Clinical trial results:
A Phase 2, Multicenter, Open-label Study to Assess the Safety, Tolerability and Pharmacokinetics of Apremilast (CC-10004) in Pediatric Subjects with Moderate to Severe Plaque Psoriasis

Summary

EudraCT number	2015-003314-24
Trial protocol	GB DE ES Outside EU/EEA
Global end of trial date	29 July 2019

Results information

Result version number	v1 (current)
This version publication date	31 January 2020
First version publication date	31 January 2020

Trial information

Trial identification

Sponsor protocol code	CC-10004-PPSO-001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02576678
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	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)	Yes
EMA paediatric investigation plan number(s)	EMEA-000715-PIP03-11
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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	29 July 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	29 July 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To select a pediatric dose of apremilast based on the safety, tolerability, and pharmacokinetics (PK) of apremilast (APR) in adolescents and children with moderate to severe plaque psoriasis.

Protection of trial subjects:

Informed Consent, Patient Confidentiality and Archiving of Essential Documents

Background therapy:

Low-potency corticosteroids for treatment of the face, axillae, and groin.

Evidence for comparator:

Not applicable

Actual start date of recruitment	13 October 2015
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	1 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Canada: 13
Country: Number of subjects enrolled	Germany: 8
Country: Number of subjects enrolled	Spain: 7
Country: Number of subjects enrolled	United States: 14
Worldwide total number of subjects	42
EEA total number of subjects	15

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)	21

Adolescents (12-17 years)	21
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 11 study centers in 4 countries, including the United States, Canada, Germany and Spain.

Pre-assignment

Screening details:

Participants were enrolled according to a staggered, stepwise approach by age range and weight starting with older and heavier participants. Dosing within and between groups was staggered based on pharmacokinetic (PK) data collected and a minimum of 2 weeks of safety data.

Period 1

Period 1 title	Overall Treatment Period (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Group 1 Adolescents: Apremilast 20 mg

Arm description:

Participants ages 12 to 17 years old, with a weight of ≥ 35 kg to < 70 kg received apremilast tablets 20 mg twice a day (BID) for 2 weeks followed by a 48-week extension of apremilast treatment.

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

Dosage and administration details:

20 mg apremilast tablets BID

Arm title	Group 1 Adolescents: Apremilast 30 mg

Arm description:

Participants ages 12 to 17 years old, with a weight of ≥ 70 kg received apremilast 30 mg tablets BID for 2 weeks followed by a 48-week extension of apremilast treatment.

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

Dosage and administration details:

30 mg apremilast tablets BID

Arm title	Group 2 Children: Apremilast 20 mg

Arm description:

Participants ages 6 to 11 years old, with a weight of ≥ 15 kg received apremilast 20 mg tablets BID for 2 weeks followed by a 48-week extension of apremilast treatment.

Arm type	Experimental

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

Dosage and administration details:

20 mg apremilast tablets BID

Number of subjects in period 1	Group 1 Adolescents: Apremilast 20 mg	Group 1 Adolescents: Apremilast 30 mg	Group 2 Children: Apremilast 20 mg
Started	13	8	21
Pharmacokinetic (PK) Population	12	8	18
Completed	8	7	16
Not completed	5	1	5
Consent withdrawn by subject	3	1	2
Adverse event, non-fatal	-	-	2
Miscellaneous	2	-	-
Lost to follow-up	-	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Group 1 Adolescents: Apremilast 20 mg
Reporting group description:	
Participants ages 12 to 17 years old, with a weight of ≥ 35 kg to < 70 kg received apremilast tablets 20 mg twice a day (BID) for 2 weeks followed by a 48-week extension of apremilast treatment.	
Reporting group title	Group 1 Adolescents: Apremilast 30 mg
Reporting group description:	
Participants ages 12 to 17 years old, with a weight of ≥ 70 kg received apremilast 30 mg tablets BID for 2 weeks followed by a 48-week extension of apremilast treatment.	
Reporting group title	Group 2 Children: Apremilast 20 mg
Reporting group description:	
Participants ages 6 to 11 years old, with a weight of ≥ 15 kg received apremilast 20 mg tablets BID for 2 weeks followed by a 48-week extension of apremilast treatment.	

Reporting group values	Group 1 Adolescents: Apremilast 20 mg	Group 1 Adolescents: Apremilast 30 mg	Group 2 Children: Apremilast 20 mg
Number of subjects	13	8	21
Age Categorical Units: Participants			
6 to 11 years	0	0	21
12 to 17 years	13	8	0
Age Continuous Units: Years			
arithmetic mean	13.8	14.8	9.3
standard deviation	± 1.77	± 2.05	± 1.35
Sex: Female, Male Units: Participants			
Female	9	1	13
Male	4	7	8
Race/Ethnicity, Customized Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	2	0	2
Black or African American	0	0	2
Native Hawaiian or other Pacific Islander	0	1	0
White or Caucasian	10	6	16
Other	1	1	1
Baseline Weight Category (kg) Units: Subjects			
< 15 kg	0	0	0
≥ 15 - < 35 kg	0	0	13
≥ 35 - < 50 kg	3	0	4
≥ 50 - < 70 kg	10	0	4
≥ 70 kg	0	8	0
Baseline Body Mass Index (BMI) Category Units: Subjects			

Healthy Weight	7	1	15
Overweight	2	1	1
Obesity	4	6	5
Ethnicity Units: Subjects			
Hispanic or Latino	1	3	5
Not Hispanic or Latino	12	5	16
Duration of Plaque Psoriasis Units: Years			
arithmetic mean	7.41	6.96	2.75
standard deviation	± 3.190	± 4.057	± 2.057
Psoriasis Area Severity Index (PASI)			
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).			
Units: Units on a scale			
arithmetic mean	18.78	15.65	18.09
standard deviation	± 11.693	± 3.430	± 6.144

Reporting group values	Total		
Number of subjects	42		
Age Categorical Units: Participants			
6 to 11 years	21		
12 to 17 years	21		
Age Continuous Units: Years			
arithmetic mean			
standard deviation	-		
Sex: Female, Male Units: Participants			
Female	23		
Male	19		
Race/Ethnicity, Customized Units: Subjects			
American Indian or Alaska Native	0		
Asian	4		
Black or African American	2		
Native Hawaiian or other Pacific Islander	1		
White or Caucasian	32		
Other	3		
Baseline Weight Category (kg) Units: Subjects			
< 15 kg	0		
≥ 15 - < 35 kg	13		
≥ 35 - < 50 kg	7		
≥ 50 - < 70 kg	14		
≥ 70 kg	8		
Baseline Body Mass Index (BMI)			

Category Units: Subjects			
Healthy Weight	23		
Overweight	4		
Obesity	15		
Ethnicity Units: Subjects			
Hispanic or Latino	9		
Not Hispanic or Latino	33		
Duration of Plaque Psoriasis Units: Years arithmetic mean standard deviation	- -		
Psoriasis Area Severity Index (PASI)			
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).			
Units: Units on a scale arithmetic mean standard deviation	 -		

End points

End points reporting groups

Reporting group title	Group 1 Adolescents: Apremilast 20 mg
Reporting group description:	
Participants ages 12 to 17 years old, with a weight of ≥ 35 kg to < 70 kg received apremilast tablets 20 mg twice a day (BID) for 2 weeks followed by a 48-week extension of apremilast treatment.	
Reporting group title	Group 1 Adolescents: Apremilast 30 mg
Reporting group description:	
Participants ages 12 to 17 years old, with a weight of ≥ 70 kg received apremilast 30 mg tablets BID for 2 weeks followed by a 48-week extension of apremilast treatment.	
Reporting group title	Group 2 Children: Apremilast 20 mg
Reporting group description:	
Participants ages 6 to 11 years old, with a weight of ≥ 15 kg received apremilast 20 mg tablets BID for 2 weeks followed by a 48-week extension of apremilast treatment.	

Primary: Number of Participants with Treatment Emergent Adverse Events (TEAEs)

End point title	Number of Participants with Treatment Emergent Adverse Events (TEAEs)[1]
End point description:	
A TEAE is an adverse event with a start date on or after the date of the first dose of apremilast and no later than 28 days after the last dose of apremilast. An adverse event is any noxious, unintended, or untoward medical occurrence that may appear or worsen in a subject during the course of a study. It may be a new intercurrent illness, a worsening concomitant illness, an injury, or any concomitant impairment of the subject's health, including laboratory test values, regardless of etiology. A serious AE is any untoward AE that results in death, is life threatening, requires inpatient hospitalization or prolongation of existing hospitalization or in persistent or significant disability/incapacity, results in a congenital anomaly/birth defect or constitutes an important medical event. The investigator assessment of severity/intensity of an event was defined as mild, moderate or severe. The safety population consisted of all enrolled subjects who took at least one dose of apremilast.	
End point type	Primary
End point timeframe:	
From first dose of apremilast until 28 days after the last dose; up to 29 July 2019; median treatment duration for adolescents apremilast 20 mg and 30 mg was 50.00 and 50.57 weeks respectively and for children was 50.00 weeks.	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Adverse events were analyzed using descriptive statistics based on the safety population. The safety population consisted of all participants who received at least 1 dose of apremilast.

End point values	Group 1 Adolescents: Apremilast 20 mg	Group 1 Adolescents: Apremilast 30 mg	Group 2 Children: Apremilast 20 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	13	8	21	
Units: Participants				
Any TEAE	13	7	20	
Any Drug Related TEAE	11	6	17	
Any Severe TEAE	1	0	1	
Any Serious TEAE	0	0	1	
Any Serious Drug-Related TEAE	0	0	0	

Any TEAE Leading to Drug Interruption	1	0	4	
Any TEAE Leading to Drug Withdrawal	0	0	2	
Any TEAE Leading to Death	0	0	0	

Statistical analyses

No statistical analyses for this end point

Primary: Maximum Observed Plasma Concentration (Cmax) of Apremilast

End point title	Maximum Observed Plasma Concentration (Cmax) of Apremilast[2]

End point description:

Maximum observed plasma concentration (Cmax) of apremilast. PK parameters were calculated using non-compartmental methods, plasma concentrations and actual blood sampling times from the intensive sampling schedule. The pharmacokinetic (PK) population consisted of all enrolled subjects who took at least one dose of apremilast and had evaluable PK data. PK data were considered evaluable if there were measurable drug levels of apremilast in plasma from at least 3 time points which extended over a minimal 5-hour period within 12 hours post a dose, eg, predose, 2 and 8 hours post a dose.

End point type	Primary

End point timeframe:

For adolescents, a pre-dose sample prior to morning dose and on Day 14 as well as at hours 1, 2, 3, 5, 8 and 12 post dose; for the children, samples were collected 2 hours at predose (prior to morning dose) and at 2, 5 and 12 hours post morning dose.

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: PK parameters were calculated using non-compartmental method for plasma concentrations and actual blood sampling times from the intensive sampling schedule. Actual sampling times were used in the calculations of PK parameters. PK parameters for apremilast were summarized using descriptive statistics based on the PK population, which consisted of all participants who took at least one dose of study drug and had evaluable PK data.

End point values	Group 1 Adolescents: Apremilast 20 mg	Group 1 Adolescents: Apremilast 30 mg	Group 2 Children: Apremilast 20 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	12	8	18	
Units: ng/mL				
geometric mean (geometric coefficient of variation)	274.272 (± 34.3)	410.929 (± 39.7)	348.146 (± 47.4)	

Statistical analyses

No statistical analyses for this end point

Primary: Time to Maximum Plasma Concentration (Tmax) of Apremilast

End point title	Time to Maximum Plasma Concentration (Tmax) of

End point description:

Time to maximum observed plasma concentration obtained directly from the observed concentration

versus time data. PK parameters were calculated using non-compartmental methods, plasma concentrations and actual blood sampling times from the intensive sampling schedule. The PK population consisted of all enrolled subjects who took at least one dose of apremilast and had evaluable PK data. PK data were considered evaluable if there were measurable drug levels of apremilast in plasma from at least 3 time points which extended over a minimal 5-hour period within 12 hours post a dose, eg, predose, 2 and 8 hours post a dose.

End point type	Primary

End point timeframe:

For adolescents, a pre-dose sample prior to morning dose and on Day 14 as well as at hours 1, 2, 3, 5, 8 and 12 post dose; for the children, samples were collected 2 hours at predose (prior to morning dose) and at 2, 5 and 12 hours post morning dose.

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: PK parameters were calculated using non-compartmental method for plasma concentrations and actual blood sampling times from the intensive sampling schedule. Actual sampling times were used in the calculations of PK parameters. PK parameters for apremilast were summarized using descriptive statistics based on the PK population, which consisted of all participants who took at least one dose of study drug and had evaluable PK data.

End point values	Group 1 Adolescents: Apremilast 20 mg	Group 1 Adolescents: Apremilast 30 mg	Group 2 Children: Apremilast 20 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	12	8	18	
Units: hours				
median (full range (min-max))	2.467 (1.00 to 3.00)	3.000 (1.00 to 5.00)	2.000 (1.90 to 5.00)	

Statistical analyses

No statistical analyses for this end point

Primary: Area Under the Plasma Concentration-time Curve from Time Zero to 12 hours Post Dose of Apremilast (AUC0-12)

End point title	Area Under the Plasma Concentration-time Curve from Time Zero to 12 hours Post Dose of Apremilast (AUC0-12)[4]

End point description:

Area under the plasma concentration-time curve from time zero to the 12 hours post dose was calculated using non-compartmental methods, plasma concentrations and actual blood sampling times from the intensive sampling schedule. The PK population consisted of all enrolled subjects who took at least one dose of apremilast and had evaluable PK data. PK data were considered evaluable if there were measurable drug levels of apremilast in plasma from at least 3 time points which extended over a minimal 5-hour period within 12 hours post a dose, eg, predose, 2 and 8 hours post a dose.

End point type	Primary

End point timeframe:

For adolescents, a pre-dose sample prior to morning dose and on Day 14 as well as at hours 1, 2, 3, 5, 8 and 12 post dose; for the children, samples were collected 2 hours at predose (prior to morning dose) and at 2, 5 and 12 hours post morning dose.

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: PK parameters were calculated using non-compartmental method for plasma concentrations and actual blood sampling times from the intensive sampling schedule. Actual sampling times were used in the calculations of PK parameters. PK parameters for apremilast were summarized

using descriptive statistics based on the PK population, which consisted of all participants who took at least one dose of study drug and had evaluable PK data.

End point values	Group 1 Adolescents: Apremilast 20 mg	Group 1 Adolescents: Apremilast 30 mg	Group 2 Children: Apremilast 20 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	12	8	17	
Units: ng*h/mL				
geometric mean (geometric coefficient of variation)	1799.717 (± 36.0)	2901.795 (± 41.2)	2544.874 (± 40.8)	

Statistical analyses

No statistical analyses for this end point

Primary: Area Under the Plasma Concentration-time Curve from Time Zero to the Last Measurable Concentration of Apremilast (AUC0-t)

End point title	Area Under the Plasma Concentration-time Curve from Time Zero to the Last Measurable Concentration of Apremilast (AUC0-t)[5]

End point description:

Area under the plasma concentration-time curve from time zero to the last quantifiable time point and was calculated using non-compartmental methods, plasma concentrations and actual blood sampling times from the intensive sampling schedule. The PK population consisted of all enrolled subjects who took at least one dose of apremilast and had evaluable PK data. PK data were considered evaluable if there were measurable drug levels of apremilast in plasma from at least 3 time points which extended over a minimal 5-hour period within 12 hours post a dose, eg, predose, 2 and 8 hours post a dose.

End point type	Primary

End point timeframe:

For adolescents, a pre-dose sample prior to morning dose and on Day 14 as well as at hours 1, 2, 3, 5, 8 and 12 post dose; for the children, samples were collected 2 hours at predose (prior to morning dose) and at 2, 5 and 12 hours post morning dose.

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: PK parameters were calculated using non-compartmental method for plasma concentrations and actual blood sampling times from the intensive sampling schedule. Actual sampling times were used in the calculations of PK parameters. PK parameters for apremilast were summarized using descriptive statistics based on the PK population, which consisted of all participants who took at least one dose of study drug and had evaluable PK data.

End point values	Group 1 Adolescents: Apremilast 20 mg	Group 1 Adolescents: Apremilast 30 mg	Group 2 Children: Apremilast 20 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	12	8	18	
Units: ng*h/mL				
geometric mean (geometric coefficient of variation)	1794.815 (± 35.9)	2900.472 (± 41.4)	2367.641 (± 50.2)	

Statistical analyses

No statistical analyses for this end point

Primary: Apparent Total Plasma Clearance when Dosed Orally (CL/F) for Apremilast

End point title	Apparent Total Plasma Clearance when Dosed Orally (CL/F) for Apremilast[6]

End point description:

Apparent total plasma clearance (CL/F) of apremilast was calculated using non-compartmental methods, plasma concentrations and actual blood sampling times from the intensive sampling schedule. The PK population consisted of all enrolled subjects who took at least one dose of apremilast and had evaluable PK data. PK data were considered evaluable if there were measurable drug levels of apremilast in plasma from at least 3 time points which extended over a minimal 5-hour period within 12 hours post a dose, eg, predose, 2 and 8 hours post a dose.

End point type	Primary

End point timeframe:

For adolescents, a pre-dose sample prior to morning dose and on Day 14 as well as at hours 1, 2, 3, 5, 8 and 12 post dose; for the children, samples were collected 2 hours at predose (prior to morning dose) and at 2, 5 and 12 hours post morning dose.

Notes:

[6] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: PK parameters were calculated using non-compartmental method for plasma concentrations and actual blood sampling times from the intensive sampling schedule. Actual sampling times were used in the calculations of PK parameters. PK parameters for apremilast were summarized using descriptive statistics based on the PK population, which consisted of all participants who took at least one dose of study drug and had evaluable PK data. .

End point values	Group 1 Adolescents: Apremilast 20 mg	Group 1 Adolescents: Apremilast 30 mg	Group 2 Children: Apremilast 20 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	12	8	17	
Units: Liters/hour				
geometric mean (geometric coefficient of variation)	11.113 (± 36.0)	10.338 (± 41.2)	7.859 (± 40.8)	

Statistical analyses

No statistical analyses for this end point

Primary: Apparent Total Volume of Distribution when Dosed Orally, Based on Study-State (Vss/F) or in the Terminal Phase (Vz/F)

End point title	Apparent Total Volume of Distribution when Dosed Orally, Based on Study-State (Vss/F) or in the Terminal Phase (Vz/F)[7]

End point description:

Apparent total volume of distribution when dosed orally, based on study-state (Vss/F) or in the terminal phase (Vz/F). Pharmacokinetic parameters were calculated using non-compartmental methods, plasma concentrations and actual blood sampling times from the intensive sampling schedule. The PK population consisted of all enrolled subjects who took at least one dose of apremilast and had evaluable PK data. PK data were considered evaluable if there were measurable drug levels of apremilast in plasma from at least 3 time points which extended over a minimal 5-hour period within 12 hours post a dose, eg, predose, 2 and 8 hours post a dose.

End point type	Primary

End point timeframe:

For adolescents, a pre-dose sample prior to morning dose and on Day 14 as well as at hours 1, 2, 3, 5, 8 and 12 post dose; for the children, samples were collected 2 hours at predose (prior to morning dose) and at 2, 5 and 12 hours post morning dose.

Notes:

[7] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: PK parameters were calculated using non-compartmental method for plasma concentrations and actual blood sampling times from the intensive sampling schedule. Actual sampling times were used in the calculations of PK parameters. PK parameters for apremilast were summarized using descriptive statistics based on the PK population, which consisted of all participants who took at least one dose of study drug and had evaluable PK data.

End point values	Group 1 Adolescents: Apremilast 20 mg	Group 1 Adolescents: Apremilast 30 mg	Group 2 Children: Apremilast 20 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	12	8	17	
Units: Liters				
geometric mean (geometric coefficient of variation)	86.870 (± 56.1)	101.049 (± 31.6)	55.126 (± 51.2)	

Statistical analyses

No statistical analyses for this end point

Primary: Terminal Phase Elimination Half-Life

End point title	Terminal Phase Elimination Half-Life[8]

End point description:

Terminal-phase elimination half-life (t ½). PK parameters were calculated using non-compartmental methods, plasma concentrations and actual blood sampling times from the intensive sampling schedule. The PK population consisted of all enrolled subjects who took at least one dose of apremilast and had evaluable PK data. PK data were considered evaluable if there were measurable drug levels of apremilast in plasma from at least 3 time points which extended over a minimal 5-hour period within 12 hours post a dose, eg, predose, 2 and 8 hours post a dose.

End point type	Primary

End point timeframe:

For adolescents, a pre-dose sample prior to morning dose and on Day 14 as well as at hours 1, 2, 3, 5, 8 and 12 post dose; for the children, samples were collected 2 hours at predose (prior to morning dose) and at 2, 5 and 12 hours post morning dose.

Notes:

[8] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Pharmacokinetic (PK) parameters were calculated using non-compartmental method for plasma concentrations and actual blood sampling times from the intensive sampling schedule. Actual sampling times were used in the calculations of PK parameters. PK parameters for apremilast were

summarized using descriptive statistics based on the PK population, which consisted of all participants who took at least one dose of study drug and had evaluable PK data.

End point values	Group 1 Adolescents: Apremilast 20 mg	Group 1 Adolescents: Apremilast 30 mg	Group 2 Children: Apremilast 20 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	12	8	17	
Units: hours				
geometric mean (geometric coefficient of variation)	5.418 (± 43.1)	6.775 (± 50.3)	4.862 (± 30.2)	

Statistical analyses

No statistical analyses for this end point

Secondary: Taste and Acceptability of Apremilast Tablets Using the Faces Likert Scale

End point title	Taste and Acceptability of Apremilast Tablets Using the Faces Likert Scale

End point description:

Taste and acceptability of the apremilast tablet was assessed using a faces Likert Scale on Day 1, initial dosing. The scale consists of options from 1 (dislike very much, illustrated by a frowning face) to 5 (like very much, illustrated by a smiling face). This population consisted of all enrolled subjects who took at least one dose of apremilast.

End point type	Secondary

End point timeframe:

Day 1

End point values	Group 1 Adolescents: Apremilast 20 mg	Group 1 Adolescents: Apremilast 30 mg	Group 2 Children: Apremilast 20 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	13	8	21	
Units: Participants				
1 (Dislike Very Much)	0	0	3	
2 (Dislike a Little)	1	0	1	
3 (Not Sure)	5	4	3	
4 (Like a Little)	1	1	4	
5 (Like Very Much)	6	3	10	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose of apremilast until 28 days after the last dose; up to 198 weeks; median treatment duration for adolescents apremilast 20 mg and 30 mg was 50.00 and 50.57 weeks respectively and for children was 50.00 weeks;

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups

Reporting group title	Group 1 Adolescents: Apremilast 20 mg

Reporting group description:

Participants ages 12 to 17 years old, with a weight of ≥ 35 kg to < 70 kg received apremilast tablets 20 mg twice a day (BID) for 2 weeks followed by a 48-week extension of apremilast treatment.

Reporting group title	Group 1 Adolescents: Apremilast 30 mg

Reporting group description:

Participants ages 12 to 17 years old, with a weight of ≥ 70 kg received apremilast 30 mg tablets BID for 2 weeks followed by a 48-week extension of apremilast treatment.

Reporting group title	Group 2: Children Apremilast 20 mg

Reporting group description:

Participants ages 6 to 11 years old, with a weight of ≥ 15 kg received apremilast 20 mg tablets BID for 2 weeks followed by a 48-week extension of apremilast treatment.

Serious adverse events	Group 1 Adolescents: Apremilast 20 mg	Group 1 Adolescents: Apremilast 30 mg	Group 2: Children Apremilast 20 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 13 (0.00%)	0 / 8 (0.00%)	1 / 21 (4.76%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Nervous system disorders			
Syncope			
subjects affected / exposed	0 / 13 (0.00%)	0 / 8 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Group 1 Adolescents: Apremilast 20 mg	Group 1 Adolescents: Apremilast 30 mg	Group 2: Children Apremilast 20 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	13 / 13 (100.00%)	7 / 8 (87.50%)	19 / 21 (90.48%)
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	2 / 13 (15.38%)	0 / 8 (0.00%)	0 / 21 (0.00%)
occurrences (all)	2	0	0
Influenza like illness			
subjects affected / exposed	1 / 13 (7.69%)	0 / 8 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Pyrexia			
subjects affected / exposed	1 / 13 (7.69%)	1 / 8 (12.50%)	2 / 21 (9.52%)
occurrences (all)	1	1	3
Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed	2 / 13 (15.38%)	0 / 8 (0.00%)	1 / 21 (4.76%)
occurrences (all)	8	0	1
Respiratory, thoracic and mediastinal disorders			
Asthma exercise induced			
subjects affected / exposed	1 / 13 (7.69%)	0 / 8 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Cough			
subjects affected / exposed	3 / 13 (23.08%)	1 / 8 (12.50%)	2 / 21 (9.52%)
occurrences (all)	4	1	2
Nasal congestion			
subjects affected / exposed	1 / 13 (7.69%)	0 / 8 (0.00%)	1 / 21 (4.76%)
occurrences (all)	1	0	1
Oropharyngeal pain			
subjects affected / exposed	2 / 13 (15.38%)	0 / 8 (0.00%)	3 / 21 (14.29%)
occurrences (all)	3	0	7
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 13 (7.69%)	0 / 8 (0.00%)	1 / 21 (4.76%)
occurrences (all)	1	0	1
Attention deficit/hyperactivity disorder			

subjects affected / exposed	0 / 13 (0.00%)	1 / 8 (12.50%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Depressed mood			
subjects affected / exposed	1 / 13 (7.69%)	0 / 8 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Insomnia			
subjects affected / exposed	2 / 13 (15.38%)	0 / 8 (0.00%)	1 / 21 (4.76%)
occurrences (all)	2	0	1
Intentional self-injury			
subjects affected / exposed	1 / 13 (7.69%)	0 / 8 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Mood swings			
subjects affected / exposed	1 / 13 (7.69%)	0 / 8 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Investigations			
Blood creatinine increased			
subjects affected / exposed	0 / 13 (0.00%)	1 / 8 (12.50%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Blood glucose increased			
subjects affected / exposed	1 / 13 (7.69%)	0 / 8 (0.00%)	1 / 21 (4.76%)
occurrences (all)	1	0	1
Electrocardiogram abnormal			
subjects affected / exposed	0 / 13 (0.00%)	1 / 8 (12.50%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Eosinophil count increased			
subjects affected / exposed	0 / 13 (0.00%)	0 / 8 (0.00%)	3 / 21 (14.29%)
occurrences (all)	0	0	3
Monocyte count increased			
subjects affected / exposed	0 / 13 (0.00%)	0 / 8 (0.00%)	2 / 21 (9.52%)
occurrences (all)	0	0	2
Protein urine present			
subjects affected / exposed	1 / 13 (7.69%)	0 / 8 (0.00%)	2 / 21 (9.52%)
occurrences (all)	1	0	2
Weight decreased			
subjects affected / exposed	2 / 13 (15.38%)	0 / 8 (0.00%)	0 / 21 (0.00%)
occurrences (all)	2	0	0

White blood cells urine positive			
subjects affected / exposed	1 / 13 (7.69%)	0 / 8 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Injury, poisoning and procedural complications			
Dislocation of vertebra			
subjects affected / exposed	1 / 13 (7.69%)	0 / 8 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Ligament sprain			
subjects affected / exposed	0 / 13 (0.00%)	1 / 8 (12.50%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 13 (7.69%)	0 / 8 (0.00%)	0 / 21 (0.00%)
occurrences (all)	2	0	0
Headache			
subjects affected / exposed	7 / 13 (53.85%)	1 / 8 (12.50%)	11 / 21 (52.38%)
occurrences (all)	17	2	21
Syncope			
subjects affected / exposed	0 / 13 (0.00%)	1 / 8 (12.50%)	1 / 21 (4.76%)
occurrences (all)	0	1	2
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	0 / 13 (0.00%)	1 / 8 (12.50%)	1 / 21 (4.76%)
occurrences (all)	0	2	1
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	1 / 13 (7.69%)	1 / 8 (12.50%)	3 / 21 (14.29%)
occurrences (all)	2	1	3
Abdominal pain			
subjects affected / exposed	6 / 13 (46.15%)	1 / 8 (12.50%)	11 / 21 (52.38%)
occurrences (all)	15	1	43
Abdominal pain upper			
subjects affected / exposed	2 / 13 (15.38%)	1 / 8 (12.50%)	4 / 21 (19.05%)
occurrences (all)	2	11	5
Change of bowel habit			

subjects affected / exposed	1 / 13 (7.69%)	0 / 8 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Constipation			
subjects affected / exposed	1 / 13 (7.69%)	0 / 8 (0.00%)	1 / 21 (4.76%)
occurrences (all)	1	0	1
Diarrhoea			
subjects affected / exposed	6 / 13 (46.15%)	4 / 8 (50.00%)	5 / 21 (23.81%)
occurrences (all)	23	18	7
Dyspepsia			
subjects affected / exposed	2 / 13 (15.38%)	1 / 8 (12.50%)	1 / 21 (4.76%)
occurrences (all)	2	1	1
Flatulence			
subjects affected / exposed	1 / 13 (7.69%)	0 / 8 (0.00%)	1 / 21 (4.76%)
occurrences (all)	1	0	1
Gastrointestinal disorder			
subjects affected / exposed	1 / 13 (7.69%)	0 / 8 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Haematemesis			
subjects affected / exposed	1 / 13 (7.69%)	0 / 8 (0.00%)	0 / 21 (0.00%)
occurrences (all)	2	0	0
Nausea			
subjects affected / exposed	8 / 13 (61.54%)	4 / 8 (50.00%)	10 / 21 (47.62%)
occurrences (all)	11	7	18
Vomiting			
subjects affected / exposed	4 / 13 (30.77%)	1 / 8 (12.50%)	8 / 21 (38.10%)
occurrences (all)	8	1	12
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	1 / 13 (7.69%)	0 / 8 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 13 (7.69%)	0 / 8 (0.00%)	2 / 21 (9.52%)
occurrences (all)	1	0	2
Foot deformity			

subjects affected / exposed	1 / 13 (7.69%)	0 / 8 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Joint swelling			
subjects affected / exposed	1 / 13 (7.69%)	0 / 8 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal pain			
subjects affected / exposed	1 / 13 (7.69%)	0 / 8 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Pain in extremity			
subjects affected / exposed	2 / 13 (15.38%)	0 / 8 (0.00%)	0 / 21 (0.00%)
occurrences (all)	2	0	0
Patellofemoral pain syndrome			
subjects affected / exposed	1 / 13 (7.69%)	0 / 8 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	2 / 13 (15.38%)	1 / 8 (12.50%)	5 / 21 (23.81%)
occurrences (all)	2	2	5
Gastroenteritis viral			
subjects affected / exposed	2 / 13 (15.38%)	0 / 8 (0.00%)	1 / 21 (4.76%)
occurrences (all)	2	0	3
Influenza			
subjects affected / exposed	2 / 13 (15.38%)	0 / 8 (0.00%)	1 / 21 (4.76%)
occurrences (all)	2	0	1
Localised infection			
subjects affected / exposed	1 / 13 (7.69%)	0 / 8 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Nasopharyngitis			
subjects affected / exposed	6 / 13 (46.15%)	3 / 8 (37.50%)	7 / 21 (33.33%)
occurrences (all)	11	3	12
Pharyngitis streptococcal			
subjects affected / exposed	1 / 13 (7.69%)	1 / 8 (12.50%)	0 / 21 (0.00%)
occurrences (all)	1	1	0
Tooth infection			
subjects affected / exposed	0 / 13 (0.00%)	0 / 8 (0.00%)	2 / 21 (9.52%)
occurrences (all)	0	0	2

Upper respiratory tract infection			
subjects affected / exposed	0 / 13 (0.00%)	0 / 8 (0.00%)	2 / 21 (9.52%)
occurrences (all)	0	0	2
Urinary tract infection			
subjects affected / exposed	1 / 13 (7.69%)	2 / 8 (25.00%)	0 / 21 (0.00%)
occurrences (all)	1	2	0
Viral infection			
subjects affected / exposed	1 / 13 (7.69%)	1 / 8 (12.50%)	0 / 21 (0.00%)
occurrences (all)	1	1	0
Tonsillitis streptococcal			
subjects affected / exposed	1 / 13 (7.69%)	0 / 8 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	2 / 13 (15.38%)	1 / 8 (12.50%)	1 / 21 (4.76%)
occurrences (all)	3	1	1
Obesity			
subjects affected / exposed	0 / 13 (0.00%)	1 / 8 (12.50%)	0 / 21 (0.00%)
occurrences (all)	0	1	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 August 2015	1. Primary objective was clarified to reflect that the study was being conducted to select a pediatric dose of apremilast (APR) 2. Adjusted age ranges of subject groups 3. The C-SSRS questionnaire was added at Screening, Baseline and other visits (except Week 102 follow up) 4. Exclusion criterion was added (mandated ineligibility if any question was answered YES at Screening) 4. Psychiatric Evaluation Section was updated 5. Added Tanner Staging Assessment and description 6. Added Extension Treatment Period; Optional open label was deleted in the Extension Treatment Period; 50-week Treatment Extension Period was changed to 48-week Treatment Extension Period; Length of study was shortened to 107 weeks 7. Two more visits at Week 24 and Week 40 were added to comply with safety assessments and language was updated from 5 visits to 7 additional visits 8. Added Short-term follow-up and adjusted to 4 weeks and 8 weeks after the last dose of APR; Week 56 short-term Follow-up Visit changed to Weeks 54 and 58 9. Number of subjects was changed to at least 32 and at least 16 subjects in each group 10. Daily Stool Diary was added 11. Updated Frequency of Height Measurements 12. Study Timeline Schematic was updated to reflect FDA changes; included length of Extension Treatment Period, addition of post 8-week follow-up, and adjustment to length of study 13. Two additional ECG readings were added 14. Psoriasis flare and rebound were not considered AEs 15. Canada was added as a participating country 16. Prior treatment with APR was added as an exclusion criterion 17. Pregnancy was added as reason for withdrawal 18. Added Moderate to Severe to protocol title 19. Removed text that described use of a subject pill diary 20. Added a faces Likert Scale 21. Psoriasis Flare and Rebound section title was changed to Worsening Psoriasis and Rebound Assessments 22. Added pregnancy tests to Overview of Safety Assessments 23. Two sentences were added to dosing scenario for Group 1. and Group 2.
29 April 2016	1. Revised WBC count, platelet count, and hemoglobin levels for subject eligibility; gender- and age-specific allowed for up to 10% lower than the LLN for hemoglobin and platelet count levels, and for up to 20% lower for the WBC counts 2. Added the excipients of apremilast to screen for potential sensitivity; excipients of apremilast were specified and listed in the exclusion criterion 3. Added an exclusion criterion for deficiencies in lactose metabolism; an exclusion criterion was added for subjects who may have had an allergy to lactose 4. Extended eligibility to subjects previously exposed to biologic therapy; the amendment allowed inclusion of potential subjects who had been previously exposed to a systemic biologic therapy; Inclusion Criterion #12 was modified. Exclusion Criterion #19 was added to specify required washout periods for previous biologic therapies 5. Removal of the 24-hour post-Day 14 dosing PK blood draw time point; removed the last blood draw (24 hours after the Day 14 dose) from the intensive PK assessments for Group 1; 6. A reminder to take the Day 14 dose only after the 12-hour; postdose blood draw was added for clarification 7. Modified highly effective to effective in the Option 1 description of contraception methods for females 8. A statement was added to show the percentage of subjects in Studies PSOR-008 and PSOR-009 who had prior exposure to biologic therapy 9. Additional text was included to clarify that the consenting/assenting process must be repeated for any subject who fails Screening and returns to be rescreened 10. Text was added to clarify that not all 16 subjects in Group 1 needed to have both the DBS assay and a venous blood draw if the DBS method of blood sample analysis was validated before all Group 1 subjects had blood taken using both methods 11. More sites were to be added to the study so an update of the approximate number of sites was entered 12. Text describing the shipping of PK samples was clarified

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported