Clinical trial results:
A Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel Group Study Followed by an Active Treatment Phase to Evaluate the Efficacy and Safety of Apremilast (CC-10004) in the Treatment of Subjects With Active Behçet's Disease

Summary

EudraCT number	2014-002108-25
Trial protocol	DE IT GR
Global end of trial date	17 July 2020

Results information

Result version number	v1 (current)
This version publication date	18 July 2021
First version publication date	18 July 2021

Trial information

Trial identification

Sponsor protocol code	CC-10004-BCT-002

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02307513
WHO universal trial number (UTN)	-
Other trial identifiers	20200054: Amgen Study ID

Notes:

Sponsors

Sponsor organisation name	Amgen, Inc
Sponsor organisation address	One Amgen Center Drive, Thousand Oaks, CA, United States, 91320
Public contact	IHQ Medical Info-Clinical Trials, Amgen (EUROPE) GmbH, MedInfoInternational@amgen.com
Scientific contact	IHQ Medical Info-Clinical Trials, Amgen (EUROPE) GmbH, MedInfoInternational@amgen.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	17 July 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	17 July 2020
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 apremilast (APR) in the treatment of oral ulcers in active Behçet's disease (BD).

Protection of trial subjects:

This trial was conducted in accordance with the ethical principles of Good Clinical Practice (GCP), according to the International Council for Harmonisation (ICH) Harmonised Tripartite Guideline and in accordance with the general ethical principles outlined in the Declaration of Helsinki.
The protocol, amendments, and informed consent form (ICF) were reviewed and approved by each study site's Institutional Review Board (IRB)/Independent Ethics Committee (IEC) prior to the start of the study.
The investigator obtained informed consent of a subject and/or a subject's legal representative prior to any study-related procedures.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	16 December 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	France: 22
Country: Number of subjects enrolled	Germany: 7
Country: Number of subjects enrolled	Greece: 11
Country: Number of subjects enrolled	Italy: 12
Country: Number of subjects enrolled	United States: 25
Country: Number of subjects enrolled	Japan: 39
Country: Number of subjects enrolled	Korea, Republic of: 22
Country: Number of subjects enrolled	Israel: 11
Country: Number of subjects enrolled	Lebanon: 4
Country: Number of subjects enrolled	Turkey: 54
Worldwide total number of subjects	207
EEA total number of subjects	52

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)	200
From 65 to 84 years	7
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 53 sites in Europe, Asia, the United States, Israel, Lebanon, and Turkey. The study included a 12-week placebo-controlled phase and a 52-week active treatment phase. Participants in Germany had the opportunity to enter an optional open-label extension phase at week 64.

Pre-assignment

Screening details:

Participants were randomized in a 1:1 ratio to receive either apremilast or placebo in the placebo-controlled treatment phase. After completion of 12 weeks, all participants were to receive apremilast for 52 weeks in the active treatment phase.
Participants were stratified by gender, history of uveitis and region (Japan and Other Regions).

Period 1

Period 1 title	Placebo Controlled Phase (Weeks 0-12)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Assessor, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Participants received identically appearing placebo tablets twice a day (BID) from weeks 0 to 12 during the placebo-controlled treatment phase.

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

Dosage and administration details:

Tablets taken orally twice a day

Arm title	Apremilast 30 mg BID

Arm description:

Participants received apremilast 30 mg tablets BID from weeks 0 to 12 during the placebo-controlled treatment phase.

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

Dosage and administration details:

Tablets taken orally twice a day

Number of subjects in period 1	Placebo	Apremilast 30 mg BID
Started	103	104
Completed	83	96
Not completed	20	8
Consent withdrawn by subject	5	4
Non-Compliance with Study Drug	1	-
Adverse event, non-fatal	4	3
Lost to follow-up	1	-
Lack of efficacy	8	-
Protocol deviation	1	1

Period 2

Period 2 title	Active Treatment Phase (Weeks 13-64)
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo / Apremilast 30 mg BID

Arm description:

Participants who received placebo during the placebo-controlled treatment phase were switched at week 12 to apremilast 30 mg tablets BID for 52 weeks up to week 64 in the active treatment phase.

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

Dosage and administration details:

Tablets taken orally twice a day

Arm title	Apremilast 30 mf BID / Apremilast 30 mg BID

Arm description:

Participants who received apremilast during the placebo-controlled treatment phase continued to receive apremilast 30 mg BID for 52 weeks up to week 64 in the active treatment phase.

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

Dosage and administration details:

Tablets taken orally twice a day

Number of subjects in period 2[1]	Placebo / Apremilast 30 mg BID	Apremilast 30 mf BID / Apremilast 30 mg BID
Started	83	95
Completed	68	75
Not completed	15	20
Consent withdrawn by subject	7	7
Adverse event, non-fatal	4	9
Pregnancy	1	-
Miscellaneous	-	1
Lost to follow-up	1	1
Lack of efficacy	2	2

Notes:

[1] - 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: One participant completed Week 12 but did not enter into active treatment.

Period 3

Period 3 title	Long-term Extension
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Placebo / Apremilast 30 mg BID

Arm description:

Participants in Germany had the option to continue receiving apremilast 30 mg BID in the open-label extension phase.

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

Dosage and administration details:

Tablets taken orally twice a day

Number of subjects in period 3[2]	Placebo / Apremilast 30 mg BID
Started	2
Completed	1
Not completed	1
Physician decision	1

Notes:

[2] - 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: Only participants in Germany had the option to continue receiving apremilast 30 mg BID in the extension phase.

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Participants received identically appearing placebo tablets twice a day (BID) from weeks 0 to 12 during the placebo-controlled treatment phase.	
Reporting group title	Apremilast 30 mg BID
Reporting group description:	
Participants received apremilast 30 mg tablets BID from weeks 0 to 12 during the placebo-controlled treatment phase.	

Reporting group values	Placebo	Apremilast 30 mg BID	Total
Number of subjects	103	104	207
Age categorical Units: Subjects			
Adults (18-64 years)	99	101	200
From 65-84 years	4	3	7
Age Continuous Units: Years			
arithmetic mean	40.6	39.4	
standard deviation	± 12.66	± 12.12	-
Sex: Female, Male Units: Participants			
Female	63	64	127
Male	40	40	80
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	1	0	1
Asian	30	32	62
Native Hawaiian or Other Pacific Islander	1	0	1
Black or African American	0	1	1
White	68	69	137
More than one race	0	0	0
Unknown or Not Reported	3	2	5
Region of the World Units: Subjects			
Europe	27	25	52
North America	11	14	25
Asia	29	32	61
Rest of World	36	33	69
Duration of Behcet's Disease Units: Years			
arithmetic mean	6.94	6.74	
standard deviation	± 7.966	± 7.397	-
Oral Ulcer Count Units: Oral ulcers			
arithmetic mean	3.9	4.2	

standard deviation	± 2.70	± 3.65	-
Pain of Oral Ulcers Visual Analog Scale (VAS)			
The oral ulcer pain visual analog scale ranges from 0 to 100 mm, with 0 mm representing no pain and 100 mm representing the worst possible pain.			
Units: mm			
arithmetic mean	60.8	61.2	
standard deviation	± 26.92	± 27.55	-
Behçet's Disease Current Activity Index (BDCAI) Score			
The BD Current Activity Index (as measured by the BD Current Activity Form) includes 12 questions regarding disease manifestations over the past 4 weeks, including oral and genital disease activity as well as manifestations involving the skin, joints, gastrointestinal tract, eyes, nervous system, and vascular system. The BDCAI ranges from 0 to 12, where higher scores indicate a higher level of disease activity.			
Units: Units on a scale			
arithmetic mean	3.6	3.7	
standard deviation	± 1.67	± 1.58	-
Behçet's Syndrome Activity Score (BSAS)			
The Behçet's Syndrome Activity Score contains 10 questions that assess the number of new oral and genital ulcers and skin lesions, gastrointestinal (GI), central nervous system (CNS), vascular, and ocular involvement, and the participant's current level of discomfort, each on a scale from 0 to 100 (worst). The item scores are totaled to create a score ranging from 0 to 100, with a higher score indicating a higher level of disease activity.			
Units: scores on a scale			
arithmetic mean	44.30	42.75	
standard deviation	± 16.862	± 16.224	-
Behçet's Disease Quality of Life (BD QoL)			
The BD QoL consists of 30 self-completed items that measure disease-related restrictions on the participant's activities and their emotional response to these restrictions. The BD QoL total score ranges from 0 to 30, with 0 representing no influence of BD on quality of life and 30 representing the greatest influence.			
Units: Units on a scale			
arithmetic mean	11.24	10.22	
standard deviation	± 8.157	± 8.245	-

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Participants received identically appearing placebo tablets twice a day (BID) from weeks 0 to 12 during the placebo-controlled treatment phase.	
Reporting group title	Apremilast 30 mg BID
Reporting group description:	
Participants received apremilast 30 mg tablets BID from weeks 0 to 12 during the placebo-controlled treatment phase.	
Reporting group title	Placebo / Apremilast 30 mg BID
Reporting group description:	
Participants who received placebo during the placebo-controlled treatment phase were switched at week 12 to apremilast 30 mg tablets BID for 52 weeks up to week 64 in the active treatment phase.	
Reporting group title	Apremilast 30 mf BID / Apremilast 30 mg BID
Reporting group description:	
Participants who received apremilast during the placebo-controlled treatment phase continued to receive apremilast 30 mg BID for 52 weeks up to week 64 in the active treatment phase.	
Reporting group title	Placebo / Apremilast 30 mg BID
Reporting group description:	
Participants in Germany had the option to continue receiving apremilast 30 mg BID in the open-label extension phase.	

Primary: Area Under the Curve (AUC) for the Number of Oral Ulcers from Baseline Through Week 12 (AUC W0-12)

End point title	Area Under the Curve (AUC) for the Number of Oral Ulcers from Baseline Through Week 12 (AUC W0-12)
End point description:	
The number of oral ulcers that was counted for the analysis of the primary endpoint included current and recurrent ulcers at each time point; a single oral ulcer could be recounted multiple times if it persisted or recurred at subsequent visits. The intent to treat (ITT) population included all randomized participants who received at least 1 dose of study drug. Multiple imputation (MI) was used to impute missing oral ulcer counts.	
End point type	Primary
End point timeframe:	
Oral ulcers were assessed at weeks 0 (baseline), 1, 2, 4, 6, 8, 10, and 12 during the placebo-controlled period.	

End point values	Placebo	Apremilast 30 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	103	104		
Units: Ulcers*days				
least squares mean (standard error)	222.14 (± 15.886)	129.54 (± 15.943)		

Statistical analyses

Statistical analysis title	Treatment Comparison (Apremilast – Placebo)

Statistical analysis description:

The AUC W0-12 for oral ulcer counts was compared between the placebo treatment group and the apremilast 30 BID treatment group using a 2-tailed parametric analysis of covariance (ANCOVA) test at the 0.05 significance level.

Comparison groups	Placebo v Apremilast 30 mg BID
Number of subjects included in analysis	207
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [1]
Method	ANCOVA
Parameter estimate	Difference in LS Mean
Point estimate	-92.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-130.59
upper limit	-54.6

Notes:

[1] - ANCOVA model with AUC W0-12 as the response variables; treatment arm, sex, region as factors and the number of oral ulcers at baseline as a covariate.

Secondary: Change from Baseline in Oral Ulcer Pain as Measured by Visual Analog Scale (VAS) at Week 12

End point title	Change from Baseline in Oral Ulcer Pain as Measured by Visual Analog Scale (VAS) at Week 12

End point description:

Pain of oral ulcers was measured using a 100 mm VAS scale. The participant was asked to draw a single line perpendicular to the VAS line at the point that represented the severity of their pain during the previous week, with 0 mm (the left-hand end of the scale) representing no pain and 100 mm (the right-hand end of the scale) representing the worst pain imaginable. The distance of the perpendicular line from the left-hand end of the scale was recorded.
A negative change from baseline indicates improvement.
The analysis was conducted in the the intent to treat population with available baseline data. Last observation carried forward (LOCF) imputation was used for missing values at week 12.

End point type	Secondary

End point timeframe:

Baseline to week 12

End point values	Placebo	Apremilast 30 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	102	103		
Units: mm				
least squares mean (standard error)	-15.9 (± 3.31)	-40.7 (± 3.34)		

Statistical analyses

Statistical analysis title	Treatment Comparison (Apremilast – Placebo)
Comparison groups	Placebo v Apremilast 30 mg BID
Number of subjects included in analysis	205
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [2]
Method	ANCOVA
Parameter estimate	Difference in LS Mean
Point estimate	-24.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-32.8
upper limit	-16.8

Notes:

[2] - Based on an ANCOVA model for the change from baseline with the treatment arm, sex, region as factors and the baseline value as a covariate.

Secondary: Change from Baseline in Disease Activity as Measured by Behçet's Syndrome Activity Score (BSAS) at Week 12

End point title	Change from Baseline in Disease Activity as Measured by Behçet's Syndrome Activity Score (BSAS) at Week 12

End point description:

The Behçet's Syndrome Activity Score (BSAS) contains 10 questions that assess the number of new oral and genital ulcers and skin lesions, GI, CNS, vascular, and ocular involvement, and the participant's current level of discomfort. The Behçet's Syndrome Activity Score ranges from 0 to 100, with a higher score indicating a higher level of disease activity. A negative change from baseline indicates improvement.
The analysis was conducted in the intent to treat population with available baseline data. LOCF imputation was used for missing values at week 12.

End point type	Secondary

End point timeframe:

Baseline to week 12

End point values	Placebo	Apremilast 30 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	103	104		
Units: Units on a scale				
least squares mean (standard error)	-5.41 (± 1.776)	-17.35 (± 1.796)		

Statistical analyses

Statistical analysis title	Treatment Comparison (Apremilast – Placebo)
Comparison groups	Placebo v Apremilast 30 mg BID

Number of subjects included in analysis	207
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [3]
Method	ANCOVA
Parameter estimate	Difference in LS Mean
Point estimate	-11.94
Confidence interval	
level	95 %
sides	2-sided
lower limit	-16.2
upper limit	-7.67

Notes:

[3] - Based on an ANCOVA model for the change from baseline with the treatment arm, sex, region as factors and the baseline value as a covariate.

Secondary: Change from Baseline in Disease Activity as Measured by Behçet's Disease Current Activity Form (BDCAF): Behçet's Disease Current Activity Index (BDCAI) at Week 12

End point title	Change from Baseline in Disease Activity as Measured by Behçet's Disease Current Activity Form (BDCAF): Behçet's Disease Current Activity Index (BDCAI) at Week 12

End point description:

The Behçet's Disease Current Activity Form (BDCAF) consists of 3 component scores: the Behçet's Disease Current Activity Index (BDCAI) score, the Patient's Perception of Disease Activity, and the Clinician's Overall Perception of Disease Activity. The BDCAI consists of 12 questions regarding disease manifestations over the previous 4 weeks, including oral and genital disease activity, as well as other manifestations of BD involving the skin, joints, GI tract, eyes, nervous system, and vascular system. The BDCAI score is the sum score of 12 items and ranges from 0 to 12. A higher score indicates higher level of disease activity (worsening), and a negative change from baseline indicates improvement. The analysis was conducted in the intent to treat population with available baseline data. LOCF imputation was used for missing values at week 12.

End point type	Secondary

End point timeframe:

Baseline to week 12

End point values	Placebo	Apremilast 30 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	102	104		
Units: Units on a scale				
least squares mean (standard error)	-0.4 (± 0.20)	-0.9 (± 0.20)		

Statistical analyses

Statistical analysis title	Treatment Comparison (Apremilast – Placebo)
Comparison groups	Placebo v Apremilast 30 mg BID

Number of subjects included in analysis	206
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0335 [4]
Method	ANCOVA
Parameter estimate	Difference in LS Means
Point estimate	-0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1
upper limit	0

Notes:

[4] - Based on an ANCOVA model for the change from baseline with the treatment arm, sex, region as factors and the baseline value as a covariate.

Secondary: Change from Baseline in Disease Activity as Measured by Behçet's Disease Current Activity Form (BDCAF): Patient's Perception of Disease Activity at Week 12

End point title	Change from Baseline in Disease Activity as Measured by Behçet's Disease Current Activity Form (BDCAF): Patient's Perception of Disease Activity at Week 12

End point description:

The Behçet's Disease Current Activity Form (BDCAF) consists of 3 component scores: the Behçet's Disease Current Activity Index (BDCAI) score, the Patient's Perception of Disease Activity, and the Clinician's Overall Perception of Disease Activity. The Patient's Perception of Disease Activity was assessed on a scale from 1 to 7, where a higher score indicates a higher level of disease activity and a negative change from baseline indicates improvement.
The study was conducted in the intent to treat population with available data. LOCF imputation was used for missing values at week 12.

End point type	Secondary

End point timeframe:

Baseline to week 12

End point values	Placebo	Apremilast 30 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	102	104		
Units: Units on a scale				
least squares mean (standard error)	-0.7 (± 0.18)	-1.7 (± 0.18)		

Statistical analyses

Statistical analysis title	Treatment Comparison (Apremilast – Placebo)
Comparison groups	Placebo v Apremilast 30 mg BID

Number of subjects included in analysis	206
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [5]
Method	ANCOVA
Parameter estimate	Difference in LS Means
Point estimate	-1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.4
upper limit	-0.6

Notes:

[5] - Based on an ANCOVA model for the change from baseline with the treatment arm, sex, region as factors and the baseline value as a covariate.

Secondary: Change from Baseline in Disease Activity as Measured by Behçet's Disease Current Activity Form (BDCAF): Clinician's Overall Perception of Disease Activity at Week 12

End point title	Change from Baseline in Disease Activity as Measured by Behçet's Disease Current Activity Form (BDCAF): Clinician's Overall Perception of Disease Activity at Week 12

End point description:

The Behçet's Disease Current Activity Form (BDCAF) consists of 3 component scores: the Behçet's disease Current Activity Index (BDCAI) score, the Patient's Perception of Disease Activity, and the Clinician's Overall Perception of Disease Activity. The Clinician's Overall Perception of Disease Activity was assessed on a scale from 1 to 7, where a higher score indicates a higher level of disease activity and a negative change from baseline indicates improvement.
The analysis was conducted in the intent to treat population with available baseline data. LOCF imputation was used for missing values at week 12.

End point type	Secondary

End point timeframe:

Baseline to week 12

End point values	Placebo	Apremilast 30 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	102	104		
Units: Units on a scale				
least squares mean (standard error)	-0.7 (± 0.17)	-1.6 (± 0.17)		

Statistical analyses

Statistical analysis title	Treatment Comparison (Apremilast – Placebo)
Comparison groups	Placebo v Apremilast 30 mg BID

Number of subjects included in analysis	206
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [6]
Method	ANCOVA
Parameter estimate	Difference in LS Means
Point estimate	-0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.3
upper limit	-0.5

Notes:

[6] - Based on an ANCOVA model for the change from baseline with the treatment arm, sex, region as factors and the baseline value as a covariate.

Secondary: Percentage of Participants who Achieved an Oral Ulcer Complete Response (Oral Ulcer-Free) by Week 6 and Remained Oral Ulcer-Free for at Least 6 Additional Weeks

End point title	Percentage of Participants who Achieved an Oral Ulcer Complete Response (Oral Ulcer-Free) by Week 6 and Remained Oral Ulcer-Free for at Least 6 Additional Weeks

End point description:

Participants who were oral ulcer-free by week 6 and remained oral ulcer-free for at least 6 consecutive weeks during the 12-week placebo-controlled treatment phase.

End point type	Secondary

End point timeframe:

Baseline to week 12

End point values	Placebo	Apremilast 30 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	103	104		
Units: Percentage of participants				
number (not applicable)	4.9	29.8		

Statistical analyses

Statistical analysis title	Treatment Comparison (Apremilast – Placebo)

Statistical analysis description:

The adjusted difference in percentages is the weighted average of the treatment differences across the 4 strata of combined sex and region factors with the CMH weights.

Comparison groups	Placebo v Apremilast 30 mg BID

Number of subjects included in analysis	207
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [7]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted difference in percentages
Point estimate	25.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	15.5
upper limit	34.6

Notes:

[7] - 2-sided p-value based on the CMH test adjusting for sex and region.

Secondary: Time to Oral Ulcer Resolution (Complete Response)

End point title	Time to Oral Ulcer Resolution (Complete Response)

End point description:

Time to oral ulcer resolution (defined as oral ulcer-free) was the time between the first dose date and the date when a complete response was achieved for the first time during the placebo-controlled treatment phase. For participants who did not achieve complete response or discontinued treatment before a complete response was achieved during the placebo-controlled treatment phase, time to event was censored at the last oral ulcer assessment date during the placebo-controlled treatment phase or the first dose date if there were no postbaseline ulcer assessments. Median and 95% confidence interval was based on Kaplan-Meier estimates.

"99999" indicates values that could not be estimated due to the low number of events at the time of analysis.

End point type	Secondary

End point timeframe:

Baseline to week 12

End point values	Placebo	Apremilast 30 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	103	104		
Units: Weeks				
median (confidence interval 95%)	8.1 (4.7 to 99999)	2.1 (2.0 to 4.0)		

Statistical analyses

Statistical analysis title	Treatment Comparison
Comparison groups	Placebo v Apremilast 30 mg BID

Number of subjects included in analysis	207
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [8]
Method	Stratified Log-Rank Test
Parameter estimate	Hazard ratio (HR)
Point estimate	2.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.692
upper limit	3.405

Notes:

[8] - Stratified log-rank test, with sex and region as the stratification factors

Secondary: Percentage of Participants who Experienced an Oral Ulcer Complete Response at Week 12

End point title	Percentage of Participants who Experienced an Oral Ulcer Complete Response at Week 12

End point description:

A complete response at week 12 was defined as participants who were oral ulcer free at week 12.
The analysis was conducted in the intent to treat population; participants with missing data at week 12 were classified as non-responders.

End point type	Secondary

End point timeframe:

Week 12

End point values	Placebo	Apremilast 30 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	103	104		
Units: Percentage of participants				
number (not applicable)	22.3	52.9		

Statistical analyses

Statistical analysis title	Treatment Comparison (Apremilast – Placebo)

Statistical analysis description:

The adjusted difference in percntages was the weighted average of the treatment differences across the 4 strata of combined sex and region factors with the CMH weights.

Comparison groups	Placebo v Apremilast 30 mg BID
Number of subjects included in analysis	207
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [9]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted difference in percentages
Point estimate	30.6

Confidence interval	
level	95 %
sides	2-sided
lower limit	18.1
upper limit	43.1

Notes:

[9] - 2-sided p-value based on the CMH test adjusting for sex and region.

Secondary: Change from Baseline in Behçet's Disease Quality of Life (BD Qol) Scores at Week 12

End point title	Change from Baseline in Behçet's Disease Quality of Life (BD Qol) Scores at Week 12

End point description:

The Behçet's Disease Quality of Life questionnaire was developed to measure the influence of BD on a particpant's life. It consists of 30 self-completed itemized questions that measure disease-related restrictions on the participant's activities and their emotional response to these restrictions. The total score is the sum of all 30 items (each yes scores 1 and each no scores 0), with 0 representing no influence of Behçet's disease on a participant's quality of life and 30 representing the most severe influence. A negative change from baseline indicates improvement.
The analysis was conducted in the intent to treat population; LOCF was used for missing values at week 12.

End point type	Secondary

End point timeframe:

Baseline to week 12

End point values	Placebo	Apremilast 30 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	103	104		
Units: Units on a scale				
least squares mean (standard error)	-0.5 (± 0.66)	-3.5 (± 0.67)		

Statistical analyses

Statistical analysis title	Treatment Comparison (Apremilast – Placebo)
Comparison groups	Placebo v Apremilast 30 mg BID
Number of subjects included in analysis	207
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0003 [10]
Method	ANCOVA
Parameter estimate	Difference in LS Mean
Point estimate	-3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.5
upper limit	-1.4

Notes:

[10] - Based on an ANCOVA model for the change from baseline with the treatment arm, sex, region as factors and the baseline value as a covariate.

Secondary: Percentage of Participants who Experienced a Complete Response For Genital Ulcers at Week 12

End point title	Percentage of Participants who Experienced a Complete Response For Genital Ulcers at Week 12

End point description:

A genital ulcer complete response at week 12 was defined as participants who were genital ulcer-free at week 12.
The analysis was conducted in the intent to treat population who had genital ulcers at baseline. Participants with missing data at week 12 were classified as non-responders.

End point type	Secondary

End point timeframe:

Week 12

End point values	Placebo	Apremilast 30 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17[11]	17[12]		
Units: Percentage of participants				
number (not applicable)	41.2	70.6		

Notes:

[11] - Participants with genital ulcers at baseline

[12] - Participants with genital ulcers at baseline

Statistical analyses

Statistical analysis title	Treatment Comparison (Apremilast – Placebo)

Statistical analysis description:

The adjusted difference in percentages was the weighted average of the treatment differences across the 4 strata of combined sex and region factors with the CMH weights.

Comparison groups	Placebo v Apremilast 30 mg BID
Number of subjects included in analysis	34
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.11 [13]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted difference in percentages
Point estimate	28.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.6
upper limit	60.4

Notes:

[13] - Two-sided p-value was based on the CMH test, adjusting for sex and region

Secondary: Percentage of Participants with no Oral Ulcers Following a Complete Response

End point title	Percentage of Participants with no Oral Ulcers Following a Complete Response

End point description:

The percentage of participants who remained oral ulcer-free through week 12 after achieving a complete response (oral ulcer-free) prior to week 12.
The analysis was conducted in the intent to treat population who had a complete response prior to week 12.

End point type	Secondary

End point timeframe:

Baseline to week 12

End point values	Placebo	Apremilast 30 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53[14]	83[15]		
Units: Percentage of participants				
number (not applicable)	13.2	31.3		

Notes:

[14] - Participants with a complete response prior to week 12

[15] - Participants with a complete response prior to week 12

Statistical analyses

Statistical analysis title	Treatment Comparison (Apremilast – Placebo)

Statistical analysis description:

The adjusted difference in percentages was the weighted average of the treatment differences across the 4 strata of combined sex and region factors with the CMH weights.

Comparison groups	Placebo v Apremilast 30 mg BID
Number of subjects included in analysis	136
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0204 [16]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted difference in percentages
Point estimate	17.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.2
upper limit	30.7

Notes:

[16] - Two-sided p-value was based on the CMH test, adjusting for sex and region.

Secondary: Time to Recurrence of Oral Ulcers Following Loss of Complete Response

End point title	Time to Recurrence of Oral Ulcers Following Loss of Complete Response

End point description:

Time to recurrence of oral ulcers following the loss of complete response (oral ulcer-free) was defined as the first instance when a participant had a reappearance of oral ulcers following a complete response, during the placebo-controlled treatment phase. For participants who did not have oral ulcer recurrence or discontinued treatment before any oral ulcer recurrence during the placebo-controlled treatment phase, time to event was censored at the last oral ulcer assessment during placebo-controlled treatment

phase; For participants without any oral ulcer assessment following the first complete response, time to event was censored to the first complete response date.
The analysis was conducted in the intent to treat population who had a complete response prior to week 12.

End point type	Secondary

End point timeframe:

Baseline through week 12

End point values	Placebo	Apremilast 30 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53[17]	83[18]		
Units: Weeks				
median (confidence interval 95%)	2.3 (2.1 to 4.1)	4.6 (3.1 to 6.1)		

Notes:

[17] - Participants with a complete response prior to week 12

[18] - Participants with a complete response prior to week 12

Statistical analyses

Statistical analysis title	Treatment Comparison
Comparison groups	Placebo v Apremilast 30 mg BID
Number of subjects included in analysis	136
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0112 [19]
Method	Stratified Log Rank Test
Parameter estimate	Hazard ratio (HR)
Point estimate	0.611
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.408
upper limit	0.915

Notes:

[19] - Stratified log-rank test, with sex and region as the stratification factors.

Secondary: Number of Oral Ulcers Following Loss of Complete Response Through Week 12

End point title	Number of Oral Ulcers Following Loss of Complete Response Through Week 12

End point description:

Number of oral ulcers reported at the time of the first loss of complete response, ie, at the first instance when a participant had a reappearance of oral ulcers following a complete response, during the placebo-controlled treatment phase.
The analysis was conducted in the intent to treat population who had a complete response prior to week 12.

End point type	Secondary

End point timeframe:

Baseline to week 12

End point values	Placebo	Apremilast 30 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53[20]	83[21]		
Units: oral ulcers				
least squares mean (standard error)	1.5 (± 0.21)	1.1 (± 0.18)		

Notes:

[20] - Participants with a complete response prior to week 12

[21] - Participants with a complete response prior to week 12

Statistical analyses

Statistical analysis title	Treatment Comparison (Apremilast – Placebo)
Comparison groups	Placebo v Apremilast 30 mg BID
Number of subjects included in analysis	136
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0683 [22]
Method	ANCOVA
Parameter estimate	Difference in LS Means
Point estimate	-0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.9
upper limit	0

Notes:

[22] - ANCOVA model with treatment group, sex and region as factors and the baseline ulcers number as a covariate.

Secondary: Change from Baseline in the Total Score of the Static Physician’s Global Assessment (PGA) of BD Skin Lesions at Week 12

End point title	Change from Baseline in the Total Score of the Static Physician’s Global Assessment (PGA) of BD Skin Lesions at

End point description:

BD-related skin lesions (including acne-like lesions, folliculitis, and erythema nodosum) were evaluated according to the Static Physician’s Global Assessment as follows:
Score 0 = clear skin.
Score 1 = mild in severity with the presence of 1 to 10 lesions (papules, pustules, cysts) or nodules at any anatomical site.
Score 2 = Moderate severity; presence of 11 to 20 nodules or lesions (papules, pustules, cysts) at any anatomical site.
Score 3 = Severe; presence of > 20 nodules or lesions (papules, pustules, cysts) at any anatomical site.

The total sore was calculated as the sum of the acne-like lesions, folliculitis, and erythema nodosum scores, and therefore ranges from 0 to 9, where a higher score indicates a higher level of activity. A negative change from baseline indicates improvement.
The analysis was conducted in the intent to treat population who had BD skin lesions at baseline. LOCF imputation was used for missing values at week 12.

End point type	Secondary

End point timeframe:

Baseline to week 12

End point values	Placebo	Apremilast 30 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	59[23]	58[24]		
Units: scores on a scale				
least squares mean (standard error)	-0.8 (± 0.14)	-0.9 (± 0.14)		

Notes:

[23] - Participants with BD skin lesions at baseline

[24] - Participants with BD skin lesions at baseline

Statistical analyses

Statistical analysis title	Treatment Comparison (Apremilast – Placebo)
Comparison groups	Placebo v Apremilast 30 mg BID
Number of subjects included in analysis	117
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5944 [25]
Method	ANCOVA
Parameter estimate	Difference in LS Mean
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4
upper limit	0.3

Notes:

[25] - Based on an ANCOVA model for the change from baseline, with treatment arm, sex and region as factors and the baseline score as a covariate.

Secondary: Change from Baseline in Genital Ulcer Pain as Measured by VAS Score at Week 12

End point title	Change from Baseline in Genital Ulcer Pain as Measured by VAS Score at Week 12

End point description:

Pain of genital ulcers was measured using a 100 mm visual analog scale. The participant was asked to draw a single line perpendicular to the VAS line at the point that represented the severity of their pain during the previous week, with 0 mm (the left-hand end of the scale) representing no pain and 100 mm (the right-hand end of the scale) representing the worst pain imaginable. The distance of the perpendicular line from the left-hand end of the scale was recorded. A negative change from baseline indicates improvement.
The analysis was conducted in the intent to treat population who had genital ulcers at baseline. LOCF imputation was used for missing values at week 12.

End point type	Secondary

End point timeframe:

Baseline to week 12

End point values	Placebo	Apremilast 30 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17[26]	17[27]		
Units: mm				
least squares mean (standard error)	-24.5 (± 10.75)	-30.0 (± 11.22)		

Notes:

[26] - Participants with genital ulcers at baseline

[27] - Participants with genital ulcers at baseline

Statistical analyses

Statistical analysis title	Treatment Comparison (Apremilast – Placebo)
Comparison groups	Placebo v Apremilast 30 mg BID
Number of subjects included in analysis	34
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6182 [28]
Method	ANCOVA
Parameter estimate	Difference in LS Mean
Point estimate	-5.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-27.6
upper limit	16.7

Notes:

[28] - Based on an ANCOVA model for the change from baseline, with treatment arm, sex and region as factors and the baseline score as a covariate.

Secondary: Number of Participants with Treatment Emergent Adverse Events (TEAEs) During the Placebo-controlled Treatment Period

End point title	Number of Participants with Treatment Emergent Adverse Events (TEAEs) During the Placebo-controlled Treatment Period

End point description:

A TEAE is an adverse event (AE) with a start date on or after the date of the first dose of study drug and no later than 28 days after the last dose. An AE is any noxious, unintended, or untoward medical occurrence that may appear or worsen in a subject during the course of a study. A serious AE (SAE) is any AE that resulted in death; was life-threatening; required inpatient hospitalization or prolongation of existing hospitalization; resulted in persistent or significant disability/incapacity; was a congenital anomaly/birth defect; or constituted an important medical event. For both AEs and SAEs the investigator assessed the severity of the event according to the grading scale:
Mild: asymptomatic or with mild symptoms;
Moderate: symptoms causing moderate discomfort and local or noninvasive intervention is indicated;
Severe: symptoms causing severe discomfort or pain, symptoms requiring medical/surgical intervention.

End point type	Secondary

End point timeframe:

From first dose of study drug in the placebo-controlled phase to the first dose of apremilast in the active treatment phase (12 weeks) or up to 28 days after last dose for participants who did not receive study drug at week 12, whichever was earlier.

End point values	Placebo	Apremilast 30 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	103	104		
Units: Participants				
Any TEAE	74	82		
Any Drug-related TEAE	37	60		
Any Severe TEAE	6	6		
Any Serious TEAE	4	3		
Any TEAE Leading to Drug Interruption	6	9		
Any TEAE Leading to Drug Withdrawal	5	3		
Any TEAE Leading to Death	0	0		

Statistical analyses

No statistical analyses for this end point

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

End point title	Number of Participants with TEAEs During the Apremilast-Exposure Period[29]

End point description:

The apremilast-exposure period started on the date of the first dose of apremilast (week 0 for participants assigned to apremilast or week 12 for participants originally assigned to placebo who switched to apremilast at week 12) and ended 28 days after last dose in the active treatment phase. An AE is any noxious, unintended, or untoward medical occurrence that may appear or worsen in a subject during the course of a study. An SAE is any AE that resulted in death; was life-threatening; required or prolonged inpatient hospitalization; resulted in persistent or significant disability/incapacity; was a congenital anomaly/birth defect; or constituted an important medical event. The investigator assessed the severity of each event according to the grading scale:
Mild: asymptomatic or mild symptoms;
Moderate: symptoms causing moderate discomfort, local or noninvasive intervention indicated;
Severe: symptoms causing severe discomfort or pain, requiring medical/surgical intervention.

End point type	Secondary

End point timeframe:

From first dose of apremilast (week 0 for those assigned to apremilast or week 12 for those assigned to placebo) up to 28 days after last dose; up to 56 weeks and 68 weeks in each arm respectively.

Notes:

[29] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data are reported for the apremilast-exposure period.

End point values	Placebo / Apremilast 30 mg BID	Apremilast 30 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	83	104		
Units: participants				
Any TEAE	70	90		
Any Drug-related TEAE	29	64		
Any Severe TEAE	4	17		
Any Serious TEAE	7	10		
Any TEAE Leading to Drug Interruption	10	17		

Any TEAE Leading to Drug Withdrawal	3	12		
Any TEAE Leading to Death	0	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Placebo-controlled phase: Week 0 to 12.
Apremilast exposure: From first dose of APR (week 0 or 12) to 28 days after last dose; 56 and 68 weeks in each arm respectively.
Extension: From first dose of open-label APR to 28 days after last dose, max 784 days.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	Placebo-controlled Phase: Placebo

Reporting group description:

Participants received identically appearing placebo tablets twice a day from weeks 0 to 12 during the placebo-controlled treatment phase.

Reporting group title	Placebo-controlled Phase: Apremilast 30 mg BID

Reporting group description:

Participants received apremilast 30 mg tablets twice a day from weeks 0 to 12 during the placebo-controlled treatment phase.

Reporting group title	Apremilast-exposure Period: Apremilast 30 mg BID

Reporting group description:

Participants received apremilast 30 mg BID from week 0 or week 12 up to week 64.

Reporting group title	Open-label Extension: Apremilast 30 mg BID

Reporting group description:

Participants in Germany received apremilast 30 mg BID in the open-label extension phase.

Serious adverse events	Placebo-controlled Phase: Placebo	Placebo-controlled Phase: Apremilast 30 mg BID	Apremilast-exposure Period: Apremilast 30 mg BID
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 103 (3.88%)	3 / 104 (2.88%)	17 / 187 (9.09%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	0 / 103 (0.00%)	0 / 104 (0.00%)	1 / 187 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endometrial cancer			
subjects affected / exposed	0 / 103 (0.00%)	0 / 104 (0.00%)	1 / 187 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Injury, poisoning and procedural complications			
Joint dislocation			
subjects affected / exposed	0 / 103 (0.00%)	0 / 104 (0.00%)	1 / 187 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Road traffic accident			
subjects affected / exposed	0 / 103 (0.00%)	0 / 104 (0.00%)	1 / 187 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Soft tissue injury			
subjects affected / exposed	0 / 103 (0.00%)	1 / 104 (0.96%)	1 / 187 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tibia fracture			
subjects affected / exposed	0 / 103 (0.00%)	0 / 104 (0.00%)	1 / 187 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Arterial thrombosis			
subjects affected / exposed	0 / 103 (0.00%)	0 / 104 (0.00%)	1 / 187 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Behcet's syndrome			
subjects affected / exposed	0 / 103 (0.00%)	1 / 104 (0.96%)	2 / 187 (1.07%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Migraine			
subjects affected / exposed	0 / 103 (0.00%)	1 / 104 (0.96%)	1 / 187 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Mouth ulceration			

subjects affected / exposed	1 / 103 (0.97%)	0 / 104 (0.00%)	0 / 187 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis acute			
subjects affected / exposed	0 / 103 (0.00%)	0 / 104 (0.00%)	1 / 187 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Vaginal stricture			
subjects affected / exposed	0 / 103 (0.00%)	0 / 104 (0.00%)	1 / 187 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Acute febrile neutrophilic dermatosis			
subjects affected / exposed	1 / 103 (0.97%)	0 / 104 (0.00%)	0 / 187 (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
Erythema multiforme			
subjects affected / exposed	1 / 103 (0.97%)	0 / 104 (0.00%)	0 / 187 (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
Skin lesion			
subjects affected / exposed	1 / 103 (0.97%)	0 / 104 (0.00%)	0 / 187 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Myositis			
subjects affected / exposed	0 / 103 (0.00%)	0 / 104 (0.00%)	1 / 187 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Appendicitis			

subjects affected / exposed	0 / 103 (0.00%)	0 / 104 (0.00%)	2 / 187 (1.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	0 / 103 (0.00%)	0 / 104 (0.00%)	1 / 187 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea infectious			
subjects affected / exposed	1 / 103 (0.97%)	0 / 104 (0.00%)	0 / 187 (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
Genital infection			
subjects affected / exposed	1 / 103 (0.97%)	0 / 104 (0.00%)	0 / 187 (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
Genital infection fungal			
subjects affected / exposed	1 / 103 (0.97%)	0 / 104 (0.00%)	0 / 187 (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
Herpes zoster			
subjects affected / exposed	0 / 103 (0.00%)	0 / 104 (0.00%)	1 / 187 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infectious colitis			
subjects affected / exposed	0 / 103 (0.00%)	0 / 104 (0.00%)	1 / 187 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymph node tuberculosis			
subjects affected / exposed	0 / 103 (0.00%)	0 / 104 (0.00%)	1 / 187 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vestibular neuronitis			

subjects affected / exposed	0 / 103 (0.00%)	0 / 104 (0.00%)	1 / 187 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Open-label Extension: Apremilast 30 mg BID		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 2 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Endometrial cancer			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Joint dislocation			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Road traffic accident			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Soft tissue injury			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Tibia fracture			

subjects affected / exposed	0 / 2 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Arterial thrombosis			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Behcet's syndrome			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Migraine			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Mouth ulceration			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pancreatitis acute			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Vaginal stricture			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Acute febrile neutrophilic dermatosis			

subjects affected / exposed	0 / 2 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Erythema multiforme				
subjects affected / exposed	0 / 2 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Skin lesion				
subjects affected / exposed	0 / 2 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal and connective tissue disorders				
Myositis				
subjects affected / exposed	0 / 2 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Appendicitis				
subjects affected / exposed	0 / 2 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Bronchitis				
subjects affected / exposed	0 / 2 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Diarrhoea infectious				
subjects affected / exposed	0 / 2 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Genital infection				
subjects affected / exposed	0 / 2 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Genital infection fungal			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Herpes zoster			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infectious colitis			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Lymph node tuberculosis			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vestibular neuronitis			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Placebo-controlled Phase: Placebo	Placebo-controlled Phase: Apremilast 30 mg BID	Apremilast-exposure Period: Apremilast 30 mg BID
Total subjects affected by non-serious adverse events			
subjects affected / exposed	52 / 103 (50.49%)	67 / 104 (64.42%)	132 / 187 (70.59%)
Injury, poisoning and procedural complications			
Bone contusion			
subjects affected / exposed	0 / 103 (0.00%)	0 / 104 (0.00%)	0 / 187 (0.00%)
occurrences (all)	0	0	0
Vascular disorders			
Behcet's syndrome			
subjects affected / exposed	0 / 103 (0.00%)	0 / 104 (0.00%)	0 / 187 (0.00%)
occurrences (all)	0	0	0

Raynaud's phenomenon			
subjects affected / exposed	0 / 103 (0.00%)	0 / 104 (0.00%)	0 / 187 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	11 / 103 (10.68%)	15 / 104 (14.42%)	38 / 187 (20.32%)
occurrences (all)	13	21	58
Eye disorders			
Dry eye			
subjects affected / exposed	1 / 103 (0.97%)	0 / 104 (0.00%)	0 / 187 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	3 / 103 (2.91%)	4 / 104 (3.85%)	12 / 187 (6.42%)
occurrences (all)	3	4	13
Abdominal pain upper			
subjects affected / exposed	2 / 103 (1.94%)	9 / 104 (8.65%)	20 / 187 (10.70%)
occurrences (all)	2	9	27
Diarrhoea			
subjects affected / exposed	21 / 103 (20.39%)	43 / 104 (41.35%)	74 / 187 (39.57%)
occurrences (all)	35	72	157
Nausea			
subjects affected / exposed	11 / 103 (10.68%)	20 / 104 (19.23%)	36 / 187 (19.25%)
occurrences (all)	14	29	54
Vomiting			
subjects affected / exposed	2 / 103 (1.94%)	9 / 104 (8.65%)	14 / 187 (7.49%)
occurrences (all)	2	9	15
Constipation			
subjects affected / exposed	3 / 103 (2.91%)	0 / 104 (0.00%)	3 / 187 (1.60%)
occurrences (all)	3	0	3
Impaired gastric emptying			
subjects affected / exposed	0 / 103 (0.00%)	0 / 104 (0.00%)	0 / 187 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Insomnia			
subjects affected / exposed	2 / 103 (1.94%)	1 / 104 (0.96%)	12 / 187 (6.42%)
occurrences (all)	2	1	12

Depression			
subjects affected / exposed	1 / 103 (0.97%)	0 / 104 (0.00%)	1 / 187 (0.53%)
occurrences (all)	1	0	1
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	3 / 103 (2.91%)	6 / 104 (5.77%)	18 / 187 (9.63%)
occurrences (all)	3	8	24
Back pain			
subjects affected / exposed	6 / 103 (5.83%)	8 / 104 (7.69%)	16 / 187 (8.56%)
occurrences (all)	6	9	18
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	5 / 103 (4.85%)	12 / 104 (11.54%)	26 / 187 (13.90%)
occurrences (all)	5	13	32
Viral upper respiratory tract infection			
subjects affected / exposed	5 / 103 (4.85%)	7 / 104 (6.73%)	20 / 187 (10.70%)
occurrences (all)	5	8	27
Eye infection			
subjects affected / exposed	0 / 103 (0.00%)	0 / 104 (0.00%)	0 / 187 (0.00%)
occurrences (all)	0	0	0
Helicobacter infection			
subjects affected / exposed	0 / 103 (0.00%)	0 / 104 (0.00%)	0 / 187 (0.00%)
occurrences (all)	0	0	0
Urinary tract infection			
subjects affected / exposed	4 / 103 (3.88%)	1 / 104 (0.96%)	2 / 187 (1.07%)
occurrences (all)	4	1	2

Non-serious adverse events	Open-label Extension: Apremilast 30 mg BID		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 2 (100.00%)		
Injury, poisoning and procedural complications			
Bone contusion			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Vascular disorders			

Behcet's syndrome			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Raynaud's phenomenon			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences (all)	0		
Eye disorders			
Dry eye			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences (all)	0		
Abdominal pain upper			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences (all)	0		
Diarrhoea			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Nausea			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Vomiting			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences (all)	0		
Constipation			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Impaired gastric emptying			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Psychiatric disorders			

Insomnia			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences (all)	0		
Depression			
subjects affected / exposed	2 / 2 (100.00%)		
occurrences (all)	2		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences (all)	0		
Back pain			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences (all)	0		
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences (all)	0		
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences (all)	0		
Eye infection			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Helicobacter infection			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Urinary tract infection			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 February 2016	- Extended eligibility to subjects previously exposed to biologic therapy. - Revised to allow subjects to receive colchicine until 7 days prior to randomization. - Revised to allow tapering of oral and topical corticosteroids and subsequent discontinuation close to the day of randomization. - Clarified the required number of oral ulcers at screening and baseline to avoid misinterpretation. All subjects must have had at least 2 oral ulcers at the Screening Visit (Visit 1). Once 3 oral ulcers were observed, regardless of the time interval from the Screening Visit (ie, the interval of 2 weeks was not required) a subject was qualified to be randomized, provided all other eligibility criteria were met. If only 2 oral ulcers were present at Visit 2, then at least 14 days must have passed since Visit 1 before the subject could have been randomized. - Revised the static PGA of skin lesions, as described in Appendix G of the protocol. Scoring of the number of nodules/lesions was based NOT on one anatomical site at a time, but at any anatomical site with respect to the whole body.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported