



Clinical trial results:

A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Efficacy and Safety Study of Apremilast (CC-10004) in Subjects with Moderate to Severe Plaque Psoriasis

Summary

EudraCT number	2010-019992-30
Trial protocol	AT ES DE DK IT
Global end of trial date	30 November 2016

Results information

Result version number	v1 (current)
This version publication date	17 December 2017
First version publication date	17 December 2017

Trial information

Trial identification

Sponsor protocol code	CC-10004-PSOR-009
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01232283
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Celgene Corporation
Sponsor organisation address	86 Morris Avenue, Summit, United States, 07901
Public contact	Clinical Trial Disclosure, Celgene Corporation, 01 888-260-1599, ClinicalTrialDisclosure@Celgene.com
Scientific contact	Weimin Wendy Zhang, Celgene Corporation, 01 908-514-9788, weizhang@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	03 June 2017
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	30 November 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to evaluate the clinical efficacy of apremilast 30 mg BID, compared with placebo, in subjects with moderate to severe plaque psoriasis.

Protection of trial subjects:

Patient Confidentiality, Personal Data Protection

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	30 November 2010
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	4 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 206
Country: Number of subjects enrolled	Canada: 92
Country: Number of subjects enrolled	Austria: 6
Country: Number of subjects enrolled	Denmark: 4
Country: Number of subjects enrolled	France: 22
Country: Number of subjects enrolled	Germany: 52
Country: Number of subjects enrolled	Italy: 5
Country: Number of subjects enrolled	Spain: 17
Country: Number of subjects enrolled	Switzerland: 7
Worldwide total number of subjects	411
EEA total number of subjects	106

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)	375
From 65 to 84 years	36
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 46 study centers in 9 countries.

Pre-assignment

Screening details:

Subjects were eligible who had moderate to severe plaque psoriasis.

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

Blinding implementation details:

Treatment assignment blinding remained in effect; the blind was broken when all subjects completed their week 52 visit

Arms

Are arms mutually exclusive?	Yes
Arm title	Apremilast

Arm description:

Participants initially randomized to apremilast (APR) 30 mg tablets twice daily (BID) during the Placebo-controlled Phase (Weeks 0-16)

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

Dosage and administration details:

Apremilast 30 mg tablets BID during the Placebo-controlled Phase (Weeks 0-16)

Arm title	Placebo
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Arm description:

Participants initially randomized to identically matching placebo tablets (PBO) BID during the Placebo controlled Phase (Weeks 0-16)

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:

Placebo (identically-matching) tablets BID during the Placebo-controlled Phase (Weeks 0-16).

Number of subjects in period 1	Apremilast	Placebo
Started	274	137
Received apremilast	272	136
Completed	239	112
Not completed	35	25
Consent withdrawn by subject	9	7
Adverse event, non-fatal	12	8
Not specified	2	1
Noncompliance with study drug	1	-
Lost to follow-up	6	6
Lack of efficacy	3	2
Protocol deviation	2	1

Period 2

Period 2 title	Maintenance Phase (Weeks 16-32)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Assessor

Blinding implementation details:

Treatment assignment blinding remained in effect; the blind was broken when all subjects completed their week 52 visit

Arms

Are arms mutually exclusive?	Yes
Arm title	Apremilast-Apremilast

Arm description:

Participants who were initially randomized to apremilast 30 mg tablets BID during the Placebo-controlled Phase (Weeks 0-16) remained on apremilast 30 mg BID during the Maintenance Phase (Weeks 16-32).

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

Dosage and administration details:

Apremilast 30 mg tablets BID during the Maintenance Phase (Weeks 16-32)

Arm title	Placebo-Apremilast
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Arm description:

Participants who were initially randomized to placebo tablets BID during the Placebo-controlled Phase (Weeks 0-16) were switched after 16 weeks of treatment to apremilast 30 mg BID and continued dosing with apremilast 30 mg BID during the Maintenance Phase (Weeks 16-32)

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

Dosage and administration details:

Apremilast 30 mg tablets BID during the Maintenance Phase (Weeks 16-32)

Number of subjects in period 2^[1]	Apremilast-Apremilast	Placebo-Apremilast
Started	234	108
Completed	194	100
Not completed	40	8
Consent withdrawn by subject	7	1
Adverse event, non-fatal	8	2
Non-compliance with study drug	1	-
Unspecified	2	-
Lost to follow-up	3	2
Lack of efficacy	19	3

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: The Study PSOR-009 protocol allowed subjects to withdraw from the clinical trial at any time. Of the 351 subjects who completed the Placebo-controlled Phase, 9 subjects withdrew from the study for diverse reasons including adverse events, protocol violations and withdrawal by subject.

Consequently, a total of 342 subjects entered the Maintenance Phase of the trial.

Period 3

Period 3 title	Randomized Withdrawal Phase(Weeks 32-52)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Assessor

Blinding implementation details:

Treatment assignment blinding remained in effect; the blind was broken when all subjects completed their 52 week visit

Arms

Are arms mutually exclusive?	Yes
Arm title	APR-APR-Re-randomized to PBO

Arm description:

Participants who were initially randomized to apremilast 30 mg BID during the 16-week Placebo-controlled Phase continued dosing with apremilast 30 mg BID through the Maintenance Phase (Weeks 16-32). At week 32, those participants who were considered responders (ie, having a \geq PASI-50 response) were re-randomized to placebo during the Randomized Withdrawal Phase (Weeks 32-52). Those participants who lost PASI-50 response achieved at Week 32, were switched back to apremilast 30 mg BID at the time the loss was observed. Those participants who did not lose at least 50% of the PASI response remained on placebo until Week 52. All participants who completed the Randomized Withdrawal Phase at Week 52 were eligible to participate in the Long-term Extension Phase from Weeks 52-260 and received apremilast 30 mg BID for the remainder of their participation.

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

Dosage and administration details:

Placebo (identically-matching) tablets BID during the Randomized Withdrawal Phase (Weeks 32-52).

Arm title	APR-APR Re-randomized to APR
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Arm description:

Participants who were initially randomized to apremilast 30 mg tablets BID during the 16-week Placebo-controlled Phase continued dosing with apremilast 30 mg BID through the Maintenance Phase (Weeks 16-32). At week 32, those participants who were considered responders (ie, having a \geq PASI-50 response) were re-randomized to apremilast during the Randomized Withdrawal Phase (Weeks 32-52). Those participants who completed the Randomized Withdrawal Phase at Week 52 were eligible to participate in the Long-term Extension Phase from Weeks 52-260 and continued on APR 30 mg BID for the remainder of their participation.

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

Dosage and administration details:

Apremilast 30 mg tablets BID during the Randomized Withdrawal Phase (Weeks 32-52)

Arm title	APR-APR-APR + optional topicals/phototherapy
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Arm description:

Participants who were initially randomized to apremilast 30 mg BID during the 16-week Placebo-controlled Phase continued dosing with apremilast 30 mg BID through the Maintenance Phase (Weeks 16-32). At Week 32, those participants who were considered non-responders (ie, having a response of $<$ PASI-50), remained on apremilast 30 mg BID and were given the option of adding topical therapies and/or phototherapy to their regimen. A subset of these non-responders received additional topicals or phototherapy. Those participants who completed the Randomized Withdrawal Phase at Week 52 were eligible to participate in the Long-term Extension Phase from Weeks 52-260 and continued on apremilast 30 mg BID for the remainder of their participation.

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

Dosage and administration details:

Apremilast 30 mg tablets BID during the Randomized Withdrawal Phase (Weeks 32-52)

Arm title	PBO-APR-APR + optional topicals/phototherapy
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Arm description:

Participants who were initially randomized to placebo BID during the 16-week Placebo-controlled Phase (Weeks 0-16) were switched after 16 weeks of treatment to apremilast 30 mg BID and continued dosing with apremilast 30 mg BID during the Maintenance Phase (Weeks 16-32). At week 32, all participants were to maintain apremilast 30 mg BID; those who were non-responders (having a response of $<$ PASI-50), remained on apremilast 30 mg BID and were given the option of adding topical therapies and/or phototherapy to their regimen. A subset of these non-responders received additional topical or phototherapy. All participants who completed the Randomized Withdrawal Phase at week 52 were eligible to participate in the Long-term Extension Phase from Weeks 52-260 and continued on apremilast 30 mg BID for the remainder of their participation.

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

Dosage and administration details:

Apremilast 30 mg tablets BID during the Randomized Withdrawal Phase (Weeks 32-52)

Number of subjects in period 3 ^[2]	APR-APR-Re-randomized to PBO	APR-APR Re-randomized to APR	APR-APR-APR + optional topicals/phototherapy
Started	62	61	58
Treated with APR+ topicals/phototherapy	0 ^[3]	0 ^[4]	28 ^[5]
Completed	50	56	41
Not completed	12	5	17
Adverse event, serious fatal	1	-	-
Consent withdrawn by subject	3	3	3
Adverse event, non-fatal	2	1	-
Unspecified	-	1	-
Lost to follow-up	2	-	1
Lack of efficacy	4	-	13
Protocol deviation	-	-	-

Number of subjects in period 3 ^[2]	PBO-APR-APR + optional topicals/phototherapy
Started	96
Treated with APR+ topicals/phototherapy	17 ^[6]
Completed	84
Not completed	12
Adverse event, serious fatal	-
Consent withdrawn by subject	4
Adverse event, non-fatal	1
Unspecified	-
Lost to follow-up	1
Lack of efficacy	5
Protocol deviation	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: The Study PSOR-009 protocol allowed subjects to withdraw from the clinical trial at any time. Of the 294 subjects who completed the Maintenance Phase, 17 subjects withdrew from the study

for diverse reasons including lack of efficacy and withdrawal by subject. Consequently, a total of 277 subjects entered the Randomized Withdrawal Phase of the trial.

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

Justification: Of the 123 subjects who were originally randomized to APR and who achieved a PASI-75 response at Week 32, 62 subjects were re-randomized to placebo and 50 subjects in this group completed the Randomized Withdrawal Phase. Subjects in this treatment group were not permitted to receive topical and/or phototherapy during the Randomization Withdrawal Phase.

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

Justification: Of the 123 subjects who were originally randomized to APR and who achieved a PASI-75 response at Week 32, 61 subjects were re-randomized to APR and 56 subjects in this group completed the Randomized Withdrawal Phase. Subjects in this treatment group were not permitted to receive topical and/or phototherapy during the Randomization Withdrawal Phase.

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

Justification: Of the 194 subjects who were originally randomized to APR and completed the Maintenance Phase, 13 withdrew from the study for diverse reasons including lack of efficacy and withdrawal by subject. Consequently, a total of 181 subjects entered the Randomized Withdrawal Phase. Among them, 123 subjects were re-randomized (62 to PBO, 61 to APR) and 58 subjects entered this arm. Of the 58 subjects, 28 were treated with topicals and/or phototherapy, and 30 did not receive topical and/or phototherapy

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

Justification: Of the 100 subjects who were originally randomized to PBO, switched to APR and completed the Maintenance Phase with APR, 4 subjects withdrew from the study for diverse reasons including lack of efficacy and withdrawal by subject. Consequently, a total of 96 subjects entered the Randomization Withdrawal Phase of the trial. Of the 96 subjects in the PBO-APR-APR arm, 17 subjects were treated with topical therapy and/or phototherapy, and 79 subjects did not receive topical and/or phototherapy.

Period 4

Period 4 title	Long-Term Extension Phase (Weeks 52-260)
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Apremilast (Long-Term Extension Phase)

Arm description:

Participants who were initially randomized to APR 30 mg BID during the 16-week placebo-controlled phase (Weeks 0-16) continued receiving APR 30 mg BID through the Maintenance Phase (weeks 16-32) and apremilast 30 mg tablets or placebo during the Randomized Withdrawal Phase were eligible to participate in the Long-term Extension Phase from Weeks 52-260 and remained on APR 30 mg BID for the remainder of their participation.

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

Dosage and administration details:

Apremilast 30 mg tablets BID during the Long-Term Extension Phase (Weeks 52-260)

Arm title	Placebo-Apremilast (Long-term extension)
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Arm description:

Participants who were initially randomized to identically matching placebo BID during the Placebo-controlled Phase (Weeks 0-16) were switched at Week 16 to apremilast 30 mg BID during the

Maintenance Phase, received apremilast 30 mg PO BID during the Randomized Withdrawal Phase and then continued to receive apremilast 30 mg tablets BID in the long-term extension phase from weeks 52-260.

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

Dosage and administration details:

Apremilast 30 mg tablets BID during the Long-term Extension Phase (Weeks 50-260)

Number of subjects in period 4^[7]	Apremilast (Long-Term Extension Phase)	Placebo-Apremilast (Long-term extension)
Started	137	80
Completed	29	19
Not completed	108	61
Adverse event, serious fatal	1	-
Consent withdrawn by subject	30	14
Adverse event, non-fatal	11	6
Miscellaneous	7	3
Non-compliance	3	2
Lost to follow-up	9	6
Lack of efficacy	46	30
Protocol deviation	1	-

Notes:

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

Justification: The Study PSOR-009 protocol allowed subjects to withdraw from the clinical trial at any time. Of the 231 subjects who completed the Randomized Withdrawal Phase, 14 subjects withdrew from the study for diverse reasons including adverse events, lack of efficacy, non-compliance and withdrawal by subject. Consequently, a total of 217 subjects entered the Long-Term Extension of the trial.

Baseline characteristics

Reporting groups

Reporting group title	Apremilast
Reporting group description:	
Participants initially randomized to apremilast (APR) 30 mg tablets twice daily (BID) during the Placebo-controlled Phase (Weeks 0-16)	
Reporting group title	Placebo
Reporting group description:	
Participants initially randomized to identically matching placebo tablets (PBO) BID during the Placebo controlled Phase (Weeks 0-16)	

Reporting group values	Apremilast	Placebo	Total
Number of subjects	274	137	411
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	252	123	375
From 65-84 years	22	14	36
85 years and over	0	0	0
Age Continuous			
Units: years			
arithmetic mean	45.3	45.7	-
standard deviation	± 13.05	± 13.38	-
Gender, Male/Female			
Units: Subjects			
Female	98	37	135
Male	176	100	276
Race/Ethnicity, Customized			
Units: Subjects			
American Indian or Alaska Native	1	1	2
Asian	8	6	14
Black or African American	13	2	15
Native Hawaiian or Other Pacific Islander	1	0	1
White	250	128	378
Other-not specified	1	0	1
Study Specific Characteristic Duration of Plaque Psoriasis			
All participants enrolled were required to have a diagnosis of plaque psoriasis at least 12 months prior to screening, but the duration was not required for enrollment. Overall baseline population for duration of plaque psoriasis in the apremilast arm were 271 participants and 135 for those in the placebo arm.			
Units: years			
arithmetic mean	17.94	18.68	

standard deviation	± 11.367	± 12.088	-
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Subject analysis sets

Subject analysis set title	APR: Subjects with TEAEs during the APR-Exposure Phase
Subject analysis set type	Safety analysis

Subject analysis set description:

The Apremilast-exposure Period started on the date of the first dose of apremilast (Week 0 for participants originally randomized to apremilast or Week 16 for participants originally randomized to placebo) to the last dose of apremilast. Adverse events that started after 28 days of initiating placebo and before resuming apremilast treatment in the Randomized Treatment Withdrawal Phase (Weeks 32 to 52) were excluded in the Apremilast-exposure phase. A serious AE (SAE) is any untoward adverse event that is fatal, life-threatening, results in persistent or significant disability or incapacity, requires or prolongs existing in-patient hospitalization, is a congenital anomaly or birth defect, or a condition that may jeopardize the patient or may require intervention to prevent one of the outcomes listed above. An AE is a treatment emergent AE if the AE start date is on or after the date of the first dose of study drug and no later than 28 days after the last dose.

Subject analysis set title	APR: Subjects with Psoriasis Flare in the APR-Exposure Phase
Subject analysis set type	Safety analysis

Subject analysis set description:

Psoriasis flare was defined as a sudden intensification of psoriasis requiring medical intervention, or a diagnosis of new generalized erythrodermic, inflammatory, or pustular psoriasis. Rebound is defined as a severe and sudden worsening of disease that occurs after treatment has been discontinued. Note categories below. [1] Psoriasis adverse events (ie, preferred term as Guttate psoriasis, Psoriasis, Pustular psoriasis) started on or after the first dose date and on or before the last dose date within the phase. [2] Psoriasis adverse events (ie, preferred term as Guttate psoriasis, Psoriasis, Pustular psoriasis, Rebound psoriasis) started after the last dose date for participants who discontinued within the phase. [3] PASI ≥ 125% of baseline score at any visit after the last dose date for participants who discontinued within the phase and were not included in [1] and/or [2].

Reporting group values	APR: Subjects with TEAEs during the APR-Exposure Phase	APR: Subjects with Psoriasis Flare in the APR-Exposure Phase	
Number of subjects	380	380	
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age Continuous Units: years			
arithmetic mean	45.3	45.7	
standard deviation	± 13.05	± 13.38	
Gender, Male/Female Units: Subjects			
Female			
Male			

Race/Ethnicity, Customized Units: Subjects			
American Indian or Alaska Native Asian Black or African American Native Hawaiian or Other Pacific Islander White Other-not specified			
Study Specific Characteristic Duration of Plaque Psoriasis			
All participants enrolled were required to have a diagnosis of plaque psoriasis at least 12 months prior to screening, but the duration was not required for enrollment. Overall baseline population for duration of plaque psoriasis in the apremilast arm were 271 participants and 135 for those in the placebo arm.			
Units: years			
arithmetic mean	17.94	18.68	
standard deviation	± 11.37	± 12.088	

End points

End points reporting groups

Reporting group title	Apremilast
Reporting group description: Participants initially randomized to apremilast (APR) 30 mg tablets twice daily (BID) during the Placebo-controlled Phase (Weeks 0-16)	
Reporting group title	Placebo
Reporting group description: Participants initially randomized to identically matching placebo tablets (PBO) BID during the Placebo controlled Phase (Weeks 0-16)	
Reporting group title	Apremilast-Apremilast
Reporting group description: Participants who were initially randomized to apremilast 30 mg tablets BID during the Placebo-controlled Phase (Weeks 0-16) remained on apremilast 30 mg BID during the Maintenance Phase (Weeks 16-32).	
Reporting group title	Placebo-Apremilast
Reporting group description: Participants who were initially randomized to placebo tablets BID during the Placebo-controlled Phase (Weeks 0-16) were switched after 16 weeks of treatment to apremilast 30 mg BID and continued dosing with apremilast 30 mg BID during the Maintenance Phase (Weeks 16-32)	
Reporting group title	APR-APR-Re-randomized to PBO
Reporting group description: Participants who were initially randomized to apremilast 30 mg BID during the 16-week Placebo-controlled Phase continued dosing with apremilast 30 mg BID through the Maintenance Phase (Weeks 16-32). At week 32, those participants who were considered responders (ie, having a \geq PASI-50 response) were re-randomized to placebo during the Randomized Withdrawal Phase (Weeks 32-52). Those participants who lost PASI-50 response achieved at Week 32, were switched back to apremilast 30 mg BID at the time the loss was observed. Those participants who did not lose at least 50% of the PASI response remained on placebo until Week 52. All participants who completed the Randomized Withdrawal Phase at Week 52 were eligible to participate in the Long-term Extension Phase from Weeks 52-260 and received apremilast 30 mg BID for the remainder of their participation.	
Reporting group title	APR-APR Re-randomized to APR
Reporting group description: Participants who were initially randomized to apremilast 30 mg tablets BID during the 16-week Placebo-controlled Phase continued dosing with apremilast 30 mg BID through the Maintenance Phase (Weeks 16-32). At week 32, those participants who were considered responders (ie, having a \geq PASI-50 response) were re-randomized to apremilast during the Randomized Withdrawal Phase (Weeks 32-52). Those participants who completed the Randomized Withdrawal Phase at Week 52 were eligible to participate in the Long-term Extension Phase from Weeks 52-260 and continued on APR 30 mg BID for the remainder of their participation.	
Reporting group title	APR-APR-APR + optional topicals/phototherapy
Reporting group description: Participants who were initially randomized to apremilast 30 mg BID during the 16-week Placebo-controlled Phase continued dosing with apremilast 30 mg BID through the Maintenance Phase (Weeks 16-32). At Week 32, those participants who were considered non-responders (ie, having a response of $<$ PASI-50), remained on apremilast 30 mg BID and were given the option of adding topical therapies and/or phototherapy to their regimen. A subset of these non-responders received additional topicals or phototherapy. Those participants who completed the Randomized Withdrawal Phase at Week 52 were eligible to participate in the Long-term Extension Phase from Weeks 52-260 and continued on apremilast 30 mg BID for the remainder of their participation.	
Reporting group title	PBO-APR-APR + optional topicals/phototherapy
Reporting group description: Participants who were initially randomized to placebo BID during the 16-week Placebo-controlled Phase (Weeks 0-16) were switched after 16 weeks of treatment to apremilast 30 mg BID and continued dosing with apremilast 30 mg BID during the Maintenance Phase (Weeks 16-32). At week 32, all participants were to maintain apremilast 30 mg BID; those who were non-responders (having a response of $<$ PASI-50), remained on apremilast 30 mg BID and were given the option of adding topical therapies and/or phototherapy to their regimen. A subset of these non-responders received additional topical or phototherapy. All participants who completed the Randomized Withdrawal Phase at week 52 were eligible to participate in the Long-term Extension Phase from Weeks 52-260 and continued on apremilast	

30 mg BID for the remainder of their participation.

Reporting group title	Apremilast (Long-Term Extension Phase)
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Reporting group description:

Participants who were initially randomized to APR 30 mg BID during the 16-week placebo-controlled phase (Weeks 0-16) continued receiving APR 30 mg BID through the Maintenance Phase (weeks 16-32) and apremilast 30 mg tablets or placebo during the Randomized Withdrawal Phase were eligible to participate in the Long-term Extension Phase from Weeks 52-260 and remained on APR 30 mg BID for the remainder of their participation.

Reporting group title	Placebo-Apremilast (Long-term extension)
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Reporting group description:

Participants who were initially randomized to identically matching placebo BID during the Placebo-controlled Phase (Weeks 0-16) were switched at Week 16 to apremilast 30 mg BID during the Maintenance Phase, received apremilast 30 mg PO BID during the Randomized Withdrawal Phase and then continued to receive apremilast 30 mg tablets BID in the long-term extension phase from weeks 52-260.

Subject analysis set title	APR: Subjects with TEAEs during the APR-Exposure Phase
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Subject analysis set type	Safety analysis
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Subject analysis set description:

The Apremilast-exposure Period started on the date of the first dose of apremilast (Week 0 for participants originally randomized to apremilast or Week 16 for participants originally randomized to placebo) to the last dose of apremilast. Adverse events that started after 28 days of initiating placebo and before resuming apremilast treatment in the Randomized Treatment Withdrawal Phase (Weeks 32 to 52) were excluded in the Apremilast-exposure phase. A serious AE (SAE) is any untoward adverse event that is fatal, life-threatening, results in persistent or significant disability or incapacity, requires or prolongs existing in-patient hospitalization, is a congenital anomaly or birth defect, or a condition that may jeopardize the patient or may require intervention to prevent one of the outcomes listed above. An AE is a treatment emergent AE if the AE start date is on or after the date of the first dose of study drug and no later than 28 days after the last dose.

Subject analysis set title	APR: Subjects with Psoriasis Flare in the APR-Exposure Phase
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Subject analysis set type	Safety analysis
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Subject analysis set description:

Psoriasis flare was defined as a sudden intensification of psoriasis requiring medical intervention, or a diagnosis of new generalized erythrodermic, inflammatory, or pustular psoriasis. Rebound is defined as a severe and sudden worsening of disease that occurs after treatment has been discontinued. Note categories below. [1] Psoriasis adverse events (ie, preferred term as Guttate psoriasis, Psoriasis, Pustular psoriasis) started on or after the first dose date and on or before the last dose date within the phase. [2] Psoriasis adverse events (ie, preferred term as Guttate psoriasis, Psoriasis, Pustular psoriasis, Rebound psoriasis) started after the last dose date for participants who discontinued within the phase. [3] PASI \geq 125% of baseline score at any visit after the last dose date for participants who discontinued within the phase and were not included in [1] and/or [2].

Primary: Percentage of participants Who Achieved at least a 75% improvement (response) in the Psoriasis Area Severity Index (PASI-75) at Week 16 from Baseline

End point title	Percentage of participants Who Achieved at least a 75% improvement (response) in the Psoriasis Area Severity Index (PASI-75) at Week 16 from Baseline
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End point description:

PASI-75 response is the percentage of subjects who achieved at least a 75% reduction (improvement) from baseline in PASI score at week 16. The PASI is 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). Full Analysis Set (FAS) consisted of all subjects who were randomized per protocol. Subjects were included in the treatment group in which they were randomized. Last observation carried forward.

End point type	Primary
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End point timeframe:

Baseline to Week 16

End point values	Apremilast	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	274	137		
Units: percentage of participants				
number (not applicable)	28.8	5.8		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Apremilast v Placebo
Number of subjects included in analysis	411
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Chi-squared
Parameter estimate	Risk difference (RD)
Point estimate	23
Confidence interval	
level	95 %
sides	2-sided
lower limit	16.3
upper limit	29.6

Secondary: Percentage of Participants who Achieved a Static Physician Global Assessment (sPGA) Score of Clear (0) or Almost Clear (1) with at Least 2 Points Reduction from Baseline

End point title	Percentage of Participants who Achieved a Static Physician Global Assessment (sPGA) Score of Clear (0) or Almost Clear (1) with at Least 2 Points Reduction from Baseline
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End point description:

The sPGA was a 5-point scale ranging from 0 (clear), 1 (almost clear), 2 (mild), 3 (moderate), 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 must have factored 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 was 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. The FAS consisted of all subjects who were randomized per protocol. Subjects were included in the treatment group to which they were randomized APR 30 BID or placebo for the FAS. LOCF imputation was used.

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

End point values	Apremilast	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	274	137		
Units: percentage of participants				
number (not applicable)	20.4	4.4		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Apremilast v Placebo
Number of subjects included in analysis	411
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Chi-squared
Parameter estimate	Risk difference (RD)
Point estimate	16.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	10.2
upper limit	21.9

Secondary: Percent Change from Baseline in the Affected Body Surface Area (BSA) at Week 16

End point title	Percent Change from Baseline in the Affected Body Surface Area (BSA) at Week 16
End point description:	
BSA was 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 (Visit 2 Week 0) was determined at each visit of the study, which is calculated as $100 \times (\text{visit BSA} - \text{baseline BSA}) / \text{baseline BSA} (\%)$. The Full Analysis Set (FAS) consisted of all participants who were randomized per protocol. Subjects were included in the treatment group to which they were randomized APR 30 BID or placebo for the FAS. Subjects with a baseline value and at least 1 post-baseline value were included. LOCF imputation was used.	
End point type	Secondary
End point timeframe:	
Baseline and Week 16	

End point values	Apremilast	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	269	136		
Units: percent change				
least squares mean (standard error)	-48.40 (\pm 2.636)	-6.25 (\pm 3.710)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Apremilast v Placebo
Number of subjects included in analysis	405
Analysis specification	Pre-specified
Analysis type	superiority ^[1]
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Difference in LS Mean
Point estimate	-42.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	-51.11
upper limit	-33.2

Notes:

[1] - The model included treatment group as a factor and the baseline value as a covariate. The estimation and p-value were adjusted by the covariate.

Secondary: Percent Change from Baseline in the Psoriasis Area Severity Index (PASI) score at Week 16

End point title	Percent Change from Baseline in the Psoriasis Area Severity Index (PASI) score at Week 16
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End point description:

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 total qualitative score (sum of erythema, thickness, and scaling scores) is multiplied by the degree of involvement for each anatomic region and then multiplied by a constant. These values for each anatomic region are summed to yield the PASI score. FAS consisted of all subjects who were randomized per protocol. Subjects were included in the treatment group to which they were randomized APR 30 BID or placebo for the FAS. LOCF imputation was used. Subjects with a baseline value and at least 1 post-baseline value are included.

End point type	Secondary
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End point timeframe:

Baseline and Week 16

End point values	Apremilast	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	269	136		
Units: percent change				
least squares mean (standard error)	-50.8 (± 2.23)	-16.0 (± 3.15)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Apremilast v Placebo
Number of subjects included in analysis	405
Analysis specification	Pre-specified
Analysis type	superiority ^[2]
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-34.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-42.4
upper limit	-27.2

Notes:

[2] - The model included treatment group as a factor and the baseline value as a covariate. The estimation and p-value were adjusted by the covariate.

Secondary: Percentage of Participants Who Achieved a 50% Improvement (response) in the PASI Score (PASI-50) at Week 16 from Baseline

End point title	Percentage of Participants Who Achieved a 50% Improvement (response) in the PASI Score (PASI-50) at Week 16 from Baseline
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End point description:

PASI-50 response is the percentage of participants who achieved at least a 50% reduction (improvement) from baseline in PASI score at Week 16. The PASI is 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). FAS consisted of all subjects who were randomized per protocol. Subjects were included in the treatment group to which they were randomized APR 30 BID or placebo for the FAS. LOCF imputation was used.

End point type	Secondary
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End point timeframe:

Baseline and Week 16

End point values	Apremilast	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	274	137		
Units: Percentage of Participants				
number (not applicable)	55.5	19.7		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Apremilast v Placebo
Number of subjects included in analysis	411
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Chi-squared
Parameter estimate	Risk difference (RD)
Point estimate	35.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	26.9
upper limit	44.7

Secondary: Change from Baseline in Pruritus Visual Analog Scale (VAS) Score at Week 16

End point title	Change from Baseline in Pruritus Visual Analog Scale (VAS) Score at Week 16
End point description:	
<p>The Pruritus Visual Analog Scores (VAS) were used to measure the amount of itching and discomfort a participant experiences. Subject's assessment of Pruritus (Itch) asked: On average, how much itch have you had because of your condition in the past week? All VAS values range from 0 to 100. Higher scores correspond to more severe symptom or disease. Change from baseline was calculated for the VAS scale, where change = visit value – baseline value. The FAS consisted of all subjects who were randomized per protocol. Subjects were included in the treatment group to which they were randomized APR 30 BID or placebo for the FAS. LOCF imputation was used. Subjects with a baseline value and at least 1 post-baseline value are included.</p>	
End point type	Secondary
End point timeframe:	
Baseline and Week 16	

End point values	Apremilast	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	268	133		
Units: units on a scale				
least squares mean (standard error)	-33.5 (± 2.08)	-12.2 (± 2.95)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Apremilast v Placebo
Number of subjects included in analysis	401
Analysis specification	Pre-specified
Analysis type	superiority ^[3]
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-21.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-28.4
upper limit	-14.2

Notes:

[3] - The model included treatment group as a factor and the baseline value as a covariate. The estimation and p-value were adjusted by the covariate.

Secondary: Change from Baseline in Dermatology Life Quality Index (DLQI) total score at Week 16

End point title	Change from Baseline in Dermatology Life Quality Index (DLQI) total score at Week 16
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End point description:

DLQI is a practical questionnaire to assess limitations related to the impact of skin disease. DLQI contains 10 items dealing with the subject's skin. With the exception of Item Number 7, the subject responds on a 4-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 subjects skin prevented them from working or studying, and if "No," then the subject is asked how much of a problem the skin has been at work or study over the past week, with responses being "A lot," "A little," or "Not at all" (scores 2, 1, or 0 respectively). The DLQI total score was derived by summing all item scores, having a range of 0 to 30, with 30 corresponding to the worst quality of life, and 0 to the best. The FAS consisted of all subjects who were randomized per protocol. Subjects were included in the treatment group to which they were randomized for the FAS. LOCF imputation was used.

End point type	Secondary
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End point timeframe:

Baseline and Week 16

End point values	Apremilast	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	267	131		
Units: units on a scale				
least squares mean (standard error)	-6.7 (\pm 0.37)	-2.7 (\pm 0.53)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Apremilast v Placebo
Number of subjects included in analysis	398
Analysis specification	Pre-specified
Analysis type	superiority ^[4]
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.3
upper limit	-2.8

Notes:

[4] - The model included treatment group as a factor and the baseline value as a covariate. The estimation and p-value were adjusted by the covariate.

Secondary: Change from Baseline in the Mental Component Summary (MSC) Score of the Medical Outcome Study Short Form 36-item (SF-36) Health Survey Version 2.0 at Week 16

End point title	Change from Baseline in the Mental Component Summary (MSC) Score of the Medical Outcome Study Short Form 36-item (SF-36) Health Survey Version 2.0 at Week 16
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End point description:

The SF-36 was a health instrument consisting of 8 scales: physical function, role limitations–physical, vitality, general health perceptions, bodily pain, social function, role limitations–emotional and mental health. Scale scores range from 0 to 100, with higher scores indicating better health. 2 overall summary scores were obtained – a Physical Component Summary score (PCS) and a Mental Component Summary (MCS) score. Scores from the 8 scales, PCS and MCS were transformed to the norm-based scores using weights from U.S. general population, with 50 as the average and 10 as the standard deviation, 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. The FAS consisted of all subjects who were randomized per protocol. Subjects were included in the treatment group to which they were randomized. LOCF imputation was used.

End point type	Secondary
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End point timeframe:

Baseline to Week 16

End point values	Apremilast	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	267	131		
Units: units on a scale				
least squares mean (standard error)	2.60 (\pm 0.563)	-0.03 (\pm 0.804)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Apremilast v Placebo
Number of subjects included in analysis	398
Analysis specification	Pre-specified
Analysis type	superiority ^[5]
P-value	= 0.0078
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	2.63
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.69
upper limit	4.56

Notes:

[5] - The model included treatment group as a factor and the baseline value as a covariate. The estimation and p-value were adjusted by the covariate

Secondary: Percentage of Participants Who Achieved Both a 75% Improvement (response) in the PASI and sPGA score of clear (0) or almost clear (1) with at least 2 points reduction at Week 16 from Baseline

End point title	Percentage of Participants Who Achieved Both a 75% Improvement (response) in the PASI and sPGA score of clear (0) or almost clear (1) with at least 2 points reduction at Week 16 from Baseline
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End point description:

PASI-75 response is the percentage of participants who achieved at least a 75% reduction (improvement) from baseline in PASI score at Week 16. The improvement in PASI score was used as a measure of efficacy. See Outcome measure #1 for further description. sPGA is a 5-point scale ranging from 0 (clear), 1 (almost clear), 2 (mild), 3 (moderate), to 4 (severe), incorporating an assessment of the severity of the three primary signs of the disease: erythema, scaling and plaque elevation. See Outcome Measure #2 for further description. The Full Analysis Set (FAS) consisted of all participants who were randomized per protocol. Participants were included in the treatment group to which they were randomized APR 30 BID or placebo for the FAS. LOCF imputation was used.

End point type	Secondary
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End point timeframe:

Baseline to Week 16

End point values	Apremilast	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	274	137		
Units: percentage of participants				
number (not applicable)	18.6	4.4		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Apremilast v Placebo
Number of subjects included in analysis	411
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Chi-squared
Parameter estimate	Risk difference (RD)
Point estimate	14.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	8.5
upper limit	20

Secondary: Time to Loss of Effect (loss of 50% improvement in PASI score obtained at Week 32 compared to baseline) during the Randomized Treatment Withdrawal Phase

End point title	Time to Loss of Effect (loss of 50% improvement in PASI score obtained at Week 32 compared to baseline) during the Randomized Treatment Withdrawal Phase
End point description:	Time to loss was the time between the re-randomization date and the date of the first assessment with loss of 50% PASI improvement (event), or the time between the re-randomization date and the date of the last PASI assessment in the randomized withdrawal phase prior to addition of topical/phototherapy or other effective psoriasis therapies, or resumption of apremilast 30 mg BID, or discontinuation, or Week 52 if no loss (censored), whichever was earlier. Analysis population consisted of participants who were re-randomized to placebo or Apremilast 30mg BID at Week 32.
End point type	Secondary
End point timeframe:	Weeks 32 to Week 52

End point values	APR-APR-Re-randomized to PBO	APR-APR Re-randomized to APR		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	61		
Units: Weeks				
median (confidence interval 95%)	12.4 (8.3 to 20.1)	21.9 (-99999 to 99999)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	APR-APR-Re-randomized to PBO v APR-APR Re-randomized to APR
Number of subjects included in analysis	123
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	7.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.408
upper limit	17.399

Secondary: Number of Participants with Adverse Events (AE) in the Placebo Controlled Phase

End point title	Number of Participants with Adverse Events (AE) in the Placebo Controlled Phase
End point description: An AE was any noxious, unintended, or untoward medical occurrence, that may worsen in a subject 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 cause. Any worsening (ie., clinically significant adverse change in the frequency or intensity of a preexisting condition) was considered an AE. A serious AE 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 the patient or require intervention to prevent one of the outcomes above. An AE is a treatment emergent if the AE start date is on or after the date of the 1st dose of IP and no later than 28 days after the last dose. Safety population = subjects randomized and received at least 1 dose of IP.	
End point type	Secondary
End point timeframe: Baseline to Week 16	

End point values	Apremilast	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	272	136		
Units: participants				
Any TEAE	185	82		
Any drug related TEAE	106	29		
Any Severe TEAE	12	6		
Any Serious TEAE	5	3		
Any TEAE leading to drug interruption	16	4		
Any TEAE leading to drug withdrawal	15	7		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Psoriasis Flare or Rebound in the Placebo Controlled Phase

End point title	Number of Participants with Psoriasis Flare or Rebound in the Placebo Controlled Phase
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End point description:

Psoriasis flare was defined as a sudden intensification of psoriasis requiring medical intervention, or a diagnosis of new generalized erythrodermic, inflammatory, or pustular psoriasis. Rebound is defined as a severe and sudden worsening of disease that occurs after treatment has been discontinued. Note categories below. Psoriasis adverse events (ie, preferred term as Guttate psoriasis, Psoriasis, Pustular psoriasis) started on or after the first dose date and on or before the last dose date within the phase. Psoriasis adverse events (ie, preferred term as Guttate psoriasis, Psoriasis, Pustular psoriasis, Rebound psoriasis) started after the last dose date for participants who discontinued within the phase. PASI \geq 125% of baseline score at any visit after the last dose date for participants who discontinued within the phase and were not included in [1] and/or [2]. Safety population consisted of all subjects who were randomized and received at least one dose of IP

End point type	Secondary
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End point timeframe:

Week 0 to Week 16

End point values	Apremilast	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	272	136		
Units: participants				
Participants with any psoriasis flare [1]	3	7		
Participants with any psoriasis rebound [2]	1	0		
PASI \geq 125% of Baseline score after last dose [3]	1	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with TEAEs During the Apremilast-Exposure Period Through Week 260

End point title	Number of Participants with TEAEs During the Apremilast-Exposure Period Through Week 260
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End point description:

The Apremilast-exposure Period started on the date of the first dose of apremilast (Week 0 for participants originally randomized to apremilast or Week 16 for subjects originally randomized to placebo) to the last dose of apremilast. AEs that started after 28 days of initiating placebo and before resuming apremilast treatment in the Randomized Treatment Withdrawal Phase (Weeks 32 to 52) were excluded in the Apremilast-exposure phase. A serious AE (SAE) is any untoward adverse event that is fatal, life-threatening, results in persistent or significant disability or incapacity, requires or prolongs existing in-patient hospitalization, is a congenital anomaly or birth defect, or a condition that may jeopardize the patient or may require intervention to prevent one of the outcomes listed above. An AE is a treatment emergent AE if the AE start date is on or after the date of the first dose of study drug and no later than 28 days after the last dose. Apremilast subjects as treated.

End point type	Secondary
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End point timeframe:

Week 0 to Week 260; The mean duration of exposure was 100.66 weeks.

End point values	APR: Subjects with TEAEs during the APR-Exposure Phase			
Subject group type	Subject analysis set			
Number of subjects analysed	380			
Units: participants				
Any TEAE	316			
Any Drug-Related TEAE	165			
Any Severe TEAE	58			
Any Serious TEAE	44			
Any Serious Drug-Related TEAE	8			
Any TEAE Leading to Drug Interruption	56			
Any TEAE Leading to Drug Withdrawal	45			
Any TEAE Leading to Death	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Psoriasis Flare or Rebound in the Apremilast-Exposure Period

End point title	Number of Participants with Psoriasis Flare or Rebound in the Apremilast-Exposure Period
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End point description:

Psoriasis flare was defined as a sudden intensification of psoriasis requiring medical intervention, or a diagnosis of new generalized erythrodermic, inflammatory, or pustular psoriasis. Rebound is defined as a severe and sudden worsening of disease that occurs after treatment has been discontinued. Note categories below. [1] Psoriasis adverse events (ie, preferred term as Guttate psoriasis, Psoriasis,

Pustular psoriasis) started on or after the first dose date and on or before the last dose date within the phase. [2] Psoriasis adverse events (ie, preferred term as Guttate psoriasis, Psoriasis, Pustular psoriasis, Rebound psoriasis) started after the last dose date for participants who discontinued within the phase. [3] PASI \geq 125% of baseline score at any visit after the last dose date for participants who discontinued within the phase and were not included in [1] and/or [2]. The apremilast subjects as treated population.

End point type	Secondary
End point timeframe:	
Week 0 to Week 260	

End point values	APR: Subjects with Psoriasis Flare in the APR-Exposure Phase			
Subject group type	Subject analysis set			
Number of subjects analysed	380			
Units: participants				
Participants with any psoriasis flare [1]	25			
Participants with any psoriasis rebound [2]	11			
PASI \geq 125% of Baseline score after last dose [3]	12			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs are reported at: 1. Weeks 0-16: PBO-controlled phase 2. Weeks 32-52 Randomized Withdrawal participants re-randomized to PBO at Week 32 3. Weeks 0-260 APR-exposure period for participants randomized or switched to APR at any time during the study

Adverse event reporting additional description:

During the PBO-controlled Phase (Weeks 0-16), the mean duration of treatment for those randomized to APR 30 BID or PBO at Week 0, was 14.0 and 14.6, respectively; for those re-randomized to PBO at Week 32, the mean duration of PBO was 11.6 weeks; during the APR-Exposure Period (Weeks 0-260), the mean duration of exposure to APR was 100.66 weeks

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	14.0

Reporting groups

Reporting group title	Placebo: Weeks 0-16 (PBO-Controlled Phase)
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Reporting group description:

Participants randomized to identically matching placebo tablets BID during the Placebo-controlled Phase (Weeks 0-16)

Reporting group title	APR-APR-PBO: Weeks 32-52 (Randomized Withdrawal Phase)
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Reporting group description:

Participants re-randomized to placebo tablets BID at Week 32. Includes data from Week 32 up to Week 52 when participants received placebo treatment.

Reporting group title	Apremilast: Weeks 0-260 (APR-Exposure Period)
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Reporting group description:

Participants who received apremilast 30 mg tablets BID, regardless of when the apremilast exposure started (at Week 0 or at Week 16), up until Week 260. Adverse events associated with apremilast 30 mg treatment up to Week 260 were included. AEs that started more than 28 days after Placebo treatment and prior to resuming apremilast were excluded for participants who were re-randomized to Placebo at Week 32

Reporting group title	Apremilast: Weeks 0-16 (PBO-Controlled Phase)
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Reporting group description:

Participants randomized to apremilast 30 mg tablets BID during the Placebo-controlled Phase (Weeks 0-16)

Serious adverse events	Placebo: Weeks 0-16 (PBO-Controlled Phase)	APR-APR-PBO: Weeks 32-52 (Randomized Withdrawal Phase)	Apremilast: Weeks 0-260 (APR-Exposure Period)
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 136 (2.21%)	2 / 62 (3.23%)	44 / 380 (11.58%)
number of deaths (all causes)	0	1	1
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			

subjects affected / exposed	0 / 136 (0.00%)	0 / 62 (0.00%)	1 / 380 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diffuse large B-cell lymphoma			
subjects affected / exposed	0 / 136 (0.00%)	0 / 62 (0.00%)	1 / 380 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endometrial cancer			
subjects affected / exposed	0 / 136 (0.00%)	0 / 62 (0.00%)	1 / 380 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lip and/or oral cavity cancer			
subjects affected / exposed	0 / 136 (0.00%)	0 / 62 (0.00%)	1 / 380 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal cell carcinoma			
subjects affected / exposed	0 / 136 (0.00%)	0 / 62 (0.00%)	1 / 380 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine cancer			
subjects affected / exposed	0 / 136 (0.00%)	0 / 62 (0.00%)	1 / 380 (0.26%)
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			
Aortic stenosis			
subjects affected / exposed	0 / 136 (0.00%)	0 / 62 (0.00%)	1 / 380 (0.26%)
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 / 136 (0.74%)	0 / 62 (0.00%)	1 / 380 (0.26%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	0 / 136 (0.00%)	0 / 62 (0.00%)	1 / 380 (0.26%)
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			
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 136 (0.00%)	0 / 62 (0.00%)	1 / 380 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Menorrhagia			
subjects affected / exposed	0 / 136 (0.00%)	0 / 62 (0.00%)	1 / 380 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ovarian cyst			
subjects affected / exposed	0 / 136 (0.00%)	0 / 62 (0.00%)	1 / 380 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Alcoholism			
subjects affected / exposed	0 / 136 (0.00%)	0 / 62 (0.00%)	1 / 380 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Personality disorder			
subjects affected / exposed	0 / 136 (0.00%)	0 / 62 (0.00%)	1 / 380 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Schizophrenia			
subjects affected / exposed	0 / 136 (0.00%)	0 / 62 (0.00%)	1 / 380 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicide attempt			

subjects affected / exposed	0 / 136 (0.00%)	0 / 62 (0.00%)	1 / 380 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Helicobacter test positive			
subjects affected / exposed	0 / 136 (0.00%)	0 / 62 (0.00%)	1 / 380 (0.26%)
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			
Laceration			
subjects affected / exposed	0 / 136 (0.00%)	0 / 62 (0.00%)	1 / 380 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	0 / 136 (0.00%)	0 / 62 (0.00%)	1 / 380 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina unstable			
subjects affected / exposed	0 / 136 (0.00%)	0 / 62 (0.00%)	1 / 380 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	0 / 136 (0.00%)	0 / 62 (0.00%)	1 / 380 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery occlusion			
subjects affected / exposed	0 / 136 (0.00%)	0 / 62 (0.00%)	1 / 380 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	0 / 136 (0.00%)	0 / 62 (0.00%)	1 / 380 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Palpitations			
subjects affected / exposed	1 / 136 (0.74%)	0 / 62 (0.00%)	0 / 380 (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
Tachyarrhythmia			
subjects affected / exposed	0 / 136 (0.00%)	0 / 62 (0.00%)	1 / 380 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tachycardia paroxysmal			
subjects affected / exposed	0 / 136 (0.00%)	0 / 62 (0.00%)	1 / 380 (0.26%)
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			
Haemorrhage intracranial			
subjects affected / exposed	0 / 136 (0.00%)	1 / 62 (1.61%)	0 / 380 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Parkinson's disease			
subjects affected / exposed	0 / 136 (0.00%)	1 / 62 (1.61%)	1 / 380 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subarachnoid haemorrhage			
subjects affected / exposed	0 / 136 (0.00%)	0 / 62 (0.00%)	1 / 380 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	1 / 136 (0.74%)	0 / 62 (0.00%)	1 / 380 (0.26%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	0 / 136 (0.00%)	0 / 62 (0.00%)	1 / 380 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			

Angle closure glaucoma			
subjects affected / exposed	0 / 136 (0.00%)	0 / 62 (0.00%)	1 / 380 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cataract			
subjects affected / exposed	0 / 136 (0.00%)	0 / 62 (0.00%)	1 / 380 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Maculopathy			
subjects affected / exposed	0 / 136 (0.00%)	0 / 62 (0.00%)	1 / 380 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 136 (0.00%)	0 / 62 (0.00%)	1 / 380 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Duodenal ulcer haemorrhage			
subjects affected / exposed	0 / 136 (0.00%)	0 / 62 (0.00%)	1 / 380 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysphagia			
subjects affected / exposed	0 / 136 (0.00%)	0 / 62 (0.00%)	1 / 380 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric ulcer			
subjects affected / exposed	0 / 136 (0.00%)	0 / 62 (0.00%)	1 / 380 (0.26%)
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			
Psoriasis			
subjects affected / exposed	0 / 136 (0.00%)	0 / 62 (0.00%)	2 / 380 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Pustular psoriasis			
subjects affected / exposed	0 / 136 (0.00%)	0 / 62 (0.00%)	1 / 380 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Arthropathy			
subjects affected / exposed	0 / 136 (0.00%)	0 / 62 (0.00%)	1 / 380 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gouty arthritis			
subjects affected / exposed	0 / 136 (0.00%)	0 / 62 (0.00%)	1 / 380 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral disc degeneration			
subjects affected / exposed	0 / 136 (0.00%)	0 / 62 (0.00%)	1 / 380 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral disc protrusion			
subjects affected / exposed	0 / 136 (0.00%)	0 / 62 (0.00%)	2 / 380 (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
Osteoarthritis			
subjects affected / exposed	0 / 136 (0.00%)	0 / 62 (0.00%)	1 / 380 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psoriatic arthropathy			
subjects affected / exposed	0 / 136 (0.00%)	0 / 62 (0.00%)	1 / 380 (0.26%)
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			
Abdominal abscess			
subjects affected / exposed	0 / 136 (0.00%)	0 / 62 (0.00%)	1 / 380 (0.26%)
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			
subjects affected / exposed	0 / 136 (0.00%)	0 / 62 (0.00%)	2 / 380 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infectious mononucleosis			
subjects affected / exposed	0 / 136 (0.00%)	0 / 62 (0.00%)	1 / 380 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung abscess			
subjects affected / exposed	0 / 136 (0.00%)	0 / 62 (0.00%)	1 / 380 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 136 (0.00%)	0 / 62 (0.00%)	1 / 380 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia staphylococcal			
subjects affected / exposed	0 / 136 (0.00%)	0 / 62 (0.00%)	1 / 380 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Diabetes mellitus			
subjects affected / exposed	0 / 136 (0.00%)	0 / 62 (0.00%)	1 / 380 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gout			
subjects affected / exposed	0 / 136 (0.00%)	0 / 62 (0.00%)	1 / 380 (0.26%)
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	Apremilast: Weeks 0-16 (PBO-Controlled Phase)		
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 272 (1.84%)		
number of deaths (all causes)	0		

number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	0 / 272 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Diffuse large B-cell lymphoma			
subjects affected / exposed	0 / 272 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Endometrial cancer			
subjects affected / exposed	0 / 272 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Lip and/or oral cavity cancer			
subjects affected / exposed	0 / 272 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal cell carcinoma			
subjects affected / exposed	0 / 272 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Uterine cancer			
subjects affected / exposed	0 / 272 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Aortic stenosis			
subjects affected / exposed	0 / 272 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Non-cardiac chest pain			

subjects affected / exposed	0 / 272 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	0 / 272 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 272 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Menorrhagia			
subjects affected / exposed	0 / 272 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ovarian cyst			
subjects affected / exposed	0 / 272 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Alcoholism			
subjects affected / exposed	0 / 272 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Personality disorder			
subjects affected / exposed	1 / 272 (0.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Schizophrenia			
subjects affected / exposed	0 / 272 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Suicide attempt			
subjects affected / exposed	1 / 272 (0.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Investigations			
Helicobacter test positive			
subjects affected / exposed	0 / 272 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Laceration			
subjects affected / exposed	0 / 272 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	0 / 272 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Angina unstable			
subjects affected / exposed	0 / 272 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Atrial fibrillation			
subjects affected / exposed	0 / 272 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Coronary artery occlusion			
subjects affected / exposed	0 / 272 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Myocardial infarction			

subjects affected / exposed	0 / 272 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Palpitations			
subjects affected / exposed	0 / 272 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Tachyarrhythmia			
subjects affected / exposed	0 / 272 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Tachycardia paroxysmal			
subjects affected / exposed	0 / 272 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Haemorrhage intracranial			
subjects affected / exposed	0 / 272 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Parkinson's disease			
subjects affected / exposed	0 / 272 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Subarachnoid haemorrhage			
subjects affected / exposed	0 / 272 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Syncope			
subjects affected / exposed	0 / 272 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Transient ischaemic attack			

subjects affected / exposed	0 / 272 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Angle closure glaucoma			
subjects affected / exposed	0 / 272 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cataract			
subjects affected / exposed	0 / 272 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Maculopathy			
subjects affected / exposed	0 / 272 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 272 (0.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Duodenal ulcer haemorrhage			
subjects affected / exposed	0 / 272 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Dysphagia			
subjects affected / exposed	1 / 272 (0.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastric ulcer			
subjects affected / exposed	0 / 272 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			

Psoriasis			
subjects affected / exposed	1 / 272 (0.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pustular psoriasis			
subjects affected / exposed	0 / 272 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Arthropathy			
subjects affected / exposed	0 / 272 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gouty arthritis			
subjects affected / exposed	0 / 272 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Intervertebral disc degeneration			
subjects affected / exposed	0 / 272 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Intervertebral disc protrusion			
subjects affected / exposed	0 / 272 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Osteoarthritis			
subjects affected / exposed	0 / 272 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psoriatic arthropathy			
subjects affected / exposed	1 / 272 (0.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Infections and infestations Abdominal abscess subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 272 (0.00%) 0 / 0 0 / 0		
Appendicitis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 272 (0.00%) 0 / 0 0 / 0		
Infectious mononucleosis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 272 (0.00%) 0 / 0 0 / 0		
Lung abscess subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 272 (0.00%) 0 / 0 0 / 0		
Pneumonia subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 272 (0.00%) 0 / 0 0 / 0		
Pneumonia staphylococcal subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 272 (0.00%) 0 / 0 0 / 0		
Metabolism and nutrition disorders Diabetes mellitus subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 272 (0.00%) 0 / 0 0 / 0		
Gout subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 272 (0.37%) 0 / 1 0 / 0		

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

Non-serious adverse events	Placebo: Weeks 0-16 (PBO-Controlled Phase)	APR-APR-PBO: Weeks 32-52 (Randomized Withdrawal Phase)	Apremilast: Weeks 0-260 (APR-Exposure Period)
Total subjects affected by non-serious adverse events subjects affected / exposed	38 / 136 (27.94%)	17 / 62 (27.42%)	234 / 380 (61.58%)
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 136 (0.74%)	0 / 62 (0.00%)	28 / 380 (7.37%)
occurrences (all)	1	0	52
Tension headache			
subjects affected / exposed	2 / 136 (1.47%)	0 / 62 (0.00%)	31 / 380 (8.16%)
occurrences (all)	2	0	52
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	8 / 136 (5.88%)	1 / 62 (1.61%)	62 / 380 (16.32%)
occurrences (all)	9	1	96
Nausea			
subjects affected / exposed	9 / 136 (6.62%)	2 / 62 (3.23%)	68 / 380 (17.89%)
occurrences (all)	10	2	91
Vomiting			
subjects affected / exposed	5 / 136 (3.68%)	0 / 62 (0.00%)	27 / 380 (7.11%)
occurrences (all)	7	0	30
Skin and subcutaneous tissue disorders			
Psoriasis			
subjects affected / exposed	7 / 136 (5.15%)	1 / 62 (1.61%)	24 / 380 (6.32%)
occurrences (all)	7	1	37
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 136 (1.47%)	2 / 62 (3.23%)	26 / 380 (6.84%)
occurrences (all)	2	3	30
Back pain			

subjects affected / exposed	2 / 136 (1.47%)	2 / 62 (3.23%)	31 / 380 (8.16%)
occurrences (all)	2	2	42
Pain in extremity			
subjects affected / exposed	2 / 136 (1.47%)	1 / 62 (1.61%)	19 / 380 (5.00%)
occurrences (all)	3	1	19
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 136 (0.00%)	1 / 62 (1.61%)	29 / 380 (7.63%)
occurrences (all)	0	1	39
Nasopharyngitis			
subjects affected / exposed	6 / 136 (4.41%)	5 / 62 (8.06%)	69 / 380 (18.16%)
occurrences (all)	7	6	118
Upper respiratory tract infection			
subjects affected / exposed	6 / 136 (4.41%)	1 / 62 (1.61%)	53 / 380 (13.95%)
occurrences (all)	6	1	76
Urinary tract infection			
subjects affected / exposed	0 / 136 (0.00%)	1 / 62 (1.61%)	22 / 380 (5.79%)
occurrences (all)	0	1	26

Non-serious adverse events	Apremilast: Weeks 0-16 (PBO-Controlled Phase)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	128 / 272 (47.06%)		
Nervous system disorders			
Headache			
subjects affected / exposed	17 / 272 (6.25%)		
occurrences (all)	35		
Tension headache			
subjects affected / exposed	20 / 272 (7.35%)		
occurrences (all)	25		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	43 / 272 (15.81%)		
occurrences (all)	54		
Nausea			
subjects affected / exposed	50 / 272 (18.38%)		
occurrences (all)	61		

Vomiting subjects affected / exposed occurrences (all)	14 / 272 (5.15%) 15		
Skin and subcutaneous tissue disorders Psoriasis subjects affected / exposed occurrences (all)	3 / 272 (1.10%) 3		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Back pain subjects affected / exposed occurrences (all) Pain in extremity subjects affected / exposed occurrences (all)	5 / 272 (1.84%) 5 6 / 272 (2.21%) 11 6 / 272 (2.21%) 6		
Infections and infestations Bronchitis subjects affected / exposed occurrences (all) Nasopharyngitis subjects affected / exposed occurrences (all) Upper respiratory tract infection subjects affected / exposed occurrences (all) Urinary tract infection subjects affected / exposed occurrences (all)	4 / 272 (1.47%) 4 20 / 272 (7.35%) 28 13 / 272 (4.78%) 13 5 / 272 (1.84%) 6		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 January 2011	1. Clarified procedures for subjects who entered the Randomized Treatment Withdrawal Phase at Week 32 2. Clarified that Arthritis VAS only pertained to subjects with psoriatic arthritis 3. Clarified the language regarding contraception methods to ensure that acceptable methods of contraception by subjects were used and added a statement to ensure that appropriate education regarding contraception methods was provided by the investigator to the subjects 4. Limited sites to North America and Europe 5. Corrected the order of health-related quality of life (HRQoL) and VAS assessments to align with what is actually being done on the SitePad instrument 6. Aligned exclusion criteria related to past malignancies across the entire apremilast Phase 3 program in order to give investigators responsibility for determining subject eligibility for previously successfully treated local lesions 7. Clarified Statistical Efficacy Analysis deleting the "Per-protocol" analysis 8. Modified the Reasons for Discontinuation to align with what is displayed in the InForm database
10 June 2011	1. Provided updates to the contact information for the medical monitor of the study 2. Provide correction regarding the Celgene Therapeutic Area Head of the study 3. Clarified the Contraception Education that required the investigator to educate the subject on acceptable birth control any time when a subject's contraceptive measures or ability to become pregnant changed; modified to direct the investigator to Section 7.2 of the protocol where details regarding the acceptable contraception for this study may be found 4. Modified Inclusion Criterion Number 9 (female birth control) to clearly define single or multiple forms of contraception that were acceptable for this study 5. Added a footnote to Inclusion Criterion Number 9 (female birth control) to clarify that the female subject's chosen form of contraception must be fully effective by the time the female subject is randomized into the study 6. Modified Inclusion Criterion Number 10 (male birth control) to clarify that male subjects must use a "male" latex or non-latex condom 7. Deleted descriptive text on how to record onset and end dates of SAEs on the SAE Report Form because it is no longer applicable
19 April 2012	1. Provided updates to the contact information for the medical monitor of the study 2. Clarified Section 3.2.2, Efficacy, and in Section 3.3, Exploratory Endpoint(s), that the VAS scale endpoints were to be change from baseline rather than percent change 3. Modified Section 4.1, Study Design, to allow the use of topical corticosteroids, retinoids or vitamin D analog preparations and/or phototherapy after the Week 52 study visit for non-responders 4. Modified Section 4.1, Study Design, regarding the replacement of the Safety Review Panel with an independent external DMC 5. Added footnotes to the Tables of Events clarifying that vasculitis assessments and/or psychiatric evaluations were to be performed as appropriate when adverse events were reported 6. Revised the Contraception Education language in Section 6.2 and moved footnote from Section 7.2 to Section 6.2 7. Added Section 6.6.4.1, Vasculitis Assessment, providing guidance to investigators 8. Added Section 6.6.4.2, Psychiatric Evaluation, to provide precautionary guidance to investigators for the management of subjects identified as having thoughts of suicide, attempted suicide or having major psychiatric illness 9. Added open-label IP package description in Section 6.10.1, Investigational Product Dispensing and Counting for Compliance, and Section 8.4, Packaging and Labeling 10. Modified Section 9.1, Permitted Concomitant Medications, and Section 9.2, Prohibited Concomitant Medications, to allow the use of topical corticosteroids, retinoids, or vitamin D analog preparations and/or phototherapy after the Week 52 study visit for non-responders 11. Clarified that AE tables were to summarize treatment-emergent AE only 12. Changed "CRF" to "eCRF" globally throughout the document, to reflect that data captured in this study in electronic case report form pages (eCRF)

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported