baseline value as covariate.

Secondary: Change from Baseline in Bath Ankylosing Spondylitis Metrology Index-Linear (BASMI-Linear) at Week 24

End point title	Change from Baseline in Bath Ankylosing Spondylitis Metrology Index-Linear (BASMI-Linear) at Week 24

End point description:

The BASMI-Linear was designed to assess axial status (ie, cervical, dorsal and lumbar spine, hips, and pelvic soft tissue) and to define clinically significant changes in spinal movement. Five dimensions of movement (lateral lumbar flexion, tragus to wall, forward lumbar flexion, maximal intermalleolar distance, and cervical rotation) were measured and normalized on 0 to 10 unit NRS. The average of these scores was the total BASMI score, ranging from 0-10 with higher values indicating more severe limitation in spinal mobility. The mITT population included those who were randomized and received at least one dose of study drug. Missing data were imputed as baseline carried forward for participants who escaped early or discontinued early (prior to Week 24) due to lack of efficacy and LOCF for other early discontinuations.

End point type	Secondary

End point timeframe:

Baseline and Week 24

End point values	Placebo	Apremilast 20 mg	Apremilast 30 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	163	162	158	
Units: Units on a Scale				
least squares mean (standard error)	-0.19 (± 0.042)	-0.16 (± 0.043)	-0.13 (± 0.043)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Apremilast 30 mg
Number of subjects included in analysis	321
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3307 [16]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	0.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.06
upper limit	0.17

Notes:

[16] - Based on an ANCOVA model for change from baseline with treatment group, CRP and baseline BASDAI score as factors and baseline value as covariate.

Statistical analysis title	Statistical Analysis 2
Comparison groups	Placebo v Apremilast 20 mg
Number of subjects included in analysis	325
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5938 [17]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	0.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.08
upper limit	0.14

Notes:

[17] - Based on an ANCOVA model for change from baseline with treatment group, CRP and baseline BASDAI score as factors and baseline value as covariate.

Secondary: Change from Baseline in the Radiographic Score Using the Modified Stoke Ankylosing Spondylitis Spine Score (m-SASSS) at Week 104 and Week 260

End point title	Change from Baseline in the Radiographic Score Using the Modified Stoke Ankylosing Spondylitis Spine Score (m-SASSS) at Week 104 and Week 260

End point description:

The Modified Stoke Ankylosing Spondylitis Spine Score is a scoring method used to determine the amount or degree of ankylosing spondylitis disease that is in the spine based on x-ray radiographs of the spine. The m-SASSS scores 0-3.
0 = No abnormality, 1 = Erosion, Sclerosis or Squaring, 2 = Syndesmophyte, 3 = Total bony Bridging at each Site. An increase in the m-SASSS indicated a worsening of AS disease.

End point type	Secondary

End point timeframe:

Baseline to Week 104 and Week 260

End point values	Apremilast 20 mg	Apremilast 30 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	81[18]	81[19]	74[20]	35[21]
Units: Units on a Scale				
arithmetic mean (standard deviation)				
Week 104	0.99 (± 3.018)	0.65 (± 2.453)	0.98 (± 3.768)	0.82 (± 2.435)
Week 260	3.14 (± 8.292)	1.76 (± 6.997)	1.92 (± 7.363)	2.21 (± 5.959)

Notes:

[18] - N = 81, 83

[19] - N = 81, 84

[20] - N = 74, 79

[21] - N = 35, 35

End point values	Apremilast 20 mg/Apremilast 20 mg			
Subject group type	Subject analysis set			
Number of subjects analysed	46[22]			
Units: Units on a Scale				
arithmetic mean (standard deviation)				
Week 104	1.12 (± 3.417)			
Week 260	3.83 (± 9.652)			

Notes:

[22] - N = 46, 48

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Treatment Emergent Adverse Events (TEAEs) during the Placebo Controlled Phase

End point title	Number of Participants with Treatment Emergent Adverse Events (TEAEs) during the Placebo Controlled Phase

End point description:

A TEAE was an adverse event (AE) with a start date on or after the date of the first dose of investigational product and no later than 28 days after the last dose of IP for subjects who discontinued early. A serious AE = 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; constitutes an important medical event. The severity of AEs was assessed based on the following scale: Mild = asymptomatic or mild symptoms, clinical or diagnostic observations only; Moderate = symptoms cause moderate discomfort; Severe = symptoms causing severe pain discomfort. Safety population included all subjects who were randomized and received at least one dose of IP. Includes data through Week 16 for placebo-treated and apremilast 20 mg BID treated subjects who EE and data up to Week 24 for all other subjects.

End point type	Secondary

End point timeframe:

From Week 0 to Week 24; the median duration of exposure was 23.57 weeks for the placebo arm, 23.71 weeks for the apremilast 20 mg arm and 24.00 weeks for the apremilast 30 mg arm.

End point values	Placebo	Apremilast 20 mg	Apremilast 30 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	164	163	163	
Units: participants				
Any Treatment Emergent Adverse Event	83	91	88	
Any Drug-related TEAE	24	44	51	
Any Severe TEAE	0	2	5	
Any Serious TEAE	1	3	6	
Any Serious Drug-related TEAE	0	0	3	
Any TEAE Leading to Drug Interruption	14	13	14	
Any TEAE Leading to Drug Withdrawal	7	11	13	
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

End point description:

A TEAE was an adverse event (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 of IP for subjects who discontinued early. A serious AE = 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; constitutes an important medical event. The severity of AEs was assessed based on the following scale: Mild = asymptomatic or mild symptoms, clinical or diagnostic observations only; Moderate = symptoms cause moderate discomfort; Severe = symptoms causing severe pain discomfort.Apremilast Subjects as Treated were those who 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 actually received, irrespective of the treatment group to which they were randomized or re-randomized.

End point type	Secondary

End point timeframe:

Week 0 to week 260; the median duration of treatment was 24, 163, and 216 weeks in the Apremilast 20 mg, Apremilast 20/30 mg and Apremilast 30 mg treatment groups respectively.

End point values	Apremilast 20 mg (APR Exposure Period)	Apremilast 20 mg/30 mg (APR Exposure Period)	Apremilast 30 mg (APR Exposure Period)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	163	72	305	
Units: Participants				
Any Treatment Emergent Adverse Event	114	47	239	

Any Severe TEAE	5	8	23	
Any Serious TEAE	12	8	41	
Any TEAE Leading to Drug Interruption	22	11	51	
Any TEAE Leading to Drug Withdrawal	18	4	34	
Any TEAE Leading to Death	0	1	1	

Statistical analyses

No statistical analyses for this end point

Adverse events information

Timeframe for reporting adverse events:

AEs were reported for the placebo-controlled phase from Week 0 to Week 16 for placebo participants who entered EE at Week 16 and up to Week 24 for all other participants.

Adverse event reporting additional description:

AEs were reported for the apremilast (APR) exposure period from Week 0 to Week 260, irrespective of when the APR started (Week 0, 16 or 24). The median duration of treatment was 24, 163, and 216 weeks in the Apremilast 20 mg, Apremilast 20/30 mg and Apremilast 30 mg treatment groups respectively.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	14.0

Reporting groups

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

Reporting group description:

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

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

Reporting group description:

Participants initially randomized to 20 mg apremilast tablets (APR) BID in the 24-week placebo-controlled phase.

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

Reporting group description:

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

Reporting group title	Apremilast 20 mg BID (APR Exposure Period)

Reporting group description:

Participants who initially received 20 mg apremilast tablets BID at Week 0 who escaped to 30 mg apremilast BID. Only the TEAEs that occurred during the 20 mg apremilast BID dose were included.

Reporting group title	Apremilast 20/30 mg BID (APR Exposure Period)

Reporting group description:

Participants who initially received 20 mg apremilast tablets BID at Week 0 who escaped to 30 mg apremilast BID. Only the TEAEs that occurred during the 20 mg apremilast BID dose were included.

Reporting group title	Apremilast 30 mg BID (APR Exposure Period)

Reporting group description:

Participants initially randomized to 30 mg apremilast tablets BID at Week 0 and participants who received placebo at Week 0 who escaped to 30 mg apremilast tablets BID. Only the TEAEs that occurred during the 30 mg apremilast BID dose were included.

Serious adverse events	Placebo (Weeks 0-24) Placebo-Controlled Phase	Apremilast 20 mg BID (Weeks 0-24) Placebo-Controlled Phase	Apremilast 30 mg BID (Weeks 0-24) Placebo-Controlled Phase
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 164 (0.61%)	3 / 163 (1.84%)	6 / 163 (3.68%)
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 / 164 (0.00%)	0 / 163 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast cancer in situ			
subjects affected / exposed	0 / 164 (0.00%)	0 / 163 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant melanoma			
subjects affected / exposed	1 / 164 (0.61%)	0 / 163 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostate cancer			
subjects affected / exposed	0 / 164 (0.00%)	0 / 163 (0.00%)	0 / 163 (0.00%)
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 cancer			
subjects affected / exposed	0 / 164 (0.00%)	0 / 163 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine leiomyoma			
subjects affected / exposed	0 / 164 (0.00%)	0 / 163 (0.00%)	0 / 163 (0.00%)
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			
Chest pain			
subjects affected / exposed	0 / 164 (0.00%)	0 / 163 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device failure			

subjects affected / exposed	0 / 164 (0.00%)	0 / 163 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	0 / 164 (0.00%)	0 / 163 (0.00%)	0 / 163 (0.00%)
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			
Lung disorder			
subjects affected / exposed	0 / 164 (0.00%)	0 / 163 (0.00%)	0 / 163 (0.00%)
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 infiltration			
subjects affected / exposed	0 / 164 (0.00%)	0 / 163 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nasal septum deviation			
subjects affected / exposed	0 / 164 (0.00%)	0 / 163 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nasal turbinate hypertrophy			
subjects affected / exposed	0 / 164 (0.00%)	0 / 163 (0.00%)	0 / 163 (0.00%)
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 / 164 (0.00%)	0 / 163 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	0 / 164 (0.00%)	0 / 163 (0.00%)	0 / 163 (0.00%)
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			

Depression			
subjects affected / exposed	0 / 164 (0.00%)	0 / 163 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Major depression			
subjects affected / exposed	0 / 164 (0.00%)	0 / 163 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicide attempt			
subjects affected / exposed	0 / 164 (0.00%)	0 / 163 (0.00%)	0 / 163 (0.00%)
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			
Cardiac function disturbance postoperative			
subjects affected / exposed	0 / 164 (0.00%)	0 / 163 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Foot fracture			
subjects affected / exposed	0 / 164 (0.00%)	0 / 163 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Humerus fracture			
subjects affected / exposed	0 / 164 (0.00%)	0 / 163 (0.00%)	0 / 163 (0.00%)
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 limb fracture			
subjects affected / exposed	0 / 164 (0.00%)	0 / 163 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax traumatic			
subjects affected / exposed	0 / 164 (0.00%)	0 / 163 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Tibia fracture			
subjects affected / exposed	0 / 164 (0.00%)	0 / 163 (0.00%)	0 / 163 (0.00%)
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 / 164 (0.00%)	0 / 163 (0.00%)	0 / 163 (0.00%)
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 / 164 (0.00%)	0 / 163 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial tachycardia			
subjects affected / exposed	0 / 164 (0.00%)	0 / 163 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardio-respiratory arrest			
subjects affected / exposed	0 / 164 (0.00%)	0 / 163 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiomyopathy			
subjects affected / exposed	0 / 164 (0.00%)	0 / 163 (0.00%)	0 / 163 (0.00%)
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 / 164 (0.00%)	0 / 163 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sick sinus syndrome			
subjects affected / exposed	0 / 164 (0.00%)	0 / 163 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			

Ischaemic stroke			
subjects affected / exposed	0 / 164 (0.00%)	0 / 163 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Presyncope			
subjects affected / exposed	0 / 164 (0.00%)	0 / 163 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombotic cerebral infarction			
subjects affected / exposed	0 / 164 (0.00%)	0 / 163 (0.00%)	0 / 163 (0.00%)
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 / 164 (0.00%)	0 / 163 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
VIIth nerve paralysis			
subjects affected / exposed	0 / 164 (0.00%)	0 / 163 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vertebrobasilar insufficiency			
subjects affected / exposed	0 / 164 (0.00%)	0 / 163 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 164 (0.00%)	0 / 163 (0.00%)	0 / 163 (0.00%)
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 / 164 (0.00%)	0 / 163 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Eye disorders			
Iridocyclitis			
subjects affected / exposed	0 / 164 (0.00%)	0 / 163 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retinal vein occlusion			
subjects affected / exposed	0 / 164 (0.00%)	0 / 163 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Strabismus			
subjects affected / exposed	0 / 164 (0.00%)	0 / 163 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uveitis			
subjects affected / exposed	0 / 164 (0.00%)	1 / 163 (0.61%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal hernia			
subjects affected / exposed	0 / 164 (0.00%)	0 / 163 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain			
subjects affected / exposed	0 / 164 (0.00%)	0 / 163 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain upper			
subjects affected / exposed	0 / 164 (0.00%)	0 / 163 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anal fissure			
subjects affected / exposed	0 / 164 (0.00%)	0 / 163 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Diverticulum intestinal			
subjects affected / exposed	0 / 164 (0.00%)	0 / 163 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Duodenogastric reflux			
subjects affected / exposed	0 / 164 (0.00%)	0 / 163 (0.00%)	0 / 163 (0.00%)
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 / 164 (0.00%)	0 / 163 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Jejunal perforation			
subjects affected / exposed	0 / 164 (0.00%)	0 / 163 (0.00%)	0 / 163 (0.00%)
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			
subjects affected / exposed	0 / 164 (0.00%)	0 / 163 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			
subjects affected / exposed	0 / 164 (0.00%)	0 / 163 (0.00%)	0 / 163 (0.00%)
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 / 164 (0.00%)	0 / 163 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 164 (0.00%)	0 / 163 (0.00%)	0 / 163 (0.00%)
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			

Alcoholic liver disease			
subjects affected / exposed	0 / 164 (0.00%)	1 / 163 (0.61%)	0 / 163 (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
Cholelithiasis			
subjects affected / exposed	0 / 164 (0.00%)	0 / 163 (0.00%)	0 / 163 (0.00%)
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 polyp			
subjects affected / exposed	0 / 164 (0.00%)	0 / 163 (0.00%)	0 / 163 (0.00%)
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 / 164 (0.00%)	0 / 163 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Calculus urinary			
subjects affected / exposed	0 / 164 (0.00%)	1 / 163 (0.61%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal colic			
subjects affected / exposed	0 / 164 (0.00%)	1 / 163 (0.61%)	0 / 163 (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
Endocrine disorders			
Goitre			
subjects affected / exposed	0 / 164 (0.00%)	0 / 163 (0.00%)	0 / 163 (0.00%)
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			
Ankylosing spondylitis			

subjects affected / exposed	0 / 164 (0.00%)	0 / 163 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cervical spinal stenosis			
subjects affected / exposed	0 / 164 (0.00%)	0 / 163 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral disc protrusion			
subjects affected / exposed	0 / 164 (0.00%)	0 / 163 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Muscular weakness			
subjects affected / exposed	0 / 164 (0.00%)	0 / 163 (0.00%)	0 / 163 (0.00%)
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 chest pain			
subjects affected / exposed	0 / 164 (0.00%)	0 / 163 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoarthritis			
subjects affected / exposed	0 / 164 (0.00%)	0 / 163 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 164 (0.00%)	0 / 163 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	0 / 164 (0.00%)	0 / 163 (0.00%)	0 / 163 (0.00%)
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 sinusitis			

subjects affected / exposed	0 / 164 (0.00%)	0 / 163 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infected bites			
subjects affected / exposed	0 / 164 (0.00%)	0 / 163 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritonsillar abscess			
subjects affected / exposed	0 / 164 (0.00%)	0 / 163 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Apremilast 20 mg BID (APR Exposure Period)	Apremilast 20/30 mg BID (APR Exposure Period)	Apremilast 30 mg BID (APR Exposure Period)
Total subjects affected by serious adverse events			
subjects affected / exposed	12 / 163 (7.36%)	8 / 72 (11.11%)	41 / 305 (13.44%)
number of deaths (all causes)	0	1	1
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	1 / 163 (0.61%)	0 / 72 (0.00%)	1 / 305 (0.33%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast cancer in situ			
subjects affected / exposed	1 / 163 (0.61%)	0 / 72 (0.00%)	0 / 305 (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
Malignant melanoma			
subjects affected / exposed	0 / 163 (0.00%)	0 / 72 (0.00%)	0 / 305 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostate cancer			

subjects affected / exposed	0 / 163 (0.00%)	0 / 72 (0.00%)	1 / 305 (0.33%)
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 cancer			
subjects affected / exposed	1 / 163 (0.61%)	0 / 72 (0.00%)	1 / 305 (0.33%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine leiomyoma			
subjects affected / exposed	1 / 163 (0.61%)	0 / 72 (0.00%)	1 / 305 (0.33%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 163 (0.00%)	0 / 72 (0.00%)	1 / 305 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device failure			
subjects affected / exposed	0 / 163 (0.00%)	1 / 72 (1.39%)	0 / 305 (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
Pyrexia			
subjects affected / exposed	0 / 163 (0.00%)	0 / 72 (0.00%)	1 / 305 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Lung disorder			
subjects affected / exposed	1 / 163 (0.61%)	0 / 72 (0.00%)	0 / 305 (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
Lung infiltration			
subjects affected / exposed	0 / 163 (0.00%)	1 / 72 (1.39%)	0 / 305 (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

Nasal septum deviation			
subjects affected / exposed	0 / 163 (0.00%)	0 / 72 (0.00%)	1 / 305 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nasal turbinate hypertrophy			
subjects affected / exposed	0 / 163 (0.00%)	0 / 72 (0.00%)	1 / 305 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	0 / 163 (0.00%)	1 / 72 (1.39%)	0 / 305 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	0 / 163 (0.00%)	0 / 72 (0.00%)	1 / 305 (0.33%)
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			
Depression			
subjects affected / exposed	0 / 163 (0.00%)	0 / 72 (0.00%)	1 / 305 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Major depression			
subjects affected / exposed	1 / 163 (0.61%)	0 / 72 (0.00%)	0 / 305 (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
Suicide attempt			
subjects affected / exposed	1 / 163 (0.61%)	0 / 72 (0.00%)	1 / 305 (0.33%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Cardiac function disturbance postoperative			

subjects affected / exposed	0 / 163 (0.00%)	0 / 72 (0.00%)	1 / 305 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Foot fracture			
subjects affected / exposed	0 / 163 (0.00%)	0 / 72 (0.00%)	1 / 305 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Humerus fracture			
subjects affected / exposed	1 / 163 (0.61%)	0 / 72 (0.00%)	0 / 305 (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 limb fracture			
subjects affected / exposed	0 / 163 (0.00%)	1 / 72 (1.39%)	0 / 305 (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
Pneumothorax traumatic			
subjects affected / exposed	0 / 163 (0.00%)	0 / 72 (0.00%)	1 / 305 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tibia fracture			
subjects affected / exposed	0 / 163 (0.00%)	1 / 72 (1.39%)	0 / 305 (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
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 163 (0.00%)	1 / 72 (1.39%)	1 / 305 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	1 / 163 (0.61%)	1 / 72 (1.39%)	1 / 305 (0.33%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial tachycardia			

subjects affected / exposed	0 / 163 (0.00%)	0 / 72 (0.00%)	1 / 305 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardio-respiratory arrest			
subjects affected / exposed	0 / 163 (0.00%)	0 / 72 (0.00%)	1 / 305 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Cardiomyopathy			
subjects affected / exposed	0 / 163 (0.00%)	0 / 72 (0.00%)	1 / 305 (0.33%)
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	0 / 163 (0.00%)	0 / 72 (0.00%)	1 / 305 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sick sinus syndrome			
subjects affected / exposed	0 / 163 (0.00%)	0 / 72 (0.00%)	1 / 305 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Ischaemic stroke			
subjects affected / exposed	0 / 163 (0.00%)	1 / 72 (1.39%)	0 / 305 (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
Presyncope			
subjects affected / exposed	1 / 163 (0.61%)	0 / 72 (0.00%)	0 / 305 (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
Thrombotic cerebral infarction			
subjects affected / exposed	0 / 163 (0.00%)	1 / 72 (1.39%)	0 / 305 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Transient ischaemic attack			

subjects affected / exposed	0 / 163 (0.00%)	0 / 72 (0.00%)	1 / 305 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
VIIth nerve paralysis			
subjects affected / exposed	0 / 163 (0.00%)	0 / 72 (0.00%)	1 / 305 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vertebrobasilar insufficiency			
subjects affected / exposed	0 / 163 (0.00%)	0 / 72 (0.00%)	1 / 305 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 163 (0.61%)	0 / 72 (0.00%)	0 / 305 (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
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 163 (0.00%)	1 / 72 (1.39%)	1 / 305 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Iridocyclitis			
subjects affected / exposed	0 / 163 (0.00%)	1 / 72 (1.39%)	1 / 305 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retinal vein occlusion			
subjects affected / exposed	0 / 163 (0.00%)	0 / 72 (0.00%)	1 / 305 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Strabismus			
subjects affected / exposed	1 / 163 (0.61%)	0 / 72 (0.00%)	0 / 305 (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

Uveitis			
subjects affected / exposed	1 / 163 (0.61%)	0 / 72 (0.00%)	2 / 305 (0.66%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal hernia			
subjects affected / exposed	0 / 163 (0.00%)	0 / 72 (0.00%)	1 / 305 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain			
subjects affected / exposed	0 / 163 (0.00%)	0 / 72 (0.00%)	1 / 305 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain upper			
subjects affected / exposed	0 / 163 (0.00%)	0 / 72 (0.00%)	1 / 305 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anal fissure			
subjects affected / exposed	0 / 163 (0.00%)	0 / 72 (0.00%)	1 / 305 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulum intestinal			
subjects affected / exposed	0 / 163 (0.00%)	0 / 72 (0.00%)	1 / 305 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Duodenogastric reflux			
subjects affected / exposed	0 / 163 (0.00%)	0 / 72 (0.00%)	1 / 305 (0.33%)
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 / 163 (0.61%)	0 / 72 (0.00%)	0 / 305 (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
Jejunal perforation			

subjects affected / exposed	0 / 163 (0.00%)	0 / 72 (0.00%)	1 / 305 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			
subjects affected / exposed	0 / 163 (0.00%)	0 / 72 (0.00%)	1 / 305 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			
subjects affected / exposed	0 / 163 (0.00%)	0 / 72 (0.00%)	1 / 305 (0.33%)
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 / 163 (0.00%)	0 / 72 (0.00%)	1 / 305 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 163 (0.00%)	1 / 72 (1.39%)	0 / 305 (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
Hepatobiliary disorders			
Alcoholic liver disease			
subjects affected / exposed	1 / 163 (0.61%)	0 / 72 (0.00%)	0 / 305 (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
Cholelithiasis			
subjects affected / exposed	0 / 163 (0.00%)	1 / 72 (1.39%)	0 / 305 (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
Gallbladder polyp			
subjects affected / exposed	0 / 163 (0.00%)	0 / 72 (0.00%)	1 / 305 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			

Calculus ureteric			
subjects affected / exposed	0 / 163 (0.00%)	0 / 72 (0.00%)	2 / 305 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Calculus urinary			
subjects affected / exposed	1 / 163 (0.61%)	0 / 72 (0.00%)	0 / 305 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal colic			
subjects affected / exposed	1 / 163 (0.61%)	0 / 72 (0.00%)	0 / 305 (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
Endocrine disorders			
Goitre			
subjects affected / exposed	0 / 163 (0.00%)	0 / 72 (0.00%)	1 / 305 (0.33%)
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			
Ankylosing spondylitis			
subjects affected / exposed	0 / 163 (0.00%)	0 / 72 (0.00%)	1 / 305 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cervical spinal stenosis			
subjects affected / exposed	0 / 163 (0.00%)	0 / 72 (0.00%)	1 / 305 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral disc protrusion			
subjects affected / exposed	0 / 163 (0.00%)	0 / 72 (0.00%)	1 / 305 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Muscular weakness			
subjects affected / exposed	0 / 163 (0.00%)	0 / 72 (0.00%)	1 / 305 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Musculoskeletal chest pain			
subjects affected / exposed	0 / 163 (0.00%)	0 / 72 (0.00%)	1 / 305 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoarthritis			
subjects affected / exposed	1 / 163 (0.61%)	1 / 72 (1.39%)	1 / 305 (0.33%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 163 (0.00%)	0 / 72 (0.00%)	1 / 305 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	0 / 163 (0.00%)	0 / 72 (0.00%)	1 / 305 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic sinusitis			
subjects affected / exposed	0 / 163 (0.00%)	0 / 72 (0.00%)	1 / 305 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infected bites			
subjects affected / exposed	0 / 163 (0.00%)	0 / 72 (0.00%)	1 / 305 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritonsillar abscess			
subjects affected / exposed	0 / 163 (0.00%)	0 / 72 (0.00%)	1 / 305 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Placebo (Weeks 0-24) Placebo-Controlled Phase	Apremilast 20 mg BID (Weeks 0-24) Placebo-Controlled Phase	Apremilast 30 mg BID (Weeks 0-24) Placebo-Controlled Phase
Total subjects affected by non-serious adverse events			
subjects affected / exposed	37 / 164 (22.56%)	58 / 163 (35.58%)	57 / 163 (34.97%)
Vascular disorders			
Hypertension			
subjects affected / exposed	4 / 164 (2.44%)	4 / 163 (2.45%)	6 / 163 (3.68%)
occurrences (all)	4	5	6
Nervous system disorders			
Headache			
subjects affected / exposed	8 / 164 (4.88%)	9 / 163 (5.52%)	16 / 163 (9.82%)
occurrences (all)	9	13	22
Eye disorders			
Iridocyclitis			
subjects affected / exposed	0 / 164 (0.00%)	1 / 163 (0.61%)	1 / 163 (0.61%)
occurrences (all)	0	1	1
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	4 / 164 (2.44%)	3 / 163 (1.84%)	9 / 163 (5.52%)
occurrences (all)	4	3	12
Diarrhoea			
subjects affected / exposed	7 / 164 (4.27%)	22 / 163 (13.50%)	17 / 163 (10.43%)
occurrences (all)	8	51	29
Frequent bowel movements			
subjects affected / exposed	2 / 164 (1.22%)	2 / 163 (1.23%)	3 / 163 (1.84%)
occurrences (all)	2	2	5
Nausea			
subjects affected / exposed	7 / 164 (4.27%)	10 / 163 (6.13%)	14 / 163 (8.59%)
occurrences (all)	8	17	16
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 164 (0.00%)	2 / 163 (1.23%)	1 / 163 (0.61%)
occurrences (all)	0	2	1
Muscle spasms			
subjects affected / exposed	1 / 164 (0.61%)	4 / 163 (2.45%)	0 / 163 (0.00%)
occurrences (all)	1	6	0
Musculoskeletal pain			

subjects affected / exposed	0 / 164 (0.00%)	0 / 163 (0.00%)	1 / 163 (0.61%)
occurrences (all)	0	0	1
Osteoarthritis			
subjects affected / exposed	0 / 164 (0.00%)	1 / 163 (0.61%)	0 / 163 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 164 (0.61%)	4 / 163 (2.45%)	2 / 163 (1.23%)
occurrences (all)	1	5	2
Nasopharyngitis			
subjects affected / exposed	6 / 164 (3.66%)	9 / 163 (5.52%)	7 / 163 (4.29%)
occurrences (all)	6	10	8
Sinusitis			
subjects affected / exposed	1 / 164 (0.61%)	2 / 163 (1.23%)	1 / 163 (0.61%)
occurrences (all)	1	2	1
Upper respiratory tract infection			
subjects affected / exposed	8 / 164 (4.88%)	7 / 163 (4.29%)	8 / 163 (4.91%)
occurrences (all)	9	7	13

Non-serious adverse events	Apremilast 20 mg BID (APR Exposure Period)	Apremilast 20/30 mg BID (APR Exposure Period)	Apremilast 30 mg BID (APR Exposure Period)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	82 / 163 (50.31%)	38 / 72 (52.78%)	168 / 305 (55.08%)
Vascular disorders			
Hypertension			
subjects affected / exposed	6 / 163 (3.68%)	2 / 72 (2.78%)	21 / 305 (6.89%)
occurrences (all)	8	2	23
Nervous system disorders			
Headache			
subjects affected / exposed	11 / 163 (6.75%)	5 / 72 (6.94%)	28 / 305 (9.18%)
occurrences (all)	18	5	58
Eye disorders			
Iridocyclitis			
subjects affected / exposed	2 / 163 (1.23%)	4 / 72 (5.56%)	8 / 305 (2.62%)
occurrences (all)	5	6	10
Gastrointestinal disorders			
Abdominal pain upper			

subjects affected / exposed	7 / 163 (4.29%)	1 / 72 (1.39%)	16 / 305 (5.25%)
occurrences (all)	7	1	20
Diarrhoea			
subjects affected / exposed	26 / 163 (15.95%)	4 / 72 (5.56%)	38 / 305 (12.46%)
occurrences (all)	59	4	68
Frequent bowel movements			
subjects affected / exposed	3 / 163 (1.84%)	4 / 72 (5.56%)	3 / 305 (0.98%)
occurrences (all)	5	4	5
Nausea			
subjects affected / exposed	13 / 163 (7.98%)	6 / 72 (8.33%)	28 / 305 (9.18%)
occurrences (all)	20	10	44
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	6 / 163 (3.68%)	4 / 72 (5.56%)	12 / 305 (3.93%)
occurrences (all)	7	6	17
Muscle spasms			
subjects affected / exposed	5 / 163 (3.07%)	4 / 72 (5.56%)	4 / 305 (1.31%)
occurrences (all)	7	7	5
Musculoskeletal pain			
subjects affected / exposed	2 / 163 (1.23%)	4 / 72 (5.56%)	3 / 305 (0.98%)
occurrences (all)	2	4	3
Osteoarthritis			
subjects affected / exposed	2 / 163 (1.23%)	4 / 72 (5.56%)	5 / 305 (1.64%)
occurrences (all)	3	5	7
Infections and infestations			
Bronchitis			
subjects affected / exposed	8 / 163 (4.91%)	6 / 72 (8.33%)	10 / 305 (3.28%)
occurrences (all)	14	9	12
Nasopharyngitis			
subjects affected / exposed	25 / 163 (15.34%)	10 / 72 (13.89%)	55 / 305 (18.03%)
occurrences (all)	35	13	100
Sinusitis			
subjects affected / exposed	7 / 163 (4.29%)	5 / 72 (6.94%)	10 / 305 (3.28%)
occurrences (all)	10	8	12
Upper respiratory tract infection			

subjects affected / exposed occurrences (all)	17 / 163 (10.43%) 33	8 / 72 (11.11%) 11	32 / 305 (10.49%) 57

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 August 2012	Removed 3 subject questionnaires from the study: - Bath Ankylosing Spondylitis Global Score - Functional Assessment of Chronic Illness Therapy – Fatigue, version 4 - Medical Outcomes Study Sleep Scale • Decreased the frequency of certain subject questionnaires and clinical assessments after Year 1 • Moved certain subject questionnaires to visits where there were fewer questionnaires taken • Changed the joint count evaluation from 44 tender/40 swollen to 44 tender/44 swollen • Added the following sections: Study Drug Discontinuation, Early Termination Visit, Observational Follow-up Visit, Lost to Follow up, and Study Completion • Changed the assessments in the Clinical Benefit Evaluation • Changed the sequencing for section numbers and appendix letters due to deletions/additions of the certain sections in the protocol

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported