

## **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
N	

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:			
	h a weight of $\geq$ 35 kg to < 70 kg received apremilast tablets 20 ed 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, wit 2 weeks followed by a 48-week extension	h a weight of $\geq$ 70 kg received apremilast 30 mg tablets BID for on 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 2 weeks followed by a 48-week extension	a weight of $\geq$ 15 kg received apremilast 20 mg tablets BID for 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  $\geq$  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  $\geq$  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  $\geq$  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	Adolescents: Adolescents:	
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	

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

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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 diseas (erythema, thickness, and scaling) and cregions. PASI scores range from 0 to 72, Erythema, thickness, and scaling are scoregions of the body: head, trunk, upper anatomic regions is scored on a scale of	legree of skin surface with higher scores regred on a scale of 0 (n limbs, and lower limbs	area involvement on eflecting greater disea one) to 4 (very seven s. Degree of involvem	defined anatomical se severity. e) on 4 anatomic ent on each of the 4
Units: Units on a scale			
arithmetic mean			
standard deviation	-		

## **End points**

## **End points reporting groups**

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Reporting group title	Group 1 Adolescents: Apremilast 20 mg
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### Reporting group description:

Participants ages 12 to 17 years old, with a weight of  $\geq$  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  $\geq$  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  $\geq$  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)**

•	Number of Participants with Treatment Emergent Adverse Events (TEAEs) <sup>[1]</sup>
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## 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
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### 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 <sup>[2]</sup>	

### 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, eq., predose, 2 and 8 hours post a dose.

End point type	Primary
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### 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.

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End point type	IPrimary
Life point type	primitary

### 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
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### 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) <sup>[5]</sup>

### 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.

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## 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 <sup>[6]</sup>

## 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.

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End point type	IDrimary
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## 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)<sup>[7]</sup>

### 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		IPrimary
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### 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 <sup>[8]</sup>

### 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
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## 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
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Reporting group description:

Participants ages 12 to 17 years old, with a weight of  $\geq$  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
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Reporting group description:

Participants ages 12 to 17 years old, with a weight of  $\geq$  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
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Reporting group description:

Participants ages 6 to 11 years old, with a weight of  $\geq$  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

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	0 / 10 /0 000/	. (0 (10 500()	0 / 0 / (0 000/)
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
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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 / 13 (13.36%)	1 / 8 (12.30%)	1 (4.70%)	
	۷	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	
Veniting				
Vomiting subjects affected / exposed	4 / 13 (30.77%)	1 / 8 (12.50%)	8 / 21 (38.10%)	
occurrences (all)	8	1	12	
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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 / 12 /7 (00/)	0 / 9 / 0 000/ \	2 / 21 /0 520/ \	
occurrences (all)	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
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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 / 13 (13.30 %)	0	0
l seem sinces (air)	2	U	
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
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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 infaction			
Tooth infection subjects affected / exposed	0 / 13 (0.00%)	0 / 8 (0.00%)	2 / 21 (9.52%)
occurrences (all)			
decarrences (an)	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