Clinical trial results:
A Phase 3B, Multicenter, Randomized, Placebo-Controlled, Double-Blind, Double-Dummy, Study Of The Efficacy And Safety Of Apremilast (CC-10004), Etanercept, And Placebo, In Subjects With Moderate To Severe Plaque Psoriasis

Summary

EudraCT number	2012-000859-14
Trial protocol	BE DE GB NL CZ LV EE HU
Global end of trial date	04 April 2016

Results information

Result version number	v1 (current)
This version publication date	16 April 2017
First version publication date	16 April 2017

Trial information

Trial identification

Sponsor protocol code	CC-10004-PSOR-010

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01690299
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Celgene Corporation
Sponsor organisation address	86 Morris Avenue, Summit, NJ, United States, 07901
Public contact	Clinical Trial Disclosure, Celgene Corporation, 01 888-260-1599, ClinicalTrialDisclosure@celgene.com
Scientific contact	Kristine Nograles, Celgene Corporation, KNograles@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	26 June 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	04 April 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the clinical efficacy and safety of oral apremilast (APR) 30 mg twice a day (BID) compared with placebo, in subjects with moderate to severe plaque psoriasis at Week 16.

Protection of trial subjects:

Patient Confidentiality and Personal Data Protection

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	23 October 2012
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	United States: 80
Country: Number of subjects enrolled	Canada: 15
Country: Number of subjects enrolled	Belgium: 5
Country: Number of subjects enrolled	Czech Republic: 24
Country: Number of subjects enrolled	Estonia: 5
Country: Number of subjects enrolled	United Kingdom: 12
Country: Number of subjects enrolled	Hungary: 4
Country: Number of subjects enrolled	Germany: 20
Country: Number of subjects enrolled	Latvia: 73
Country: Number of subjects enrolled	Australia: 10
Country: Number of subjects enrolled	Netherlands: 2
Worldwide total number of subjects	250
EEA total number of subjects	145

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)	225
From 65 to 84 years	25
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 65 study centers in 11 countries.

Pre-assignment

Screening details:

Participants were randomized 1:1:1 to the three treatment groups. Participants were stratified according to their calculated body mass index (BMI) categories at Screening (BMI < 30 or BMI ≥ 30).

Period 1

Period 1 title	Placebo-controlled Phase (Weeks 0-16)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Participants received identically matching placebo tablets orally (PO), twice a day (BID) and 2-1 milliliter (ml) placebo subcutaneous (SC) saline injections once weekly (QW) during the 16-week randomized, double-blind, double-dummy, placebo-controlled phase.

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

Dosage and administration details:

Identically matching placebo tablets BID during the 16-week randomized, double-blind, double-dummy, placebo-controlled phase

Investigational medicinal product name	Placebo Injection
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

2-1ml placebo SC saline injections QW during the 16-week randomized, double-blind, double-dummy, placebo-controlled phase

Arm title	Apremilast

Arm description:

Participants received apremilast 30 mg PO BID plus 2-1ml placebo SC saline injections QW during the 16-week randomized, double-blind, double-dummy, placebo-controlled phase

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

Dosage and administration details: Apremilast 30 mg PO BID	
Investigational medicinal product name	Placebo Injection
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use
Dosage and administration details: 2-1ml placebo SC saline injections QW during the 16-week randomized, double-blind, double-dummy, placebo-controlled phase	
Arm title	Etanercept
Arm description: Participants received etanercept 50 mg by SC injection QW plus placebo tablets PO BID during the 16-week randomized, double-blind, double-dummy, placebo-controlled phase.	
Arm type	Active Control
Investigational medicinal product name	Etanercept
Investigational medicinal product code	
Other name	Enbrel
Pharmaceutical forms	Powder and solution for solution for injection
Routes of administration	Subcutaneous use
Dosage and administration details: Etanercept 50 mg by SC injection QW during the 16-week randomized, double-blind, double-dummy, placebo-controlled phase	
Investigational medicinal product name	Placebo tablet
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: Identically matching placebo tablets BID during the 16-week randomized, double-blind, double-dummy, placebo-controlled phase	

Number of subjects in period 1	Placebo	Apremilast	Etanercept
Started	84	83	83
Safety population	84	83	83
Completed	75	77	81
Not completed	9	6	2
Consent withdrawn by subject	1	3	-
Adverse event, non-fatal	2	2	1
Unspecified	2	1	1
Lack of efficacy	4	-	-

Period 2

Period 2 title	Apremilast Extension Phase-Weeks 16-104
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo/Apremilast

Arm description:

Participants who received placebo tablets PO BID and SC saline (placebo) injections (1mL x 2 injections SC) QW during the 16-week randomized, double-blind, double-dummy, placebo-controlled phase week were switched to 30 mg Apremilast PO BID and remained on this dose through week 104.

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

Dosage and administration details:

Apremilast 30 mg PO BID

Arm title	Apremilast/Apremilast

Arm description:

Participants who received apremilast 30 mg PO BID plus saline (placebo) injections (1mL x 2 injections SC) QW during the 16-week randomized, double-blind, double-dummy, placebo-controlled phase continued on to receive apremilast 30mg PO BID through week 104.

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

Dosage and administration details:

Apremilast 30 mg PO BID

Arm title	Etanercept/Apremilast

Arm description:

Participants who received etanercept 50 mg by SC injection QW plus placebo tablets PO BID during the 16-week randomized, double-blind, double-dummy, placebo-controlled phase, were switched at week 16 to apremilast 30 mg PO BID through week 104.

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

Dosage and administration details:

Apremilast 30 mg PO BID

Number of subjects in period 2[1]	Placebo/Apremilast	Apremilast/Apremilast	Etanercept/Apremilast
Started	73	74	80
Received Treatment	73	74	79
Completed	47	41	50
Not completed	26	33	30
Consent withdrawn by subject	8	5	11
Adverse event, non-fatal	3	4	3
Non-compliance to study drug	-	1	1
Lost to follow-up	6	13	6
Lack of efficacy	9	10	8
Protocol deviation	-	-	1

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: There are fewer participants in this period because some patients discontinued the study at or prior to Week 16. Six subjects completed Period 1 but did not continue into Period 2.

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Participants received identically matching placebo tablets orally (PO), twice a day (BID) and 2-1 milliliter (ml) placebo subcutaneous (SC) saline injections once weekly (QW) during the 16-week randomized, double-blind, double-dummy, placebo-controlled phase.	
Reporting group title	Apremilast
Reporting group description:	
Participants received apremilast 30 mg PO BID plus 2-1ml placebo SC saline injections QW during the 16-week randomized, double-blind, double-dummy, placebo-controlled phase	
Reporting group title	Etanercept
Reporting group description:	
Participants received etanercept 50 mg by SC injection QW plus placebo tablets PO BID during the 16-week randomized, double-blind, double-dummy, placebo-controlled phase.	

Reporting group values	Placebo	Apremilast	Etanercept
Number of subjects	84	83	83
Age categorical Units: Subjects			
Adults (18-64 years)	77	78	70
From 65-84 years	7	5	13
Age Continuous Units: years			
arithmetic mean	43.4	46	47
standard deviation	± 14.91	± 13.59	± 14.07
Gender, Male/Female Units: Subjects			
Female	25	34	34
Male	59	49	49

Reporting group values	Total		
Number of subjects	250		
Age categorical Units: Subjects			
Adults (18-64 years)	225		
From 65-84 years	25		
Age Continuous Units: years			
arithmetic mean			
standard deviation	-		
Gender, Male/Female Units: Subjects			
Female	93		
Male	157		

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Participants received identically matching placebo tablets orally (PO), twice a day (BID) and 2-1 milliliter (ml) placebo subcutaneous (SC) saline injections once weekly (QW) during the 16-week randomized, double-blind, double-dummy, placebo-controlled phase.	
Reporting group title	Apremilast
Reporting group description:	
Participants received apremilast 30 mg PO BID plus 2-1ml placebo SC saline injections QW during the 16-week randomized, double-blind, double-dummy, placebo-controlled phase	
Reporting group title	Etanercept
Reporting group description:	
Participants received etanercept 50 mg by SC injection QW plus placebo tablets PO BID during the 16-week randomized, double-blind, double-dummy, placebo-controlled phase.	
Reporting group title	Placebo/Apremilast
Reporting group description:	
Participants who received placebo tablets PO BID and SC saline (placebo) injections (1mL x 2 injections SC) QW during the 16-week randomized, double-blind, double-dummy, placebo-controlled phase week were switched to 30 mg Apremilast PO BID and remained on this dose through week 104.	
Reporting group title	Apremilast/Apremilast
Reporting group description:	
Participants who received apremilast 30 mg PO BID plus saline (placebo) injections (1mL x 2 injections SC) QW during the 16-week randomized, double-blind, double-dummy, placebo-controlled phase continued on to receive apremilast 30mg PO BID through week 104.	
Reporting group title	Etanercept/Apremilast
Reporting group description:	
Participants who received etanercept 50 mg by SC injection QW plus placebo tablets PO BID during the 16-week randomized, double-blind, double-dummy, placebo-controlled phase, were switched at week 16 to apremilast 30 mg PO BID through week 104.	

Primary: Percentage of Subjects Who Achieved a 75% Improvement (Response) in the Psoriasis Area Severity Index (PASI-75) for the Comparison between Apremilast and Placebo at Week 16 from Baseline

End point title	Percentage of Subjects Who Achieved a 75% Improvement (Response) in the Psoriasis Area Severity Index (PASI-75) for the Comparison between Apremilast and Placebo at Week 16 from Baseline[1]
End point description:	
The PASI was a measure of psoriatic disease severity taking into account qualitative lesion characteristics (erythema, thickness, and scaling) and degree of skin surface area involvement on defined anatomical regions. PASI scores range from 0 to 72, with higher scores reflecting greater disease severity. Erythema, thickness, and scaling are scored on a scale of 0 (none) to 4 (very severe) on 4 anatomic regions of the body: head, trunk, upper limbs, and lower limbs. Degree of involvement on each of the 4 anatomic regions is scored on a scale of 0 (no involvement) to 6 (90% to 100% involvement). The PASI score was set to missing if any severity score or degree of involvement was missing. The modified intent to treat population = all participants who were randomized and received at least one dose of study drug and had both a baseline PASI and and at least one post-treatment PASI evaluation. Missing data imputation: Last observation carried forward (LOCF).	
End point type	Primary
End point timeframe:	
Baseline to Week 16	

Notes:

[1] - 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: The primary endpoint compares placebo with apremilast only and is the reason only two arms are reported. The comparison of placebo and etanercept is a secondary endpoint. The study was not designed to compare apremilast with etanercept.

End point values	Placebo	Apremilast		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	84	83		
Units: Percentage of participants				
number (not applicable)	11.9	39.8		

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Placebo v Apremilast
Number of subjects included in analysis	167
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	< 0.0001 [3]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted Difference
Point estimate	27.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	14.9
upper limit	40.1

Notes:

[2] - The confidence interval (CI) is weighted using CMH weights according to the number of participants in the two strata.
[3] - The two-sided p-value is from a CMH test stratified by the BMI at screening.

Secondary: Percentage of Subjects who achieved a 75% improvement (response) in the Psoriasis Area and Severity Index (PASI) for the Comparison Between Etanercept 50mg SC QW and Placebo at Week 16

End point title	Percentage of Subjects who achieved a 75% improvement (response) in the Psoriasis Area and Severity Index (PASI) for the Comparison Between Etanercept 50mg SC QW and Placebo at Week 16[4]

End point description:

The improvement in PASI score was used as a measure of efficacy. The PASI was a measure of psoriatic disease severity taking into account qualitative lesion characteristics (erythema, thickness, and scaling) and degree of skin surface area involvement on defined anatomical regions. PASI scores range from 0 to 72, with higher scores reflecting greater disease severity. Erythema, thickness, and scaling are scored on a scale of 0 (none) to 4 (very severe) on 4 anatomic regions of the body: head, trunk, upper limbs, and lower limbs. Degree of involvement on each of the 4 anatomic regions is scored on a scale of 0 (no involvement) to 6 (90% to 100% involvement). The PASI score was set to missing if any severity score or degree of involvement was missing. mITT population consisted of all participants who were re-randomized and received at least one dose of study drug and had both a baseline PASI and at least one post-treatment PASI evaluation. Missing data imputation: LOCF.

End point type	Secondary

End point timeframe:

Baseline and Week 16

Notes:

[4] - 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: The secondary endpoint compares placebo with Etanercept only and is the reason only two arms are reported. The study was not designed to compare apremilast with etanercept.

End point values	Placebo	Etanercept		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	84	83		
Units: percentage of participants				
number (not applicable)	11.9	48.2		

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Placebo v Etanercept
Number of subjects included in analysis	167
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [5]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted Difference
Point estimate	35.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	23.3
upper limit	48.5

Notes:

[5] - The two-sided p-value is from a CMH test stratified by the BMI at screening.

Secondary: Percentage of subjects who achieved a Static Physician Global Assessment (sPGA) Score of clear (0) or almost clear (1) with at least 2 points reduction for comparison between Apremilast and Placebo and Etanercept and Placebo at Week 16

End point title	Percentage of subjects who achieved a Static Physician Global Assessment (sPGA) Score of clear (0) or almost clear (1) with at least 2 points reduction for comparison between Apremilast and Placebo and Etanercept and Placebo at Week 16

End point description:

The sPGA is an assessment by the Investigator of the overall disease severity at the time of evaluation. The sPGA is a 5-point scale ranging from 0 (clear) to 4 (severe), incorporating an assessment of the severity of the three primary signs of the disease: erythema, scaling and plaque elevation. When making the assessment of overall severity, the Investigator should factor in areas that have already been cleared (ie, have scores of 0) and not just evaluate remaining lesions for severity, ie, the severity of each sign is averaged across all areas of involvement, including cleared lesions. In the event of different severities across disease signs, the sign that is the predominant feature of the disease should be used to help determine the sPGA score. mITT population consisted of all participants who were randomized and received at least one dose of study drug and had both a baseline PASI and at least one post-treatment PASI evaluation. Missing data imputation: LOCF.

End point type	Secondary

End point timeframe:
Baseline and Week 16

End point values	Placebo	Apremilast	Etanercept	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	84	83	83	
Units: percentage of participants				
number (not applicable)	3.6	21.7	28.9	

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Placebo v Apremilast
Number of subjects included in analysis	167
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0005 [6]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted Difference
Point estimate	18
Confidence interval	
level	95 %
sides	2-sided
lower limit	8.4
upper limit	27.7

Notes:

[6] - The p-value is from a CMH test stratified by the BMI (Body Mass Index) at screening.

Statistical analysis title	Statistical analysis 2
Comparison groups	Placebo v Etanercept
Number of subjects included in analysis	167
Analysis specification	Pre-specified
Analysis type	superiority[7]
P-value	< 0.0001 [8]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted Difference
Point estimate	25.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	14.8
upper limit	35.5

Notes:

[7] - The Confidence Interval (CI) was weighted using CMH weights according to the number of participants in the two strata.

[8] - The p-value is from a CMH test stratified by the BMI (Body Mass Index) at screening.

Secondary: Percent change from baseline in the affected body surface area (BSA) for comparison between Apremilast and Placebo and Etanercept and Placebo at Week 16

End point title	Percent change from baseline in the affected body surface area (BSA) for comparison between Apremilast and Placebo and Etanercept and Placebo at Week 16

End point description:

BSA is a measurement of involved skin. The overall BSA affected by psoriasis was estimated based on the palm area of the participant's hand (entire palmar surface or "handprint" including the fingers), which equates to approximately 1% of total body surface area. BSA percent change from baseline was determined at each visit of the study, which is calculated as 100*(post-baseline BSA - baseline BSA) / baseline BSA. mITT population consisted of all participants who were randomized and received at least one dose of study drug and had both a baseline PASI and at least one post-treatment PASI evaluation. Missing data imputation: LOCF.

End point type	Secondary

End point timeframe:

Baseline to Week 16

End point values	Placebo	Apremilast	Etanercept	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	84	83	83	
Units: percent change				
least squares mean (confidence interval 95%)	-16.3 (-23.71 to -8.81)	-47.7 (-55.2 to -40.12)	-56.1 (-63.63 to -48.59)	

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Placebo v Apremilast
Number of subjects included in analysis	167
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [9]
Method	ANCOVA
Parameter estimate	Difference in LS Mean
Point estimate	-31.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-43.33
upper limit	-19.46

Notes:

[9] - Based on ANCOVA model with treatment and screening BMI category as factors and the baseline value as a covariate.

Statistical analysis title	Statistical analysis 2

Comparison groups	Placebo v Etanercept
Number of subjects included in analysis	167
Analysis specification	Pre-specified
Analysis type	superiority[10]
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Difference in LS Mean
Point estimate	-39.85
Confidence interval	
level	95 %
sides	2-sided
lower limit	-51.78
upper limit	-27.92

Notes:

[10] - Based on ANCOVA model with treatment and screening BMI category as factors and the baseline value as a covariate.

Secondary: Percentage of Subjects Who Achieved a 50% Improvement (Response) in the Psoriasis Area Severity Index (PASI-50) for Comparison Between Apremilast and Placebo and Etanercept and Placebo at Week 16

End point title	Percentage of Subjects Who Achieved a 50% Improvement (Response) in the Psoriasis Area Severity Index (PASI-50) for Comparison Between Apremilast and Placebo and Etanercept and Placebo at Week 16

End point description:

The PASI score was a measure of psoriatic disease severity taking into account qualitative lesion characteristics (erythema, thickness, and scaling) and degree of skin surface area involvement on defined anatomical regions. PASI scores range from 0 to 72, with higher scores reflecting greater disease severity. Erythema, thickness, and scaling are scored on a scale of 0 (none) to 4 (very severe) on 4 anatomic regions of the body: head, trunk, upper limbs, and lower limbs. Degree of involvement on each of the 4 anatomic regions is scored on a scale of 0 (no involvement) to 6 (90% to 100% involvement). The PASI score was set to missing if any severity score or degree of involvement was missing. mITT population consisted of all participants who were randomized and received at least one dose of study drug and had both a baseline PASI and at least one post-treatment PASI evaluation. Missing data imputation: LOCF.

End point type	Secondary

End point timeframe:

Baseline to Week 16

End point values	Placebo	Apremilast	Etanercept	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	84	83	83	
Units: percentage of participants				
number (not applicable)	33.3	62.7	83.1	

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Placebo v Apremilast

Number of subjects included in analysis	167
Analysis specification	Pre-specified
Analysis type	superiority[11]
P-value	= 0.0002 [12]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted Difference
Point estimate	29.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	14.9
upper limit	43.9

Notes:

[11] - The confidence interval (CI) is weighted using CMH weights according to the number of participants in the two strata
[12] - The two-sided p-value is from a CMH test stratified by the BMI at screening.

Statistical analysis title	Statistical analysis 2
Comparison groups	Placebo v Etanercept
Number of subjects included in analysis	167
Analysis specification	Pre-specified
Analysis type	superiority[13]
P-value	< 0.0001 [14]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted Difference
Point estimate	49.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	36.9
upper limit	62.7

Notes:

[13] - The confidence interval (CI) is weighted using CMH weights according to the number of participants in the two strata.
[14] - The two-sided p-value is from a CMH test stratified by the BMI at screening.

Secondary: Change from baseline in the Mental Component Summary (MCS) score of the Medical Outcome Study Short Form 36-item (SF-36) Health Survey Version 2.0 in Comparison Between Apremilast and Placebo and Etanercept and Placebo at Week 16

End point title	Change from baseline in the Mental Component Summary (MCS) score of the Medical Outcome Study Short Form 36-item (SF-36) Health Survey Version 2.0 in Comparison Between Apremilast and Placebo and Etanercept and Placebo at Week 16

End point description:

The SF-36 is a 36-item general health status instrument and consists of 8 scales: physical function (PF), role limitations-physical (RP), vitality (VT), general health perceptions (GH), bodily pain (BP), social function (SF), role limitations-emotional (RE), and mental health (MH). Scale scores range from 0 to 100, with higher scores indicating better health. Two overall summary scores were obtained − a Physical Component Summary score (PCS) and a Mental Component Summary score (MCS). Scores from the 8 scales, PCS and MCS were transformed to the norm-based scores using weights from U.S. general population, with higher scores indicating better health. For norm based scores, change from baseline were calculated for the 8 scales and the two summary scales, where change = visit value − baseline value. mITT population consisted of all participants who were randomized and received at least one dose of study drug and had both a baseline PASI and at least one post-treatment PASI evaluation.

End point type	Secondary

End point timeframe: Baseline to Week 16

End point values	Placebo	Apremilast	Etanercept	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	81	80	80	
Units: units on a scale				
least squares mean (confidence interval 95%)	2.6 (0.72 to 4.43)	3.5 (1.62 to 5.38)	4.8 (2.92 to 6.67)	

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Placebo v Apremilast
Number of subjects included in analysis	161
Analysis specification	Pre-specified
Analysis type	superiority[15]
P-value	= 0.7112 [16]
Method	ANCOVA
Parameter estimate	Difference in LS Mean
Point estimate	0.93
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.05
upper limit	3.9

Notes:

[15] - Based on ANCOVA model with treatment and screening BMI category as factors and the baseline value as a covariate.
[16] - Based on ANCOVA model with treatment and screening BMI category as factors and the change from baseline at week 16 value as a covariate.

Statistical analysis title	Statistical analysis 2
Comparison groups	Placebo v Etanercept
Number of subjects included in analysis	161
Analysis specification	Pre-specified
Analysis type	superiority[17]
P-value	= 0.1719 [18]
Method	ANCOVA
Parameter estimate	Difference in LS Mean
Point estimate	2.22
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.75
upper limit	5.19

Notes:

[17] - Based on ANCOVA model with treatment and screening BMI category as factors and the baseline value as a covariate.
[18] - Based on ANCOVA model with treatment and screening BMI category as factors and the change from baseline at week 16 value as a covariate.

Secondary: Percentage of Subjects who achieved a Lattice System Physician's Global Assessment (LS-PGA) score of clear (0) or almost clear at Week 16 in Comparison Between Apremilast and Placebo and Etanercept and Placebo at Week 16

End point title	Percentage of Subjects who achieved a Lattice System Physician's Global Assessment (LS-PGA) score of clear (0) or almost clear at Week 16 in Comparison Between Apremilast and Placebo and Etanercept and Placebo at Week 16

End point description:

The Lattice System Physician's Global Assessment is a global assessment performed by the investigator of psoriasis severity. Integrating ranges of BSA involvement with assessments of overall plaque severity (using a 4 point scale, from none to marked for the signs of plaque elevation, erythema and scale), the LS-PGA produces an overall assessment of psoriasis severity on an 8-point scale, ranging from clear to very severe. To determine the final score, the lattice portion is governed by the BSA and among the plaque qualities, weights plaque elevation as most important, erythema next, and scale least. mITT population consisted of all participants who were randomized and received at least one dose of study drug and had both a baseline PASI and at least one post-treatment PASI evaluation. Missing data imputation: LOCF.

End point type	Secondary

End point timeframe:

Baseline to Week 16

End point values	Placebo	Apremilast	Etanercept	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	84	83	83	
Units: percentage of participants				
number (not applicable)	6	24.1	22.9	

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Placebo v Apremilast
Number of subjects included in analysis	167
Analysis specification	Pre-specified
Analysis type	superiority[19]
P-value	= 0.0011 [20]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted Difference
Point estimate	18.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	7.6
upper limit	28.6

Notes:

[19] - The confidence interval (CI) is weighted using CMH weights according to the number of participants in the two strata.
[20] - The two-sided p-value is from a CMH test stratified by the BMI at screening.

Statistical analysis title	Statistical analysis 2
Comparison groups	Placebo v Etanercept
Number of subjects included in analysis	167
Analysis specification	Pre-specified
Analysis type	superiority[21]
P-value	= 0.0021 [22]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted Difference
Point estimate	16.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	6.5
upper limit	26.9

Notes:

[21] - The confidence interval (CI) is weighted using CMH weights according to the number of participants in the two strata.
[22] - The two-sided p-value is from a CMH test stratified by the BMI at screening.

Secondary: Change from Baseline in Dermatology Life Quality Index (DLQI) Total Score In Comparison Between Apremilast and Placebo and Etanercept and Placebo at Week 16

End point title	Change from Baseline in Dermatology Life Quality Index (DLQI) Total Score In Comparison Between Apremilast and Placebo and Etanercept and Placebo at Week 16

End point description:

DLQI is a simple, compact, and practical questionnaire for use in a dermatology clinical setting to assess limitations related to the impact of skin disease. The instrument contains ten items dealing with the participant's skin. With the exception of Item Number 7, the participant responds on a four-point scale, ranging from "Very Much" (score 3) to "Not at All" or "Not relevant" (score 0). Item Number 7 is a multi-part item, the first part of which ascertains whether the participant's skin prevented them from working or studying (Yes or No, scores 3 or 0 respectively), and if "No," then the participant is asked how much of a problem the skin has been at work or study over the past week, with response alternatives being "A lot," "A little," or "Not at all" (scores 2, 1, or 0 respectively). The DLQI total score is derived by summing all item scores, which has a range of 0 to 30, with 30 corresponding to the worst quality of life, and 0 corresponding to the best. mITT population; LOCF

End point type	Secondary

End point timeframe:

Baseline to Week 16

End point values	Placebo	Apremilast	Etanercept	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	81	79	80	
Units: units on a scale				
least squares mean (confidence interval 95%)	-3.9 (-5.34 to -2.42)	-8.4 (-9.84 to -6.88)	-7.8 (-9.28 to -6.34)	

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Placebo v Apremilast
Number of subjects included in analysis	160
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [23]
Method	ANCOVA
Parameter estimate	Difference in LS Mean
Point estimate	-4.48
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.82
upper limit	-2.14

Notes:

[23] - Based on ANCOVA model with treatment and screening BMI category as factors and the baseline value as a covariate.

Statistical analysis title	Statistical analysis 2
Comparison groups	Placebo v Etanercept
Number of subjects included in analysis	161
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0004 [24]
Method	ANCOVA
Parameter estimate	Difference in LS Mean
Point estimate	-3.94
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.27
upper limit	-1.6

Notes:

[24] - Based on ANCOVA model with treatment and screening BMI category as factors and the baseline value as a covariate.

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

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

End point description:

A TEAE is an 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 of study drug for subjects who discontinued early. An AE is any noxious, unintended, or untoward medical occurrence that may appear or worsen during the study. It may be a new intercurrent illness, a worsening concomitant illness, an injury, or any concomitant impairment of the subjects health, including laboratory test values, regardless of etiology. Any worsening (ie, clinically

significant adverse change in frequency or intensity of a preexisting condition) should be considered an AE. A serious AE (SAE) is any untoward AE that is fatal, life-threatening, results in persistent or significant disability or incapacity, requires or prolongs existing in-patient hospitalization, is a congenital anomaly/birth defect, or is a condition that may jeopardize or may require intervention to prevent one of the outcomes above.

End point type	Secondary

End point timeframe:

Week 0 to Week 16; mean duration of exposure was 14.90 weeks for placebo group, 15.13 weeks for apremilast group and 15.87 weeks for Etanercept group

End point values	Placebo	Apremilast	Etanercept	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	84[25]	83[26]	83[27]	
Units: participants				
Any TEAE	45	59	44	
Any Drug-related TEAE	17	27	21	
Any Severe TEAE	2	3	3	
Any Serious TEAE	0	3	2	
Any Serious Drug-related TEAE	0	2	1	
Any TEAE Leading to Drug Interruption	1	9	3	
Any TEAE Leading to Drug Withdrawal	2	3	2	
Any TEAE Leading to Death	0	0	0	

Notes:

[25] - Safety population = subjects randomized and received at least one dose of study drug

[26] - Safety population = subjects randomized and received at least one dose of study drug

[27] - Safety population = subjects randomized and received at least one dose of study drug

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with TEAEs during the Apremilast-exposure Period

End point title	Number of Subjects with TEAEs during the Apremilast-exposure Period[28]

End point description:

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

End point type	Secondary

End point timeframe:

From the first dose of apremilast (either at Week 0 for subjects originally randomized to apremilast or Week 16 for those originally randomized to placebo or etanercept who were switched to apremilast at week 16) until 28 days after last apremilast dose

Notes:

[28] - 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: No statistical analysis were performed.

End point values	Placebo/Apremilast	Apremilast	Etanercept/Apremilast	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	73	83[29]	79	
Units: participants				
Any TEAE	45	71	54	
Any Drug-related TEAE	23	36	15	
Any Severe TEAE	4	7	7	
Any Serious TEAE	5	6	4	
Any Serious Drug-related TEAE	2	2	1	
Any TEAE Leading to Drug Interruption	8	13	7	
Any TEAE Leading to Drug Withdrawal	3	7	2	
Any TEAE Leading to Death	0	0	0	

Notes:

[29] - From first APR dose at Wk 0 for those randomized to APR or for those first randomized to PBO or ETN

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects who experienced psoriasis flare/rebound in placebo-controlled phase

End point title	Number of subjects who experienced psoriasis flare/rebound in placebo-controlled phase

End point description:

Psoriasis flare is an AE and represents an atypical or unusual worsening of disease during treatment. It is defined as a sudden intensification of psoriasis requiring medical intervention or a diagnosis of new generalized erythrodermic, inflammatory, or pustular psoriasis. Rebound is an AE and is defined as a severe and sudden worsening of disease that occurs after treatment has been discontinued. This exacerbation is characterized by a PASI ≥125% of baseline or a new generalized pustular, erythrodermic, or more inflammatory psoriasis after stopping therapy. Includes safety population.

End point type	Secondary

End point timeframe:

Week 0 to Week 16; Placebo controlled phase

End point values	Placebo	Apremilast	Etanercept	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	84	83	83	
Units: subjects				
Subjects with psoriasis flare	3	1	0	
Any psoriasis rebound captured as TEAE	0	0	0	
Those with PASI ≥125% baseline score and D/C APR	1	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects who experienced psoriasis flare/rebound during the apremilast-exposure period

End point title	Number of subjects who experienced psoriasis flare/rebound during the apremilast-exposure period[30]

End point description:

Psoriasis flare is an AE and represents an atypical or unusual worsening of disease during treatment. It is defined as a sudden intensification of psoriasis requiring medical intervention or a diagnosis of new generalized erythrodermic, inflammatory, or pustular psoriasis. Rebound is an AE and is defined as a severe and sudden worsening of disease that occurs after treatment has been discontinued. This exacerbation is characterized by a PASI ≥125% of baseline or a new generalized pustular, erythrodermic, or more inflammatory psoriasis after stopping therapy. PASI ≥125% of baseline score at any visit after the last dose date for those who discontinued within the phase. Safety population.

End point type	Secondary

End point timeframe:

From the first dose of apremilast (either Week 0 or Week 16 for participants originally randomized to placebo or Etanercept who were switched at Week 16) until 28 days after the last dose of apremilast. Safety population.

Notes:

[30] - 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: No statistical analysis were performed.

End point values	Placebo/Apremilast	Apremilast	Etanercept/Apremilast	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	73	83	79	
Units: subejcts				
Subjects with psoriasis flare	1	4	0	
Subjects with psoriasis rebound	1	2	7	
Those with PASI ≥125% baseline score and D/C APR	0	0	1	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events are reported for the 16-week placebo-controlled period and up to week 104 during the apremilast exposure period for all participants who were randomized or switched to apremilast at any time during the course of the study.

Adverse event reporting additional description:

The mean duration of exposure was 14.90 weeks, 15.13 weeks, and 15.87 weeks for participants randomized to the placebo, apremilast 30 BID, and etanercept 50 mg every week treatment groups, respectively during the placebo controlled phase. The mean duration of exposure to apremilast 30 mg BID during the apremilast exposure period was 69.13 weeks.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	14.0

Reporting groups

Reporting group title	Placebo (week 0-16)

Reporting group description:

Participants received placebo tablets PO BID and 2-1 milliliter (ml) SC saline (placebo) injections QW during the 16-week randomized, double-blind, double-dummy, placebo-controlled phase

Reporting group title	Apremilast plus placebo injection (Week 0-16)

Reporting group description:

Participants received Apremilast 30 mg PO BID plus 2-1ml SC saline (placebo) injections QW during the 16-week randomized, double-blind, double-dummy, placebo-controlled phase

Reporting group title	Etanercept plus placebo tablets (Week 0-16)

Reporting group description:

Participants received etanercept 50 mg by SC injection QW plus placebo tablets PO BID during the 16-week randomized, double-blind, double-dummy, placebo-controlled phase

Reporting group title	Placebo/APR 30mg (Apremilast Exposure Phase) Weeks 16-104

Reporting group description:

Participants received identically matching placebo tablets by mouth (PO), twice a day (BID) and subcutaneous (SC) saline (placebo) injections (1mL x 2 injections SC) weekly (QW) during the 16-week randomized, double-blind, double-dummy, placebo-controlled phase; at week 16, participants were switched to 30 mg Apremilast PO BID and remained on this dose through week 104.

Reporting group title	APR/APR 30 mg (Apremilast Exposure Phase) Weeks 0-104

Reporting group description:

Participants received apremilast 30 mg PO BID plus saline (placebo) injections (1mL x 2 injections SC) QW during the 16-week randomized, double-blind, double-dummy, placebo-controlled phase; at week 16, participants continued on apremilast 30mg PO BID through week 104.

Reporting group title	Etanercept/Apremilast 30mg (Apremilast Exposure Phase) 16-104

Reporting group description:

Participants received etanercept 50 mg by SC injection QW plus placebo tablets PO BID during the 16-week randomized, double-blind, double-dummy, placebo-controlled phase; at week 16, participants were switched to apremilast 30mg PO BID through week 104.

Serious adverse events	Placebo (week 0-16)	Apremilast plus placebo injection (Week 0-16)	Etanercept plus placebo tablets (Week 0-16)
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 84 (0.00%)	3 / 83 (3.61%)	2 / 83 (2.41%)

number of deaths (all causes) number of deaths resulting from adverse events	0	0	0
Vascular disorders Peripheral arterial occlusive disease			
subjects affected / exposed	0 / 84 (0.00%)	0 / 83 (0.00%)	0 / 83 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions Non-cardiac chest pain			
subjects affected / exposed	0 / 84 (0.00%)	0 / 83 (0.00%)	0 / 83 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders Drug Hypersensitivity			
subjects affected / exposed	0 / 84 (0.00%)	0 / 83 (0.00%)	0 / 83 (0.00%)
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 Haemoptysis			
subjects affected / exposed	0 / 84 (0.00%)	0 / 83 (0.00%)	1 / 83 (1.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders Psychotic disorder			
subjects affected / exposed	0 / 84 (0.00%)	0 / 83 (0.00%)	0 / 83 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicidal ideation			
subjects affected / exposed	0 / 84 (0.00%)	0 / 83 (0.00%)	0 / 83 (0.00%)
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 Traumatic intracranial haemorrhage			

subjects affected / exposed	0 / 84 (0.00%)	0 / 83 (0.00%)	0 / 83 (0.00%)
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			
Palpitations			
subjects affected / exposed	0 / 84 (0.00%)	1 / 83 (1.20%)	0 / 83 (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
Atrioventricular block complete			
subjects affected / exposed	0 / 84 (0.00%)	0 / 83 (0.00%)	1 / 83 (1.20%)
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			
Pneumocephalus			
subjects affected / exposed	0 / 84 (0.00%)	0 / 83 (0.00%)	0 / 83 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	0 / 84 (0.00%)	0 / 83 (0.00%)	0 / 83 (0.00%)
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			
Deafness unilateral			
subjects affected / exposed	0 / 84 (0.00%)	0 / 83 (0.00%)	0 / 83 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Haematemesis			
subjects affected / exposed	0 / 84 (0.00%)	1 / 83 (1.20%)	0 / 83 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis erosive			

subjects affected / exposed	0 / 84 (0.00%)	0 / 83 (0.00%)	0 / 83 (0.00%)
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			
Cholelithiasis			
subjects affected / exposed	0 / 84 (0.00%)	0 / 83 (0.00%)	0 / 83 (0.00%)
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 / 84 (0.00%)	0 / 83 (0.00%)	0 / 83 (0.00%)
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			
Pneumonia			
subjects affected / exposed	0 / 84 (0.00%)	1 / 83 (1.20%)	1 / 83 (1.20%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 84 (0.00%)	1 / 83 (1.20%)	0 / 83 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abscess intestinal			
subjects affected / exposed	0 / 84 (0.00%)	0 / 83 (0.00%)	0 / 83 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis perforated			
subjects affected / exposed	0 / 84 (0.00%)	0 / 83 (0.00%)	0 / 83 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Salpingitis			
subjects affected / exposed	0 / 84 (0.00%)	0 / 83 (0.00%)	0 / 83 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Salpingo-oophoritis			
subjects affected / exposed	0 / 84 (0.00%)	0 / 83 (0.00%)	0 / 83 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mastoiditis			
subjects affected / exposed	0 / 84 (0.00%)	0 / 83 (0.00%)	0 / 83 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anogenital warts			
subjects affected / exposed	0 / 84 (0.00%)	0 / 83 (0.00%)	0 / 83 (0.00%)
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	Placebo/APR 30mg (Apremilast Exposure Phase) Weeks 16-104	APR/APR 30 mg (Apremilast Exposure Phase) Weeks 0-104	Etanercept/Apremilast 30mg (Apremilast Exposure Phase) 16-104
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 73 (6.85%)	6 / 83 (7.23%)	4 / 79 (5.06%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Vascular disorders			
Peripheral arterial occlusive disease			
subjects affected / exposed	0 / 73 (0.00%)	0 / 83 (0.00%)	1 / 79 (1.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Non-cardiac chest pain			
subjects affected / exposed	1 / 73 (1.37%)	0 / 83 (0.00%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Drug Hypersensitivity			
subjects affected / exposed	0 / 73 (0.00%)	1 / 83 (1.20%)	0 / 79 (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, thoracic and mediastinal disorders			

Haemoptysis			
subjects affected / exposed	0 / 73 (0.00%)	0 / 83 (0.00%)	0 / 79 (0.00%)
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			
Psychotic disorder			
subjects affected / exposed	1 / 73 (1.37%)	0 / 83 (0.00%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicidal ideation			
subjects affected / exposed	1 / 73 (1.37%)	0 / 83 (0.00%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Traumatic intracranial haemorrhage			
subjects affected / exposed	1 / 73 (1.37%)	0 / 83 (0.00%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Palpitations			
subjects affected / exposed	0 / 73 (0.00%)	1 / 83 (1.20%)	0 / 79 (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
Atrioventricular block complete			
subjects affected / exposed	0 / 73 (0.00%)	0 / 83 (0.00%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Pneumocephalus			
subjects affected / exposed	1 / 73 (1.37%)	0 / 83 (0.00%)	0 / 79 (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
Syncope			

subjects affected / exposed	1 / 73 (1.37%)	0 / 83 (0.00%)	0 / 79 (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			
Deafness unilateral			
subjects affected / exposed	0 / 73 (0.00%)	0 / 83 (0.00%)	1 / 79 (1.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Haematemesis			
subjects affected / exposed	0 / 73 (0.00%)	1 / 83 (1.20%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis erosive			
subjects affected / exposed	0 / 73 (0.00%)	1 / 83 (1.20%)	0 / 79 (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			
Cholelithiasis			
subjects affected / exposed	1 / 73 (1.37%)	0 / 83 (0.00%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Calculus ureteric			
subjects affected / exposed	0 / 73 (0.00%)	0 / 83 (0.00%)	1 / 79 (1.27%)
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			
Pneumonia			
subjects affected / exposed	0 / 73 (0.00%)	1 / 83 (1.20%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			

subjects affected / exposed	0 / 73 (0.00%)	1 / 83 (1.20%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abscess intestinal			
subjects affected / exposed	0 / 73 (0.00%)	0 / 83 (0.00%)	1 / 79 (1.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis perforated			
subjects affected / exposed	0 / 73 (0.00%)	0 / 83 (0.00%)	1 / 79 (1.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Salpingitis			
subjects affected / exposed	0 / 73 (0.00%)	0 / 83 (0.00%)	1 / 79 (1.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Salpingo-oophoritis			
subjects affected / exposed	0 / 73 (0.00%)	0 / 83 (0.00%)	1 / 79 (1.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mastoiditis			
subjects affected / exposed	0 / 73 (0.00%)	1 / 83 (1.20%)	0 / 79 (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
Anogenital warts			
subjects affected / exposed	1 / 73 (1.37%)	0 / 83 (0.00%)	0 / 79 (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

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

Non-serious adverse events	Placebo (week 0-16)	Apremilast plus placebo injection (Week 0-16)	Etanercept plus placebo tablets (Week 0-16)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	25 / 84 (29.76%)	41 / 83 (49.40%)	27 / 83 (32.53%)
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 84 (3.57%)	11 / 83 (13.25%)	5 / 83 (6.02%)
occurrences (all)	5	11	6
Tension Headache			
subjects affected / exposed	4 / 84 (4.76%)	5 / 83 (6.02%)	3 / 83 (3.61%)
occurrences (all)	6	7	3
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	1 / 84 (1.19%)	9 / 83 (10.84%)	4 / 83 (4.82%)
occurrences (all)	1	11	4
Diarrhoea			
subjects affected / exposed	3 / 84 (3.57%)	9 / 83 (10.84%)	1 / 83 (1.20%)
occurrences (all)	5	11	1
Toothache			
subjects affected / exposed	1 / 84 (1.19%)	4 / 83 (4.82%)	2 / 83 (2.41%)
occurrences (all)	1	4	3
Vomiting			
subjects affected / exposed	2 / 84 (2.38%)	4 / 83 (4.82%)	2 / 83 (2.41%)
occurrences (all)	2	4	2
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	3 / 84 (3.57%)	3 / 83 (3.61%)	4 / 83 (4.82%)
occurrences (all)	3	3	5
Oropharyngeal pain			
subjects affected / exposed	0 / 84 (0.00%)	4 / 83 (4.82%)	1 / 83 (1.20%)
occurrences (all)	0	5	1
Bronchitis			
subjects affected / exposed	0 / 84 (0.00%)	2 / 83 (2.41%)	1 / 83 (1.20%)
occurrences (all)	0	2	2
Skin and subcutaneous tissue disorders			
Psoriasis			

subjects affected / exposed	3 / 84 (3.57%)	1 / 83 (1.20%)	0 / 83 (0.00%)
occurrences (all)	3	1	0
Rebound psoriasis			
subjects affected / exposed	0 / 84 (0.00%)	0 / 83 (0.00%)	0 / 83 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 84 (2.38%)	3 / 83 (3.61%)	3 / 83 (3.61%)
occurrences (all)	2	3	4
Pain in extremity			
subjects affected / exposed	2 / 84 (2.38%)	2 / 83 (2.41%)	1 / 83 (1.20%)
occurrences (all)	3	2	1
Psoriatic arthropathy			
subjects affected / exposed	2 / 84 (2.38%)	4 / 83 (4.82%)	0 / 83 (0.00%)
occurrences (all)	5	4	0
Infections and infestations			
Upper Respiratory Tract Infection			
subjects affected / exposed	2 / 84 (2.38%)	6 / 83 (7.23%)	2 / 83 (2.41%)
occurrences (all)	2	6	2
Nasopharyngitis			
subjects affected / exposed	8 / 84 (9.52%)	4 / 83 (4.82%)	8 / 83 (9.64%)
occurrences (all)	10	6	12
Rhinitis			
subjects affected / exposed	1 / 84 (1.19%)	4 / 83 (4.82%)	4 / 83 (4.82%)
occurrences (all)	1	4	5
Sinusitis			
subjects affected / exposed	1 / 84 (1.19%)	0 / 83 (0.00%)	3 / 83 (3.61%)
occurrences (all)	1	0	3

Non-serious adverse events	Placebo/APR 30mg (Apremilast Exposure Phase) Weeks 16-104	APR/APR 30 mg (Apremilast Exposure Phase) Weeks 0-104	Etanercept/Apremilast 30mg (Apremilast Exposure Phase) 16-104
Total subjects affected by non-serious adverse events			
subjects affected / exposed	30 / 73 (41.10%)	52 / 83 (62.65%)	32 / 79 (40.51%)
Nervous system disorders			
Headache			

subjects affected / exposed	5 / 73 (6.85%)	12 / 83 (14.46%)	3 / 79 (3.80%)
occurrences (all)	6	13	6
Tension Headache			
subjects affected / exposed	3 / 73 (4.11%)	5 / 83 (6.02%)	1 / 79 (1.27%)
occurrences (all)	3	7	1
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	5 / 73 (6.85%)	12 / 83 (14.46%)	5 / 79 (6.33%)
occurrences (all)	7	14	6
Diarrhoea			
subjects affected / exposed	13 / 73 (17.81%)	12 / 83 (14.46%)	6 / 79 (7.59%)
occurrences (all)	15	15	7
Toothache			
subjects affected / exposed	2 / 73 (2.74%)	5 / 83 (6.02%)	0 / 79 (0.00%)
occurrences (all)	3	5	0
Vomiting			
subjects affected / exposed	3 / 73 (4.11%)	6 / 83 (7.23%)	2 / 79 (2.53%)
occurrences (all)	3	6	2
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 73 (1.37%)	6 / 83 (7.23%)	2 / 79 (2.53%)
occurrences (all)	1	6	2
Oropharyngeal pain			
subjects affected / exposed	1 / 73 (1.37%)	5 / 83 (6.02%)	0 / 79 (0.00%)
occurrences (all)	1	7	0
Bronchitis			
subjects affected / exposed	1 / 73 (1.37%)	6 / 83 (7.23%)	1 / 79 (1.27%)
occurrences (all)	1	6	1
Skin and subcutaneous tissue disorders			
Psoriasis			
subjects affected / exposed	2 / 73 (2.74%)	5 / 83 (6.02%)	0 / 79 (0.00%)
occurrences (all)	2	5	0
Rebound psoriasis			
subjects affected / exposed	1 / 73 (1.37%)	2 / 83 (2.41%)	7 / 79 (8.86%)
occurrences (all)	1	2	7
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	4 / 73 (5.48%)	6 / 83 (7.23%)	3 / 79 (3.80%)
occurrences (all)	4	8	4
Pain in extremity			
subjects affected / exposed	1 / 73 (1.37%)	4 / 83 (4.82%)	4 / 79 (5.06%)
occurrences (all)	1	5	5
Psoriatic arthropathy			
subjects affected / exposed	3 / 73 (4.11%)	6 / 83 (7.23%)	1 / 79 (1.27%)
occurrences (all)	4	7	3
Infections and infestations			
Upper Respiratory Tract Infection			
subjects affected / exposed	5 / 73 (6.85%)	9 / 83 (10.84%)	1 / 79 (1.27%)
occurrences (all)	5	13	1
Nasopharyngitis			
subjects affected / exposed	4 / 73 (5.48%)	5 / 83 (6.02%)	5 / 79 (6.33%)
occurrences (all)	5	11	8
Rhinitis			
subjects affected / exposed	1 / 73 (1.37%)	6 / 83 (7.23%)	2 / 79 (2.53%)
occurrences (all)	1	6	2
Sinusitis			
subjects affected / exposed	0 / 73 (0.00%)	1 / 83 (1.20%)	5 / 79 (6.33%)
occurrences (all)	0	1	5

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported