



Clinical trial results:

A Phase 2, randomized, placebo-controlled, multicenter study to investigate the efficacy and safety of apremilast (CC-10004) for treatment of subjects with active ulcerative colitis.

Summary

EudraCT number	2014-002981-64
Trial protocol	CZ BG IT
Global end of trial date	03 June 2019

Results information

Result version number	v1 (current)
This version publication date	13 March 2020
First version publication date	13 March 2020

Trial information

Trial identification

Sponsor protocol code	CC-10004-UC-001
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02289417
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	Denesh Chitkara, Celgene Corporation, 01 908-897-5751, dchitkara@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 2019
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	03 June 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the clinical efficacy of apremilast (30 mg twice daily [BID] and 40 mg BID), compared with placebo, in subjects with active ulcerative colitis (UC).

Protection of trial subjects:

Patient Confidentiality, Informed Consent, Archiving of Essential Documents

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	08 January 2015
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
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	Australia: 9
Country: Number of subjects enrolled	Bulgaria: 10
Country: Number of subjects enrolled	Canada: 3
Country: Number of subjects enrolled	Czech Republic: 6
Country: Number of subjects enrolled	France: 18
Country: Number of subjects enrolled	Germany: 3
Country: Number of subjects enrolled	Hungary: 3
Country: Number of subjects enrolled	Italy: 21
Country: Number of subjects enrolled	Netherlands: 2
Country: Number of subjects enrolled	Poland: 36
Country: Number of subjects enrolled	Russian Federation: 2
Country: Number of subjects enrolled	Ukraine: 13
Country: Number of subjects enrolled	United States: 41
Country: Number of subjects enrolled	New Zealand: 3
Worldwide total number of subjects	170
EEA total number of subjects	99

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)	158
From 65 to 84 years	12
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 61 sites in Australia (3 sites) and New Zealand (1 site); Bulgaria (6 sites), Czech Republic (2 sites), Hungary (3 sites), Poland (9 sites), Russia (1 site), and Ukraine (10 sites); Canada (2 sites) and United States (13 sites); and France (4 sites), Germany (1 site), Italy (4 sites), and the Netherlands (2 sites).

Pre-assignment

Screening details:

A total of 170 participants were randomized in a 1:1:1 ratio and received apremilast (30 mg BID or 40 mg BID), or identically appearing placebo and stratified based on concomitant use of oral corticosteroids and previous exposure to immunosuppressants.

Period 1

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

Blinding implementation details:

The blind was not to be broken during the study unless, in the opinion of the investigator, it was necessary to safely treat the subject. The decision to break the blind in emergency situations was the responsibility of the treating physician, which was not to be delayed or refused by the sponsor. However, the investigator could contact the Medical Monitor prior to breaking the blind to discuss unblinding, mainly in the interest of the subject.

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Participants were randomized to identically matching placebo capsules and received placebo capsules by mouth (PO) twice a day (BID) for 12 weeks during the double-blind placebo-controlled phase.

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

Dosage and administration details:

Placebo capsules (identical in appearance to apremilast) BID.

Arm title	Apremilast 30 mg
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Arm description:

Participants were randomized to apremilast 30 mg capsules PO BID for 12 weeks during the double-blind placebo-controlled phase.

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

Dosage and administration details:

Apremilast 30 mg capsules BID

Arm title	Apremilast 40 mg
Arm description: Participants were randomized to 40 mg apremilast capsules PO BID for 12 weeks during the double-blind placebo-controlled phase.	
Arm type	Experimental
Investigational medicinal product name	Apremilast
Investigational medicinal product code	
Other name	Otezla; CC-10004
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Apremilast 40 mg capsules BID

Number of subjects in period 1	Placebo	Apremilast 30 mg	Apremilast 40 mg
Started	58	57	55
Completed	51	53	52
Not completed	7	4	3
Consent withdrawn by subject	1	3	2
Adverse event, non-fatal	3	-	1
Lost to follow-up	-	1	-
Lack of efficacy	3	-	-

Period 2

Period 2 title	Active Treatment Phase Weeks 12-52
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

The blind was not to be broken during the study unless, in the opinion of the investigator, it was necessary to safely treat the subject. The decision to break the blind in emergency situations was the responsibility of the treating physician, which was not to be delayed or refused by the sponsor. However, the investigator could contact the Medical Monitor prior to breaking the blind to discuss unblinding, mainly in the interest of the subject.

Arms

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

Arm description:

Participants initially randomized to placebo capsules in the placebo-controlled period were re-randomized at week 12 to receive 30 mg apremilast capsules BID for 40 weeks during the active treatment phase.

Arm type	Experimental
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Investigational medicinal product name	Apremilast
Investigational medicinal product code	
Other name	Otezla; CC-10004
Pharmaceutical forms	Capsule
Routes of administration	Oral use
Dosage and administration details: Apremilast 30 mg capsules BID.	
Arm title	Placebo/Apremilast 40 mg
Arm description: Participants initially randomized to placebo in the placebo-controlled period were re-randomized at week 12 to receive 40 mg apremilast capsules BID for 40 weeks during the active treatment phase.	
Arm type	Experimental
Investigational medicinal product name	Apremilast
Investigational medicinal product code	
Other name	Otezla; CC-10004
Pharmaceutical forms	Capsule
Routes of administration	Oral use
Dosage and administration details: Apremilast 40 mg capsules BID.	
Arm title	Apremilast 30 mg/Apremilast 30 mg
Arm description: Participants were randomized to apremilast 30 mg capsules PO BID for 12 weeks during the double-blind placebo-controlled phase. At week 12, participants who achieved at least a 20% decrease from baseline in the total Mayo score (TMS) continued to receive 30 mg apremilast capsules BID for an additional 40 weeks during the active treatment phase.	
Arm type	Experimental
Investigational medicinal product name	Apremilast
Investigational medicinal product code	
Other name	Otezla; CC-10004
Pharmaceutical forms	Capsule
Routes of administration	Oral use
Dosage and administration details: Apremilast 30 mg capsules BID.	
Arm title	Apremilast 30 mg/ Apremilast 40 mg
Arm description: Participants initially randomized to 30 mg apremilast capsules BID in the placebo-controlled phase who did not achieve at least 20% decrease in the TMS were re-assigned to 40 mg apremilast capsules BID for 40 weeks during the active treatment phase.	
Arm type	Experimental
Investigational medicinal product name	Apremilast
Investigational medicinal product code	
Other name	Otezla; CC-10004
Pharmaceutical forms	Capsule
Routes of administration	Oral use
Dosage and administration details: Apremilast 40 mg capsules BID.	
Arm title	Apremilast 40 mg/Apremilast 40 mg
Arm description: Participants initially randomized to 40 mg apremilast capsules BID in the placebo-controlled phase continued to receive 40 mg apremilast capsules BID for an additional 40 weeks during the active treatment phase, regardless of achieving a 20% decrease in TMS or not.	
Arm type	Experimental

Investigational medicinal product name	Apremilast
Investigational medicinal product code	
Other name	Otezla; CC-10004
Pharmaceutical forms	Capsule
Routes of administration	Oral use
Dosage and administration details: Apremilast 40 mg capsules BID.	
Investigational medicinal product name	Apremilast
Investigational medicinal product code	
Other name	Otezla; CC-10004
Pharmaceutical forms	Capsule
Routes of administration	Oral use
Dosage and administration details: Apremilast 40 mg capsules BID.	

Number of subjects in period 2	Placebo/Apremilast 30 mg	Placebo/Apremilast 40 mg	Apremilast 30 mg/Apremilast 30 mg
Started	26	25	41
Completed	17	20	39
Not completed	9	5	2
Consent withdrawn by subject	-	1	-
Adverse event, non-fatal	2	2	1
Miscellaneous	1	-	-
Pregnancy	-	-	-
Lost to follow-up	-	-	-
Lack of efficacy	6	2	1

Number of subjects in period 2	Apremilast 30 mg/ Apremilast 40 mg	Apremilast 40 mg/Apremilast 40 mg
Started	12	52
Completed	7	39
Not completed	5	13
Consent withdrawn by subject	1	1
Adverse event, non-fatal	1	4
Miscellaneous	-	1
Pregnancy	-	1
Lost to follow-up	-	1
Lack of efficacy	3	5

Period 3

Period 3 title	Extension Phase Weeks 52-104
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Extension Phase: Apremilast 30 mg

Arm description:

Participants who completed 52 weeks of treatment and had a Mayo endoscopy score ≤ 1 at week 52 were eligible to participate in the 52-week extension phase and receive 30 mg apremilast BID for an additional 52 weeks. This includes participants assigned to 30 mg apremilast BID at week 12, and participants who entered the extension phase after implementation of Protocol Amendment 4.

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

Dosage and administration details:

Apremilast 30 mg capsules BID

Arm title	Extension Phase Apremilast 40 mg
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Arm description:

Participants who completed 52 weeks of treatment and had a Mayo endoscopy score ≤ 1 at week 52 were eligible to participate in the 52-week extension phase and receive 40 mg apremilast BID for an additional 52 weeks. This includes participants assigned to 30 mg apremilast BID at week 12. After implementation of Protocol Amendment 4 participants were switched to 30 mg apremilast BID for the remainder of the extension phase.

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

Dosage and administration details:

Apremilast 40 mg capsules BID

Number of subjects in period 3^[1]	Extension Phase: Apremilast 30 mg	Extension Phase Apremilast 40 mg
Started	45	54
Completed	38	48
Not completed	7	6
Consent withdrawn by subject	2	1
Adverse event, non-fatal	2	3
Miscellaneous	1	-
Lack of efficacy	2	2

Notes:

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

Justification: Not all subjects advanced to the next phase either by choice or due to disease.

Baseline characteristics

Reporting groups

Reporting group title	Placebo
Reporting group description: Participants were randomized to identically matching placebo capsules and received placebo capsules by mouth (PO) twice a day (BID) for 12 weeks during the double-blind placebo-controlled phase.	
Reporting group title	Apremilast 30 mg
Reporting group description: Participants were randomized to apremilast 30 mg capsules PO BID for 12 weeks during the double-blind placebo-controlled phase.	
Reporting group title	Apremilast 40 mg
Reporting group description: Participants were randomized to 40 mg apremilast capsules PO BID for 12 weeks during the double-blind placebo-controlled phase.	

Reporting group values	Placebo	Apremilast 30 mg	Apremilast 40 mg
Number of subjects	58	57	55
Age categorical Units: Subjects			
Adults (18-64 years)	54	54	50
From 65-84 years	4	3	5
85 years and over	0	0	0
Age Continuous Units: Years			
arithmetic mean	42.9	40.1	43.4
standard deviation	± 14.04	± 13.50	± 14.92
Sex: Female, Male Units: Participants			
Female	25	18	21
Male	33	39	34
Race Units: Subjects			
Asian	0	0	1
White	54	52	45
Other	1	1	1
Not Reported or Collected	3	4	8
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	2	1	5
Not Hispanic or Latino	55	54	46
Unknown or Not Reported	1	2	4
Baseline Use of Oral Corticosteroids Units: Subjects			
Use of Baseline Corticosteroids	17	14	12
Non-Use of Corticosteroids	41	43	43
Previous Exposure to Immunosuppressants Units: Subjects			

Previous Exposure to Immunosuppressants	17	18	16
No Previous Exposure to Immunosuppressants	41	39	39
Duration of Ulcerative Colitis			
Units: Years			
arithmetic mean	6.85	6.15	8.63
standard deviation	± 7.043	± 5.432	± 10.278
Baseline Total Mayo Score (TMS)			
The TMS is an instrument designed to measure disease activity of Ulcerative Colitis (UC). The Mayo score ranges from 0 to 12 points. It consists of 4 subscores, each graded from 0 to 3 with higher scores indicating more severe disease: • Stool Frequency Subscore (SFS) • Rectal Bleeding Subscore (RBS) • Endoscopy Subscore • Physician's Global Assessment (PGA)			
Units: units on a scale			
arithmetic mean	8.2	8.5	8.1
standard deviation	± 1.68	± 1.62	± 1.67
Modified Mayo Score (MMS)			
The MMS was based on the stool frequency, rectal bleeding and endoscopy subscores of the total Mayo score, and excluded the Physician's Global subscore, since this was a global measure that is subjective in nature. The MMS range from 0 to 9 points with zero indicating no symptoms of active ulcerative colitis and 9 indicating the most severe symptoms.			
Units: units on a scale			
arithmetic mean	6.1	6.4	6.0
standard deviation	± 1.51	± 1.48	± 1.47
Partial Mayo Score (PMS)			
The partial Mayo score is the sum of the rectal bleeding score, the stool frequency score and the physician's global assessment. The partial Mayo score range is from 0 to 9 points with zero indicating no symptoms of active ulcerative colitis and 9 indicating the most severe symptoms and assessment.			
Units: units on a scale			
arithmetic mean	5.6	5.8	5.5
standard deviation	± 1.46	± 1.44	± 1.57
Mayo Endoscopic Subscore (MES)			
The Mayo endoscopy subscore findings are defined as: 0 = Normal or inactive disease 1 = Mild Disease (erythema, decreased vascular pattern, mild friability) 2 = Moderate Disease (marked erythema, lack of vascular pattern, friability erosions) 3 = Severe Disease (spontaneous bleeding, ulceration).			
Units: units on a scale			
arithmetic mean	2.6	2.7	2.6
standard deviation	± 0.49	± 0.45	± 0.49

Reporting group values	Total		
Number of subjects	170		
Age categorical			
Units: Subjects			
Adults (18-64 years)	158		
From 65-84 years	12		
85 years and over	0		
Age Continuous			
Units: Years			
arithmetic mean	-		
standard deviation			
Sex: Female, Male			
Units: Participants			
Female	64		
Male	106		

Race			
Units: Subjects			
Asian	1		
White	151		
Other	3		
Not Reported or Collected	15		
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	8		
Not Hispanic or Latino	155		
Unknown or Not Reported	7		
Baseline Use of Oral Corticosteroids			
Units: Subjects			
Use of Baseline Corticosteroids	43		
Non-Use of Corticosteroids	127		
Previous Exposure to Immunosuppressants			
Units: Subjects			
Previous Exposure to Immunosuppressants	51		
No Previous Exposure to Immunosuppressants	119		
Duration of Ulcerative Colitis			
Units: Years			
arithmetic mean			
standard deviation	-		
Baseline Total Mayo Score (TMS)			
The TMS is an instrument designed to measure disease activity of Ulcerative Colitis (UC). The Mayo score ranges from 0 to 12 points. It consists of 4 subscores, each graded from 0 to 3 with higher scores indicating more severe disease: • Stool Frequency Subscore (SFS) • Rectal Bleeding Subscore (RBS) • Endoscopy Subscore • Physician's Global Assessment (PGA)			
Units: units on a scale			
arithmetic mean			
standard deviation	-		
Modified Mayo Score (MMS)			
The MMS was based on the stool frequency, rectal bleeding and endoscopy subscores of the total Mayo score, and excluded the Physician's Global subscore, since this was a global measure that is subjective in nature. The MMS range from 0 to 9 points with zero indicating no symptoms of active ulcerative colitis and 9 indicating the most severe symptoms.			
Units: units on a scale			
arithmetic mean			
standard deviation	-		
Partial Mayo Score (PMS)			
The partial Mayo score is the sum of the rectal bleeding score, the stool frequency score and the physician's global assessment. The partial Mayo score range is from 0 to 9 points with zero indicating no symptoms of active ulcerative colitis and 9 indicating the most severe symptoms and assessment.			
Units: units on a scale			
arithmetic mean			
standard deviation	-		
Mayo Endoscopic Subscore (MES)			
The Mayo endoscopy subscore findings are defined as: 0 = Normal or inactive disease 1 = Mild Disease (erythema, decreased vascular pattern, mild friability) 2 = Moderate Disease (marked erythema, lack of vascular pattern, friability erosions) 3 = Severe Disease (spontaneous bleeding, ulceration).			
Units: units on a scale			
arithmetic mean			

standard deviation	-		
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End points

End points reporting groups

Reporting group title	Placebo
Reporting group description: Participants were randomized to identically matching placebo capsules and received placebo capsules by mouth (PO) twice a day (BID) for 12 weeks during the double-blind placebo-controlled phase.	
Reporting group title	Apremilast 30 mg
Reporting group description: Participants were randomized to apremilast 30 mg capsules PO BID for 12 weeks during the double-blind placebo-controlled phase.	
Reporting group title	Apremilast 40 mg
Reporting group description: Participants were randomized to 40 mg apremilast capsules PO BID for 12 weeks during the double-blind placebo-controlled phase.	
Reporting group title	Placebo/Apremilast 30 mg
Reporting group description: Participants initially randomized to placebo capsules in the placebo-controlled period were re-randomized at week 12 to receive 30 mg apremilast capsules BID for 40 weeks during the active treatment phase.	
Reporting group title	Placebo/Apremilast 40 mg
Reporting group description: Participants initially randomized to placebo in the placebo-controlled period were re-randomized at week 12 to receive 40 mg apremilast capsules BID for 40 weeks during the active treatment phase.	
Reporting group title	Apremilast 30 mg/Apremilast 30 mg
Reporting group description: Participants were randomized to apremilast 30 mg capsules PO BID for 12 weeks during the double-blind placebo-controlled phase. At week 12, participants who achieved at least a 20% decrease from baseline in the total Mayo score (TMS) continued to receive 30 mg apremilast capsules BID for an additional 40 weeks during the active treatment phase.	
Reporting group title	Apremilast 30 mg/ Apremilast 40 mg
Reporting group description: Participants initially randomized to 30 mg apremilast capsules BID in the placebo-controlled phase who did not achieve at least 20% decrease in the TMS were re-assigned to 40 mg apremilast capsules BID for 40 weeks during the active treatment phase.	
Reporting group title	Apremilast 40 mg/Apremilast 40 mg
Reporting group description: Participants initially randomized to 40 mg apremilast capsules BID in the placebo-controlled phase continued to receive 40 mg apremilast capsules BID for an additional 40 weeks during the active treatment phase, regardless of achieving a 20% decrease in TMS or not.	
Reporting group title	Extension Phase: Apremilast 30 mg
Reporting group description: Participants who completed 52 weeks of treatment and had a Mayo endoscopy score ≤ 1 at week 52 were eligible to participate in the 52-week extension phase and receive 30 mg apremilast BID for an additional 52 weeks. This includes participants assigned to 30 mg apremilast BID at week 12, and participants who entered the extension phase after implementation of Protocol Amendment 4.	
Reporting group title	Extension Phase Apremilast 40 mg
Reporting group description: Participants who completed 52 weeks of treatment and had a Mayo endoscopy score ≤ 1 at week 52 were eligible to participate in the 52-week extension phase and receive 40 mg apremilast BID for an additional 52 weeks. This includes participants assigned to 30 mg apremilast BID at week 12. After implementation of Protocol Amendment 4 participants were switched to 30 mg apremilast BID for the remainder of the extension phase.	
Subject analysis set title	Apremilast 30 mg
Subject analysis set type	Safety analysis

Subject analysis set description:

TEAEs during the apremilast 30 mg BID treatment for participants who received 30 mg apremilast capsules BID only and participants who initially received 30 mg apremilast capsules BID and switched to 40 mg apremilast capsules BID at Week 12, and participants who initially received placebo capsules BID and switched to 30 mg apremilast capsules BID at Week 12.

Subject analysis set title	Apremilast 40 mg
Subject analysis set type	Safety analysis

Subject analysis set description:

TEAEs during the apremilast 40 mg BID treatment for participants who received 40 mg apremilast capsules BID only, and participants who initially received placebo BID and switched to 40 mg apremilast capsules BID at Week 12.

Subject analysis set title	Apremilast 30 mg/Apremilast 40 mg
Subject analysis set type	Safety analysis

Subject analysis set description:

TEAEs during the apremilast 40 mg BID treatment for participants who initially received 30 mg apremilast BID and switched to 40 mg apremilast BID at Week 12.

Subject analysis set title	Extension Phase: Apremilast 30 mg
Subject analysis set type	Safety analysis

Subject analysis set description:

Participants who completed 52 weeks of treatment and had a Mayo endoscopy score ≤ 1 at week 52 were eligible to participate in the 52-week extension phase and received 30 mg apremilast BID for an additional 52 weeks. Includes participants assigned to 30 mg apremilast BID at week 12, and participants who entered the extension phase after implementation of Protocol Amendment 4.

Subject analysis set title	Extension Phase Apremilast 40 mg
Subject analysis set type	Safety analysis

Subject analysis set description:

Participants who completed 52 weeks of treatment and had a Mayo endoscopy score ≤ 1 at week 52 were eligible to participate in the 52-week extension phase and received 40 mg apremilast BID for an additional 52 weeks. After implementation of Protocol Amendment 4 participants were switched to 30 mg apremilast BID for the remainder of the extension phase

Primary: Percentage of Participants who Achieved a Clinical Remission by Total Mayo Score (TMS) at Week 12

End point title	Percentage of Participants who Achieved a Clinical Remission by Total Mayo Score (TMS) at Week 12
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End point description:

Clinical remission was defined as a total Mayo score ≤ 2 points, with no individual subscore exceeding 1 point. The TMS is an instrument designed to measure disease activity of UC. The Mayo score ranges from 0 to 12 points. It consists of 4 subscores, each graded from 0 to 3 with higher scores indicating more severe disease.

- Stool Frequency Subscore (SFS)
- Rectal Bleeding Subscore (RBS)
- Endoscopy Subscore
- Physician's Global Assessment (PGA).

Two-sided 95% confidence intervals (CI) for the within-group proportions are based on the Wilson score method. The intent to treat (ITT) population included all participants who received at least one dose of IP. Participants with insufficient data for response determination were considered non-responders.

End point type	Primary
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End point timeframe:

Week 12

End point values	Placebo	Apremilast 30 mg	Apremilast 40 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	58	57	55	
Units: Percentage of Participants				
number (confidence interval 95%)	12.1 (6.0 to 22.9)	31.6 (21.0 to 44.5)	21.8 (12.9 to 34.4)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Apremilast 30 mg
Number of subjects included in analysis	115
Analysis specification	Pre-specified
Analysis type	superiority ^[1]
P-value	= 0.0142 ^[2]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Stratified Differences in Percentages
Point estimate	19.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.4
upper limit	33.6

Notes:

[1] - Stratified difference in percentages is the weighted average of the treatment differences across the strata with the CMH weights, with 2-sided 95% CI based on the stratified Newcombe method.

[2] - Stratification was based on baseline use of PO corticosteroids and previously used immunosuppressants (yes/no).

Statistical analysis title	Statistical Analysis 2
Comparison groups	Placebo v Apremilast 40 mg
Number of subjects included in analysis	113
Analysis specification	Pre-specified
Analysis type	superiority ^[3]
P-value	= 0.2689 ^[4]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Stratified
Point estimate	7.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.9
upper limit	22.9

Notes:

[3] - Stratified difference in percentages is the weighted average of the treatment differences across the strata with the CMH weights, with 2-sided 95% CI based on the stratified Newcombe method

[4] - Stratification was based on baseline use of PO corticosteroids and previously used immunosuppressants (yes/no).

Secondary: Percentage of Participants who Achieved a Clinical Response by Total Mayo Score and the Reduction in the Rectal Bleeding Subscore at Week 12

End point title	Percentage of Participants who Achieved a Clinical Response by Total Mayo Score and the Reduction in the Rectal Bleeding Subscore at Week 12
<p>End point description:</p> <p>Clinical response was defined as a decrease from baseline in the TMS of at least 3 points and at least 30%, along with a reduction in the rectal bleeding subscore (RBS) of at least 1 point or an absolute RBS of ≤ 1. The TMS is an instrument designed to measure disease activity of UC. The Mayo score ranges from 0 to 12 points. It consists of 4 subscores, each graded from 0 to 3 with higher scores indicating more severe disease.</p> <ul style="list-style-type: none"> • Stool Frequency Subscore (SFS) • Rectal Bleeding Subscore • Endoscopy Subscore • Physician's Global Assessment (PGA) <p>Rectal bleeding (subscore 0-3) was defined as:</p> <p>0 = No blood seen</p> <p>1 = Streaks of blood with stool less than half the time</p> <p>2 = Obvious blood with stool</p> <p>3 = Blood alone passes</p> <p>Two-sided 95% CI for the within-group proportions are based on the Wilson score method.</p> <p>The ITT population included all participants who received at least one dose of IP. Participants with insufficient data for response determination were considered non-responders.</p>	
End point type	Secondary
<p>End point timeframe:</p> <p>Baseline to Week 12</p>	

End point values	Placebo	Apremilast 30 mg	Apremilast 40 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	58	57	55	
Units: Percentage of Participants				
number (confidence interval 95%)	46.6 (34.3 to 59.2)	61.4 (48.4 to 72.9)	67.3 (54.1 to 78.2)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Apremilast 30 mg
Number of subjects included in analysis	115
Analysis specification	Pre-specified
Analysis type	equivalence ^[5]
P-value	= 0.1224 ^[6]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Stratified Difference
Point estimate	14.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.6
upper limit	31.5

Notes:

[5] - Stratified difference in percentages is the weighted average of the treatment differences across the strata with the CMH weights, with 2-sided 95% CI based on the stratified Newcombe method.

[6] - Stratification was based on baseline use of PO corticosteroids and previously used immunosuppressants (yes/no).

Statistical analysis title	Statistical Analysis 2
Comparison groups	Placebo v Apremilast 40 mg
Number of subjects included in analysis	113
Analysis specification	Pre-specified
Analysis type	superiority ^[7]
P-value	= 0.0401 ^[8]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Stratified Difference
Point estimate	19.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.1
upper limit	36

Notes:

[7] - Stratified difference in percentages is the weighted average of the treatment differences across the strata with the CMH weights, with 2-sided 95% CI based on the stratified Newcombe method.

[8] - Stratification was based on baseline use of PO corticosteroids and previously used immunosuppressants (yes/no).

Secondary: Percentage of Participants who Achieved an Endoscopic Remission at Week 12

End point title	Percentage of Participants who Achieved an Endoscopic Remission at Week 12
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End point description:

An endoscopic remission was defined as a Mayo endoscopic subscore (MES) of 0 at Week 12.

The MES subscore findings were defined as:

0 = Normal or inactive disease

1 = Mild Disease (erythema, decreased vascular pattern, mild friability)

2 = Moderate Disease (marked erythema, lack of vascular pattern, friability erosions) 3 = Severe Disease (spontaneous bleeding, ulceration)

The endoscopy subscores consisted of findings that were centrally read through proctosigmoidoscopy, graded from 0 to 3 with higher scores indicating more severe disease. Two-sided 95% CIs for the within-group percentage were based on the Wilson score method.

The intent to treat population included all participants who received at least one dose of IP. Participants with insufficient data for response determination were considered non-responders.

End point type	Secondary
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End point timeframe:

Week 12

End point values	Placebo	Apremilast 30 mg	Apremilast 40 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	58	57	55	
Units: Percentage of Participants				
number (confidence interval 95%)	3.4 (1.0 to 11.7)	8.8 (3.8 to 18.9)	7.3 (2.9 to 17.3)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Apremilast 30 mg
Number of subjects included in analysis	115
Analysis specification	Pre-specified
Analysis type	superiority ^[9]
P-value	= 0.2472 ^[10]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Stratified Difference
Point estimate	5.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.7
upper limit	16.7

Notes:

[9] - Stratified difference in percentages is the weighted average of the treatment differences across the strata with the CMH weights, with 2-sided 95% CI based on the stratified Newcombe method.

[10] - Stratification was based on baseline use of PO corticosteroids and previously used immunosuppressants (yes/no).

Statistical analysis title	Statistical Analysis 2
Comparison groups	Placebo v Apremilast 40 mg
Number of subjects included in analysis	113
Analysis specification	Pre-specified
Analysis type	superiority ^[11]
P-value	= 0.4628 ^[12]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Stratified Difference
Point estimate	3.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.5
upper limit	14.6

Notes:

[11] - Stratified difference in percentages is the weighted average of the treatment differences across the strata with the CMH weights, with 2-sided 95% CI based on the stratified Newcombe method.

[12] - Stratification was based on baseline use of PO corticosteroids and previously used immunosuppressants (yes/no).

Secondary: Percentage of Participants who Achieved an Endoscopic Response at Week 12

End point title	Percentage of Participants who Achieved an Endoscopic Response at Week 12
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End point description:

An endoscopic response is defined as a decrease from baseline of at least 1 point in the MES at Week

12. The Mayo endoscopy subscore findings were defined as:

0 = Normal or inactive disease

1 = Mild Disease (erythema, decreased vascular pattern, mild friability)

2 = Moderate Disease (marked erythema, lack of vascular pattern, friability erosions) 3 = Severe Disease (spontaneous bleeding, ulceration).

The endoscopy subscores consisted of findings that were centrally read through proctosigmoidoscopy, graded from 0 to 3 with higher scores indicating more severe disease. Two-sided 95% CIs for the within-group percentage were based on the Wilson score method.

The intent to treat population included all participants who received at least one dose of IP. Participants with insufficient data for response determination were considered non-responders.

End point type	Secondary
End point timeframe:	
Week 12	

End point values	Placebo	Apremilast 30 mg	Apremilast 40 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	58	57	55	
Units: Percentage of Participants				
number (confidence interval 95%)	41.4 (29.6 to 54.2)	73.7 (61.0 to 83.4)	47.3 (34.7 to 60.2)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Apremilast 30 mg
Number of subjects included in analysis	115
Analysis specification	Pre-specified
Analysis type	superiority ^[13]
P-value	= 0.0005 ^[14]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Stratified Difference
Point estimate	32
Confidence interval	
level	95 %
sides	2-sided
lower limit	13.8
upper limit	47.4

Notes:

[13] - Stratified difference in percentages is the weighted average of the treatment differences across the strata with the CMH weights, with 2-sided 95% CI based on the stratified Newcombe method.

[14] - Stratification was based on baseline use of PO corticosteroids and previously used immunosuppressants (yes/no).

Statistical analysis title	Statistical Analysis 2
Comparison groups	Placebo v Apremilast 40 mg

Number of subjects included in analysis	113
Analysis specification	Pre-specified
Analysis type	superiority ^[15]
P-value	= 0.6878 ^[16]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Stratified Difference
Point estimate	3.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-14.4
upper limit	21.5

Notes:

[15] - Stratified difference in percentages is the weighted average of the treatment differences across the strata with the CMH weights, with 2-sided 95% CI based on the stratified Newcombe method.

[16] - Stratification was based on baseline use of PO corticosteroids and previously used immunosuppressants (yes/no).

Secondary: Percentage of Participants Who Achieved a Rectal Bleeding Subscore (RBS) of ≤ 1 at Week 12

End point title	Percentage of Participants Who Achieved a Rectal Bleeding Subscore (RBS) of ≤ 1 at Week 12
End point description:	
The RBS was measured as:	
0 = No blood seen	
1 = Streaks of blood with stool less than half the time	
2 = Obvious blood with stool most of the time	
3 = Blood alone passes	
The daily bleeding score represents the most severe bleeding of the day. Two-sided 95% CI for the within-group proportions are based on the Wilson score method.	
The intent to treat population included all participants who received at least one dose of IP. Participants with insufficient data for response determination were considered non-responders.	
End point type	Secondary
End point timeframe:	
Week 12	

End point values	Placebo	Apremilast 30 mg	Apremilast 40 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	58	57	55	
Units: Percentage of Participants				
number (confidence interval 95%)	72.4 (59.8 to 82.2)	84.2 (72.6 to 91.5)	87.3 (76.0 to 93.7)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Apremilast 30 mg

Number of subjects included in analysis	115
Analysis specification	Pre-specified
Analysis type	superiority ^[17]
P-value	= 0.1388 ^[18]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Stratified Difference
Point estimate	11.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.1
upper limit	26.1

Notes:

[17] - Stratified difference in percentages is the weighted average of the treatment differences across the strata with the CMH weights, with 2-sided 95% CI based on the stratified Newcombe method.

[18] - Stratification was based on baseline use of PO corticosteroids and previously used immunosuppressants (yes/no).

Statistical analysis title	Statistical Analysis 2
Comparison groups	Placebo v Apremilast 40 mg
Number of subjects included in analysis	113
Analysis specification	Pre-specified
Analysis type	superiority ^[19]
P-value	= 0.0788 ^[20]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Stratified Difference
Point estimate	13.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.6
upper limit	27.7

Notes:

[19] - Stratified difference in percentages is the weighted average of the treatment differences across the strata with the CMH weights, with 2-sided 95% CI based on the stratified Newcombe method.

[20] - Stratification was based on baseline use of PO corticosteroids and previously used immunosuppressants (yes/no).

Secondary: Percentage of Participants Who Achieved Clinical Remission in the Modified Mayo Subscore (MMS) at Week 12

End point title	Percentage of Participants Who Achieved Clinical Remission in the Modified Mayo Subscore (MMS) at Week 12
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End point description:

Clinical remission was defined as a modified Mayo score of ≤ 2 , with no individual subscore > 1 , at Week 12. The MMS was based on a modification of the total Mayo score (TMS) which included the stool frequency, rectal bleeding, and endoscopic subscores of the TMS and excluded the Physician's Global Assessment (PGA) subscore, since this was a global measure that is subjective in nature. The MMS ranges from 0 to 9 points with higher scores indicating greater disease severity. The endoscopy subscores were centrally reviewed. Two-sided confidence intervals for the within-group percentage were based on the Wilson score method. The intent to treat population included all participants who received at least one dose of IP. Participants with insufficient data for response determination were considered non-responders.

End point type	Secondary
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End point timeframe:

Week 12

End point values	Placebo	Apremilast 30 mg	Apremilast 40 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	58	57	55	
Units: Percentage of Participants				
number (confidence interval 95%)	19.0 (10.9 to 30.9)	43.9 (31.8 to 56.7)	27.3 (17.3 to 40.2)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Apremilast 30 mg
Number of subjects included in analysis	115
Analysis specification	Pre-specified
Analysis type	superiority ^[21]
P-value	= 0.0046 ^[22]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Stratified Difference
Point estimate	24.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	7.5
upper limit	40.1

Notes:

[21] - Stratified difference in percentages is the weighted average of the treatment differences across the strata with the CMH weights, with 2-sided 95% CI based on the stratified Newcombe method.

[22] - Stratification was based on baseline use of PO corticosteroids and previously used immunosuppressants (yes/no).

Statistical analysis title	Statistical Analysis 2
Comparison groups	Placebo v Apremilast 40 mg
Number of subjects included in analysis	113
Analysis specification	Pre-specified
Analysis type	superiority ^[23]
P-value	= 0.4476 ^[24]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Stratified Difference
Point estimate	6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.8
upper limit	21.6

Notes:

[23] - Stratified difference in percentages is the weighted average of the treatment differences across the strata with the CMH weights, with 2-sided 95% CI based on the stratified Newcombe method.

Secondary: Percentage of Participants Who Achieved Clinical Response in the Modified Mayo Subscore (MMS) at Week 12

End point title	Percentage of Participants Who Achieved Clinical Response in the Modified Mayo Subscore (MMS) at Week 12
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End point description:

Clinical response in the MMS was defined as a decrease from baseline in the MMS of at least 2 points and at least 25%, along with a reduction in the RBS of at least 1 point or an absolute RBS ≤ 1 . The MMS was based on the stool frequency, rectal bleeding, and endoscopic subscores of the TMS and excluded the PGA subscore. The MMS ranges from 0 to 9 points with higher scores indicating greater disease severity. The RBS was measured as: 0 = No blood seen 1 = Streaks of blood with stool less than half the time 2 = Obvious blood with stool most of the time 3 = Blood alone passes. The daily bleeding score represents the most severe bleeding of the day. The endoscopy subscores was centrally reviewed. Two-sided confidence intervals for the within-group percentage were based on the Wilson score method. The intent to treat population included all participants who received at least one dose of IP. Participants with insufficient data for response determination were considered non-responders.

End point type	Secondary
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End point timeframe:

Week 12

End point values	Placebo	Apremilast 30 mg	Apremilast 40 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	58	57	55	
Units: Percentage of Participants				
number (confidence interval 95%)	46.6 (34.3 to 59.2)	63.2 (50.2 to 74.5)	67.3 (54.1 to 78.2)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
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Statistical analysis description:

Stratified difference in percentages is the weighted average of the treatment differences across the strata with the CMH weights, with 2-sided 95% CI based on the stratified Newcombe method.

Comparison groups	Placebo v Apremilast 30 mg
Number of subjects included in analysis	115
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0755 [25]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Stratified difference in proportions
Point estimate	16.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.4
upper limit	33.5

Notes:

[25] - Stratification was based on baseline use of PO corticosteroids and previously used immunosuppressants (yes/no).

Statistical analysis title	Statistical Analysis 2
Comparison groups	Placebo v Apremilast 40 mg
Number of subjects included in analysis	113
Analysis specification	Pre-specified
Analysis type	superiority ^[26]
P-value	= 0.037 ^[27]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Stratified difference in proportions
Point estimate	19.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.5
upper limit	36.4

Notes:

[26] - Stratified difference in percentages is the weighted average of the treatment differences across the strata with the CMH weights, with 2-sided 95% CI based on the stratified Newcombe method.

[27] - Stratification was based on baseline use of PO corticosteroids and previously used immunosuppressants (yes/no).

Secondary: Percentage of Participants Who Achieved Clinical Remission in the Partial Mayo Subscore (PMS) With no Individual Subscore >1 at Week 8

End point title	Percentage of Participants Who Achieved Clinical Remission in the Partial Mayo Subscore (PMS) With no Individual Subscore >1 at Week 8
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End point description:

Clinical remission in the partial Mayo subscore was defined as a PMS of 2 points or lower, with no individual subscore >1. The PMS is a discrete ordinal scale ranging from 0 (normal or inactive disease) to 9 (severe disease) and is a composite of 3 subscores:

Stool Frequency Subscore, Rectal Bleeding Subscore, and Physician's Global Assessment Subscore, each of which ranges from 0 (normal) to 3 (severe disease).

Two-sided 95% CI for the within-group proportions are based on the Wilson score method. The intent to treat population included all participants who received at least one dose of IP. Participants with insufficient data for response determination were considered non-responders.

End point type	Secondary
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End point timeframe:

Week 8

End point values	Placebo	Apremilast 30 mg	Apremilast 40 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	58	57	55	
Units: Percentage of Participants				
number (confidence interval 95%)	32.8 (22.1 to 45.6)	47.4 (35.0 to 60.1)	52.7 (39.8 to 65.3)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Apremilast 30 mg
Number of subjects included in analysis	115
Analysis specification	Pre-specified
Analysis type	superiority ^[28]
P-value	= 0.1167 ^[29]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Stratified Difference
Point estimate	14.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.3
upper limit	31.4

Notes:

[28] - Stratified difference in percentages is the weighted average of the treatment differences across the strata with the CMH weights, with 2-sided 95% CI based on the stratified Newcombe method.

[29] - Stratification was based on baseline use of PO corticosteroids and previously used immunosuppressants (yes/no).

Statistical analysis title	Statistical Analysis 2
Comparison groups	Placebo v Apremilast 40 mg
Number of subjects included in analysis	113
Analysis specification	Pre-specified
Analysis type	superiority ^[30]
P-value	= 0.0534 ^[31]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Stratified Difference
Point estimate	18.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.3
upper limit	34.9

Notes:

[30] - Stratified difference in percentages is the weighted average of the treatment differences across the strata with the CMH weights, with 2-sided 95% CI based on the stratified Newcombe method.

[31] - Stratification was based on baseline use of PO corticosteroids and previously used immunosuppressants (yes/no).

Secondary: Percentage of Participants Who Achieved Clinical Response in the Partial Mayo Subscore at Week 8

End point title	Percentage of Participants Who Achieved Clinical Response in the Partial Mayo Subscore at Week 8
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End point description:

Clinical response in the PMS was defined as a decrease from baseline in PMS of at least 2 points and at least 25%, with an accompanying decrease in the RBS of at least 1 point or an absolute RBS of 0 or 1. The PMS score is a discrete ordinal scale ranging from 0 (normal or inactive disease) to 9 (severe disease) and is a composite of 3 subscores:

Stool Frequency Subscore, Rectal Bleeding Subscore, and Physician's Global Assessment Subscore, each of which ranges from 0 (normal) to 3 (severe disease).

Two-sided 95% CI for the within-group proportions are based on the Wilson score method. The intent to treat population included all participants who received at least one dose of IP. Participants with insufficient data for response determination were considered non-responders.

End point type	Secondary
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End point timeframe:

Week 8

End point values	Placebo	Apremilast 30 mg	Apremilast 40 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	58	57	55	
Units: Percentage of Participants				
number (confidence interval 95%)	48.3 (35.9 to 60.8)	64.9 (51.9 to 76.0)	81.8 (69.7 to 89.8)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Apremilast 30 mg
Number of subjects included in analysis	115
Analysis specification	Pre-specified
Analysis type	superiority ^[32]
P-value	= 0.0758 ^[33]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Stratified Difference
Point estimate	16.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.5
upper limit	33.3

Notes:

[32] - Stratified difference in percentages is the weighted average of the treatment differences across the strata with the CMH weights, with 2-sided 95% CI based on the stratified Newcombe method.

[33] - Stratification was based on baseline use of PO corticosteroids and previously used immunosuppressants (yes/no).

Statistical analysis title	Statistical Analysis 2
Comparison groups	Placebo v Apremilast 40 mg
Number of subjects included in analysis	113
Analysis specification	Pre-specified
Analysis type	superiority ^[34]
P-value	= 0.0004 ^[35]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Stratified Difference
Point estimate	32.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	14.9
upper limit	47.5

Notes:

[34] - Stratified difference in percentages is the weighted average of the treatment differences across the strata with the CMH weights, with 2-sided 95% CI based on the stratified Newcombe method.

[35] - Stratification was based on baseline use of PO corticosteroids and previously used immunosuppressants (yes/no).

Secondary: The Number of Participants Who Experienced Treatment Emergent Adverse Events (TEAEs) During the Placebo-Controlled Phase

End point title	The Number of Participants Who Experienced Treatment Emergent Adverse Events (TEAEs) During the Placebo-Controlled Phase
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End point description:

A TEAE was defined as any adverse event (AE) occurring or worsening on or after the first treatment of apremilast and up to 28 days after the last apremilast dose or the last follow-up date, whichever occurred earlier. A serious AE = any AE which results in death; is life-threatening; requires inpatient hospitalization or prolongation of existing hospitalization; results in persistent or significant disability/incapacity; is a congenital anomaly/birth defect; constitutes an important medical event. The severity of AEs was assessed by the investigator and based on the following scale: Mild = asymptomatic or mild symptoms; clinical or diagnostic observations only; Moderate = Symptoms cause moderate discomfort; Severe (could be non-serious or serious) = symptoms causing severe discomfort/pain. Safety population included all participants who were enrolled and received at least 1 dose of IP.

End point type	Secondary
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End point timeframe:

From the first dose of investigational product (IP) and no later than 28 days after the last dose of IP for those who had completed the study or discontinued (D/C) early; maximum duration of exposure to treatment was 12.00 weeks

End point values	Placebo	Apremilast 30 mg	Apremilast 40 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	58	57	55	
Units: participants				
Any TEAE	31	28	36	
Any IP-related TEAE	12	13	20	
Any Severe TEAE	4	0	1	
Any Serious TEAE	2	0	1	
Any Serious IP-related TEAE	0	0	0	
Any TEAE Leading to IP Withdrawal	5	0	1	
Any TEAE Leading to IP Interruption	1	0	0	
Any TEAE Leading to Death	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: The Number of Participants Who Discontinued Apremilast due to Treatment Emergent Adverse Events During the Placebo-Controlled Period

End point title	The Number of Participants Who Discontinued Apremilast due to Treatment Emergent Adverse Events During the Placebo-Controlled Period
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End point description:

A TEAE was defined as any AE occurring or worsening on or after the first treatment of apremilast and

up to 28 days after the last apremilast dose or the last follow-up date, whichever occurred earlier. A serious AE = any AE which results in death; is life-threatening; requires inpatient hospitalization or prolongation of existing hospitalization; results in persistent or significant disability/incapacity; is a congenital anomaly/birth defect; constitutes an important medical event. The severity of AEs was assessed by the investigator and based on the following scale: Mild = asymptomatic or mild symptoms; clinical or diagnostic observations only; Moderate = Symptoms cause moderate discomfort; Severe (could be non-serious or serious) = symptoms causing severe discomfort/pain. Safety population included all participants who were enrolled and received at least 1 dose of IP.

End point type	Secondary
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End point timeframe:

From the first dose of IP and no later than 28 days after the last dose of IP for those who had completed the study or discontinued early; median duration of exposure to treatment was 12.00 weeks

End point values	Placebo	Apremilast 30 mg	Apremilast 40 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	58	57	55	
Units: participants	5	0	2	

Statistical analyses

No statistical analyses for this end point

Secondary: The Number of Participants Who Experienced TEAEs During the Apremilast (APR) Exposure Period (Active Treatment Phase) Through Week 52

End point title	The Number of Participants Who Experienced TEAEs During the Apremilast (APR) Exposure Period (Active Treatment Phase) Through Week 52
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End point description:

A TEAE was defined as any AE occurring or worsening on or after the first treatment of apremilast and up to 28 days after the last apremilast dose or the last follow-up date, whichever occurred earlier. A serious AE = any AE which results in death; is life-threatening; requires inpatient hospitalization or prolongation of existing hospitalization; results in persistent or significant disability/incapacity; is a congenital anomaly/birth defect; constitutes an important medical event. The severity of AEs was assessed by the investigator and based on the following scale: Mild = asymptomatic or mild symptoms; clinical or diagnostic observations only; Moderate = Symptoms cause moderate discomfort; Severe (could be non-serious or serious) = symptoms causing severe discomfort/pain. Safety population included all participants who were enrolled and received at least 1 dose of IP.

End point type	Secondary
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End point timeframe:

From first dose of IP and no later than 28 days after last dose of IP for those who completed the active treatment phase or D/C early; median duration of exposure = 41.00, 44.15 and 40.00 weeks respectively for 30 mg, 40 mg and 30 mg/40 mg APR arms

End point values	Apremilast 30 mg	Apremilast 40 mg	Apremilast 30 mg/Apremilast 40 mg	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	83	80	11	
Units: participants				
Any TEAE	60	67	8	
Any Severe TEAE	5	6	0	
Any Serious TEAE	6	8	1	
Any TEAE Leading to Drug Withdrawal	3	9	1	
Any TEAE Leading to Drug Interruption	1	4	0	
Any TEAE Leading to Death	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: The Number of Participants Who Experienced TEAEs During Week 52 to Week 104 (Extension Phase)

End point title	The Number of Participants Who Experienced TEAEs During Week 52 to Week 104 (Extension Phase)
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End point description:

A TEAE was defined as any AE occurring or worsening on or after the first treatment of apremilast and up to 28 days after the last apremilast dose or the last follow-up date, whichever occurred earlier. A serious AE = any AE which results in death; is life-threatening; requires inpatient hospitalization or prolongation of existing hospitalization; results in persistent or significant disability/incapacity; is a congenital anomaly/birth defect; constitutes an important medical event. The severity of AEs was assessed by the investigator and based on the following scale: Mild = asymptomatic or mild symptoms; clinical or diagnostic observations only; Moderate = Symptoms cause moderate discomfort; Severe (could be non-serious or serious) = symptoms causing severe discomfort/pain

End point type	Secondary
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End point timeframe:

From the first dose of IP at Week 52 and no later than 28 days after the last dose of IP for those who completed the study or had discontinued early; median exposure of apremilast for the total apremilast group was 52 weeks.

End point values	Extension Phase: Apremilast 30 mg	Extension Phase: Apremilast 40 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	45	54		
Units: participants				
Any TEAE	16	27		
Any Severe TEAE	1	0		
Any Serious TEAE	4	3		
Any Serious IP-related TEAE	0	1		
Any TEAE Leading to IP Withdrawal	2	1		
Any TEAE Leading to IP Interruption	1	0		
Any TEAE Leading to Death	0	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose of IP and no later than 28 days after the last dose of IP for those who had completed the study D/C early. AEs are reported for the placebo-controlled phase from Week 0 to Week 12 and for the APR exposure period from Week 0 to Week 104.

Adverse event reporting additional description:

Median duration of study drug was 12 weeks in the placebo controlled phase, 41.00, 44.15 and 40.00 weeks respectively for 30 mg, 40 mg and 30 mg/40 mg APR arms in the active treatment phase and 52 weeks in the extension phase; MedDRA Version 20.1 was used in the placebo controlled phase and Version 22 in the active treatment and extension phase.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups

Reporting group title	Placebo (Placebo Controlled Period)
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Reporting group description:

TEAEs for participants who were randomized to identically matching placebo capsules twice a day (BID) for 12 weeks during the double-blind placebo-controlled phase.

Reporting group title	Apremilast 30 mg BID (Placebo Controlled Period)
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Reporting group description:

TEAEs for participants who were randomized to apremilast 30 mg capsules PO BID for 12 weeks during the double-blind placebo-controlled phase.

Reporting group title	Apremilast 40 mg BID (Placebo Controlled Period)
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Reporting group description:

TEAEs for participants who were randomized to apremilast 40 mg capsules PO BID for 12 weeks during the double-blind placebo-controlled phase.

Reporting group title	Apremilast 30 mg BID (Apremilast Exposure Period)
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Reporting group description:

TEAEs during the apremilast 30 mg BID treatment for participants who received 30 mg apremilast capsules BID only and participants who initially received 30 mg apremilast capsules BID and switched to 40 mg apremilast capsules BID at Week 12, and participants who initially received placebo capsules BID and switched to 30 mg apremilast capsules BID at Week 12.

Reporting group title	Apremilast 40 mg BID (Apremilast Exposure Period)
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Reporting group description:

TEAEs during the apremilast 40 mg BID treatment for participants who received 40 mg apremilast capsules BID only, and participants who initially received placebo BID and switched to 40 mg apremilast capsules BID at Week 12.

Reporting group title	Apremilast 30/40 mg BID (Apremilast Exposure Period)
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Reporting group description:

TEAEs during the apremilast 40 mg BID treatment for participants who initially received 30 mg apremilast BID and switched to apremilast 40 mg BID at Week 12

Serious adverse events	Placebo (Placebo Controlled Period)	Apremilast 30 mg BID (Placebo Controlled Period)	Apremilast 40 mg BID (Placebo Controlled Period)
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 58 (3.45%)	0 / 57 (0.00%)	1 / 55 (1.82%)
number of deaths (all causes)	0	0	0
number of deaths resulting from	0	0	0

adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Epididymal neoplasm			
subjects affected / exposed	0 / 58 (0.00%)	0 / 57 (0.00%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 58 (0.00%)	0 / 57 (0.00%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Congestive cardiomyopathy			
subjects affected / exposed	0 / 58 (0.00%)	0 / 57 (0.00%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Colitis ulcerative			
subjects affected / exposed	2 / 58 (3.45%)	0 / 57 (0.00%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			
subjects affected / exposed	0 / 58 (0.00%)	0 / 57 (0.00%)	1 / 55 (1.82%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal hernia			
subjects affected / exposed	0 / 58 (0.00%)	0 / 57 (0.00%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Crohn's disease			
subjects affected / exposed	0 / 58 (0.00%)	0 / 57 (0.00%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			

subjects affected / exposed	0 / 58 (0.00%)	0 / 57 (0.00%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inguinal hernia			
subjects affected / exposed	0 / 58 (0.00%)	0 / 57 (0.00%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Menorrhagia			
subjects affected / exposed	0 / 58 (0.00%)	0 / 57 (0.00%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 58 (0.00%)	0 / 57 (0.00%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	0 / 58 (0.00%)	0 / 57 (0.00%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal colic			
subjects affected / exposed	0 / 58 (0.00%)	0 / 57 (0.00%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 58 (0.00%)	0 / 57 (0.00%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Clostridium difficile infection			

subjects affected / exposed	0 / 58 (0.00%)	0 / 57 (0.00%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epididymitis tuberculous			
subjects affected / exposed	0 / 58 (0.00%)	0 / 57 (0.00%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pilonidal cyst			
subjects affected / exposed	0 / 58 (0.00%)	0 / 57 (0.00%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal abscess			
subjects affected / exposed	0 / 58 (0.00%)	0 / 57 (0.00%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 58 (0.00%)	0 / 57 (0.00%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Apremilast 30 mg BID (Apremilast Exposure Period)	Apremilast 40 mg BID (Apremilast Exposure Period)	Apremilast 30/40 mg BID (Apremilast Exposure Period)
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 83 (10.84%)	11 / 80 (13.75%)	1 / 11 (9.09%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Epididymal neoplasm			
subjects affected / exposed	0 / 83 (0.00%)	1 / 80 (1.25%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute myocardial infarction			

subjects affected / exposed	1 / 83 (1.20%)	0 / 80 (0.00%)	0 / 11 (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
Congestive cardiomyopathy			
subjects affected / exposed	1 / 83 (1.20%)	0 / 80 (0.00%)	0 / 11 (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
Gastrointestinal disorders			
Colitis ulcerative			
subjects affected / exposed	1 / 83 (1.20%)	3 / 80 (3.75%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			
subjects affected / exposed	0 / 83 (0.00%)	1 / 80 (1.25%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal hernia			
subjects affected / exposed	0 / 83 (0.00%)	1 / 80 (1.25%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Crohn's disease			
subjects affected / exposed	0 / 83 (0.00%)	1 / 80 (1.25%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	0 / 83 (0.00%)	1 / 80 (1.25%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inguinal hernia			
subjects affected / exposed	0 / 83 (0.00%)	0 / 80 (0.00%)	1 / 11 (9.09%)
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			

Menorrhagia			
subjects affected / exposed	0 / 83 (0.00%)	1 / 80 (1.25%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 83 (1.20%)	0 / 80 (0.00%)	0 / 11 (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
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	1 / 83 (1.20%)	0 / 80 (0.00%)	0 / 11 (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
Renal colic			
subjects affected / exposed	1 / 83 (1.20%)	2 / 80 (2.50%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 83 (1.20%)	0 / 80 (0.00%)	0 / 11 (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
Infections and infestations			
Clostridium difficile infection			
subjects affected / exposed	1 / 83 (1.20%)	0 / 80 (0.00%)	0 / 11 (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
Epididymitis tuberculous			
subjects affected / exposed	0 / 83 (0.00%)	1 / 80 (1.25%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pilonidal cyst			

subjects affected / exposed	1 / 83 (1.20%)	0 / 80 (0.00%)	0 / 11 (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
Rectal abscess			
subjects affected / exposed	0 / 83 (0.00%)	1 / 80 (1.25%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	1 / 83 (1.20%)	0 / 80 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Placebo (Placebo Controlled Period)	Apremilast 30 mg BID (Placebo Controlled Period)	Apremilast 40 mg BID (Placebo Controlled Period)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	20 / 58 (34.48%)	26 / 57 (45.61%)	25 / 55 (45.45%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Angiomyolipoma			
subjects affected / exposed	0 / 58 (0.00%)	1 / 57 (1.75%)	0 / 55 (0.00%)
occurrences (all)	0	1	0
Vascular disorders			
Angiopathy			
subjects affected / exposed	0 / 58 (0.00%)	1 / 57 (1.75%)	0 / 55 (0.00%)
occurrences (all)	0	1	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	2 / 58 (3.45%)	3 / 57 (5.26%)	1 / 55 (1.82%)
occurrences (all)	2	3	1
Influenza like illness			
subjects affected / exposed	0 / 58 (0.00%)	1 / 57 (1.75%)	1 / 55 (1.82%)
occurrences (all)	0	1	1
Pyrexia			

subjects affected / exposed occurrences (all)	2 / 58 (3.45%) 2	1 / 57 (1.75%) 1	1 / 55 (1.82%) 1
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 58 (1.72%)	0 / 57 (0.00%)	1 / 55 (1.82%)
occurrences (all)	1	0	1
Dysphonia			
subjects affected / exposed	0 / 58 (0.00%)	0 / 57 (0.00%)	0 / 55 (0.00%)
occurrences (all)	0	0	0
Nasal congestion			
subjects affected / exposed	0 / 58 (0.00%)	1 / 57 (1.75%)	0 / 55 (0.00%)
occurrences (all)	0	1	0
Respiratory tract congestion			
subjects affected / exposed	0 / 58 (0.00%)	1 / 57 (1.75%)	0 / 55 (0.00%)
occurrences (all)	0	1	0
Rhinitis allergic			
subjects affected / exposed	0 / 58 (0.00%)	0 / 57 (0.00%)	0 / 55 (0.00%)
occurrences (all)	0	0	0
Rhinorrhoea			
subjects affected / exposed	0 / 58 (0.00%)	1 / 57 (1.75%)	0 / 55 (0.00%)
occurrences (all)	0	1	0
Psychiatric disorders			
Depressed mood			
subjects affected / exposed	0 / 58 (0.00%)	0 / 57 (0.00%)	1 / 55 (1.82%)
occurrences (all)	0	0	1
Depression			
subjects affected / exposed	1 / 58 (1.72%)	0 / 57 (0.00%)	1 / 55 (1.82%)
occurrences (all)	1	0	1
Insomnia			
subjects affected / exposed	0 / 58 (0.00%)	2 / 57 (3.51%)	1 / 55 (1.82%)
occurrences (all)	0	2	1
Investigations			
Blood lactate dehydrogenase increased			
subjects affected / exposed	0 / 58 (0.00%)	0 / 57 (0.00%)	0 / 55 (0.00%)
occurrences (all)	0	0	0
Faecal calprotectin increased			

subjects affected / exposed occurrences (all)	0 / 58 (0.00%) 0	1 / 57 (1.75%) 1	1 / 55 (1.82%) 1
Nervous system disorders			
Headache			
subjects affected / exposed	4 / 58 (6.90%)	12 / 57 (21.05%)	14 / 55 (25.45%)
occurrences (all)	10	17	20
Migraine			
subjects affected / exposed	0 / 58 (0.00%)	1 / 57 (1.75%)	1 / 55 (1.82%)
occurrences (all)	0	1	2
Sciatica			
subjects affected / exposed	0 / 58 (0.00%)	1 / 57 (1.75%)	0 / 55 (0.00%)
occurrences (all)	0	1	0
Sinus headache			
subjects affected / exposed	0 / 58 (0.00%)	1 / 57 (1.75%)	0 / 55 (0.00%)
occurrences (all)	0	1	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 58 (1.72%)	1 / 57 (1.75%)	0 / 55 (0.00%)
occurrences (all)	1	1	0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 58 (1.72%)	3 / 57 (5.26%)	0 / 55 (0.00%)
occurrences (all)	1	3	0
Nausea			
subjects affected / exposed	5 / 58 (8.62%)	3 / 57 (5.26%)	6 / 55 (10.91%)
occurrences (all)	6	3	7
Dyspepsia			
subjects affected / exposed	1 / 58 (1.72%)	1 / 57 (1.75%)	0 / 55 (0.00%)
occurrences (all)	1	1	0
Anorectal discomfort			
subjects affected / exposed	0 / 58 (0.00%)	0 / 57 (0.00%)	0 / 55 (0.00%)
occurrences (all)	0	0	0
Colitis ulcerative			
subjects affected / exposed	1 / 58 (1.72%)	0 / 57 (0.00%)	0 / 55 (0.00%)
occurrences (all)	1	0	0
Diarrhoea			

subjects affected / exposed occurrences (all)	2 / 58 (3.45%) 2	1 / 57 (1.75%) 1	0 / 55 (0.00%) 0
Gastritis subjects affected / exposed occurrences (all)	0 / 58 (0.00%) 0	0 / 57 (0.00%) 0	0 / 55 (0.00%) 0
Inguinal hernia subjects affected / exposed occurrences (all)	0 / 58 (0.00%) 0	0 / 57 (0.00%) 0	0 / 55 (0.00%) 0
Swollen tongue subjects affected / exposed occurrences (all)	0 / 58 (0.00%) 0	0 / 57 (0.00%) 0	0 / 55 (0.00%) 0
Vomiting subjects affected / exposed occurrences (all)	1 / 58 (1.72%) 1	2 / 57 (3.51%) 2	2 / 55 (3.64%) 2
Skin and subcutaneous tissue disorders Eczema subjects affected / exposed occurrences (all)	0 / 58 (0.00%) 0	0 / 57 (0.00%) 0	1 / 55 (1.82%) 1
Pruritus subjects affected / exposed occurrences (all)	0 / 58 (0.00%) 0	0 / 57 (0.00%) 0	0 / 55 (0.00%) 0
Rash subjects affected / exposed occurrences (all)	0 / 58 (0.00%) 0	1 / 57 (1.75%) 1	0 / 55 (0.00%) 0
Renal and urinary disorders Haematuria subjects affected / exposed occurrences (all)	0 / 58 (0.00%) 0	0 / 57 (0.00%) 0	0 / 55 (0.00%) 0
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all)	1 / 58 (1.72%) 1	0 / 57 (0.00%) 0	3 / 55 (5.45%) 3
Arthralgia subjects affected / exposed occurrences (all)	2 / 58 (3.45%) 2	0 / 57 (0.00%) 0	1 / 55 (1.82%) 1
Osteochondrosis			

subjects affected / exposed occurrences (all)	0 / 58 (0.00%) 0	1 / 57 (1.75%) 1	0 / 55 (0.00%) 0
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	1 / 58 (1.72%)	4 / 57 (7.02%)	2 / 55 (3.64%)
occurrences (all)	2	4	2
Upper respiratory tract infection			
subjects affected / exposed	2 / 58 (3.45%)	1 / 57 (1.75%)	0 / 55 (0.00%)
occurrences (all)	2	1	0
Gastroenteritis			
subjects affected / exposed	1 / 58 (1.72%)	0 / 57 (0.00%)	0 / 55 (0.00%)
occurrences (all)	1	0	0
Influenza			
subjects affected / exposed	1 / 58 (1.72%)	0 / 57 (0.00%)	1 / 55 (1.82%)
occurrences (all)	1	0	1
Periodontitis			
subjects affected / exposed	0 / 58 (0.00%)	1 / 57 (1.75%)	0 / 55 (0.00%)
occurrences (all)	0	1	0
Pneumonia			
subjects affected / exposed	0 / 58 (0.00%)	0 / 57 (0.00%)	1 / 55 (1.82%)
occurrences (all)	0	0	1
Sinusitis			
subjects affected / exposed	0 / 58 (0.00%)	1 / 57 (1.75%)	0 / 55 (0.00%)
occurrences (all)	0	1	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 58 (1.72%)	2 / 57 (3.51%)	1 / 55 (1.82%)
occurrences (all)	1	2	1
Iron deficiency			
subjects affected / exposed	0 / 58 (0.00%)	0 / 57 (0.00%)	0 / 55 (0.00%)
occurrences (all)	0	0	0
Non-serious adverse events	Apremilast 30 mg BID (Apremilast Exposure Period)	Apremilast 40 mg BID (Apremilast Exposure Period)	Apremilast 30/40 mg BID (Apremilast Exposure Period)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	49 / 83 (59.04%)	53 / 80 (66.25%)	11 / 11 (100.00%)

Neoplasms benign, malignant and unspecified (incl cysts and polyps) Angiomyolipoma subjects affected / exposed occurrences (all)	1 / 83 (1.20%) 1	0 / 80 (0.00%) 0	1 / 11 (9.09%) 1
Vascular disorders Angiopathy subjects affected / exposed occurrences (all)	1 / 83 (1.20%) 1	0 / 80 (0.00%) 0	1 / 11 (9.09%) 1
General disorders and administration site conditions Asthenia subjects affected / exposed occurrences (all) Influenza like illness subjects affected / exposed occurrences (all) Pyrexia subjects affected / exposed occurrences (all)	5 / 83 (6.02%) 5 2 / 83 (2.41%) 2 1 / 83 (1.20%) 1	3 / 80 (3.75%) 5 2 / 80 (2.50%) 2 2 / 80 (2.50%) 3	2 / 11 (18.18%) 2 1 / 11 (9.09%) 1 2 / 11 (18.18%) 2
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) Dysphonia subjects affected / exposed occurrences (all) Nasal congestion subjects affected / exposed occurrences (all) Respiratory tract congestion subjects affected / exposed occurrences (all) Rhinitis allergic subjects affected / exposed occurrences (all) Rhinorrhoea	0 / 83 (0.00%) 0 0 / 83 (0.00%) 0 1 / 83 (1.20%) 1 1 / 83 (1.20%) 1 0 / 83 (0.00%) 0	5 / 80 (6.25%) 6 0 / 80 (0.00%) 0 0 / 80 (0.00%) 0 0 / 80 (0.00%) 0 0 / 80 (0.00%) 0	0 / 11 (0.00%) 0 1 / 11 (9.09%) 1 1 / 11 (9.09%) 1 1 / 11 (9.09%) 1 1 / 11 (9.09%) 1

subjects affected / exposed occurrences (all)	1 / 83 (1.20%) 1	0 / 80 (0.00%) 0	1 / 11 (9.09%) 1
Psychiatric disorders			
Depressed mood			
subjects affected / exposed	2 / 83 (2.41%)	4 / 80 (5.00%)	0 / 11 (0.00%)
occurrences (all)	2	4	0
Depression			
subjects affected / exposed	0 / 83 (0.00%)	1 / 80 (1.25%)	1 / 11 (9.09%)
occurrences (all)	0	1	1
Insomnia			
subjects affected / exposed	3 / 83 (3.61%)	2 / 80 (2.50%)	1 / 11 (9.09%)
occurrences (all)	3	2	1
Investigations			
Blood lactate dehydrogenase increased			
subjects affected / exposed	0 / 83 (0.00%)	0 / 80 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Faecal calprotectin increased			
subjects affected / exposed	1 / 83 (1.20%)	1 / 80 (1.25%)	1 / 11 (9.09%)
occurrences (all)	1	1	1
Nervous system disorders			
Headache			
subjects affected / exposed	17 / 83 (20.48%)	25 / 80 (31.25%)	2 / 11 (18.18%)
occurrences (all)	25	35	2
Migraine			
subjects affected / exposed	2 / 83 (2.41%)	3 / 80 (3.75%)	1 / 11 (9.09%)
occurrences (all)	2	7	1
Sciatica			
subjects affected / exposed	1 / 83 (1.20%)	1 / 80 (1.25%)	1 / 11 (9.09%)
occurrences (all)	1	1	1
Sinus headache			
subjects affected / exposed	1 / 83 (1.20%)	0 / 80 (0.00%)	1 / 11 (9.09%)
occurrences (all)	1	0	3
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	4 / 83 (4.82%)	4 / 80 (5.00%)	0 / 11 (0.00%)
occurrences (all)	4	5	0

Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	4 / 83 (4.82%)	3 / 80 (3.75%)	1 / 11 (9.09%)
occurrences (all)	4	3	1
Nausea			
subjects affected / exposed	8 / 83 (9.64%)	9 / 80 (11.25%)	3 / 11 (27.27%)
occurrences (all)	8	10	4
Dyspepsia			
subjects affected / exposed	2 / 83 (2.41%)	0 / 80 (0.00%)	1 / 11 (9.09%)
occurrences (all)	2	0	2
Anorectal discomfort			
subjects affected / exposed	0 / 83 (0.00%)	0 / 80 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Colitis ulcerative			
subjects affected / exposed	2 / 83 (2.41%)	6 / 80 (7.50%)	0 / 11 (0.00%)
occurrences (all)	2	7	0
Diarrhoea			
subjects affected / exposed	5 / 83 (6.02%)	6 / 80 (7.50%)	2 / 11 (18.18%)
occurrences (all)	5	6	2
Gastritis			
subjects affected / exposed	1 / 83 (1.20%)	4 / 80 (5.00%)	0 / 11 (0.00%)
occurrences (all)	1	4	0
Inguinal hernia			
subjects affected / exposed	0 / 83 (0.00%)	0 / 80 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Swollen tongue			
subjects affected / exposed	0 / 83 (0.00%)	0 / 80 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Vomiting			
subjects affected / exposed	3 / 83 (3.61%)	3 / 80 (3.75%)	3 / 11 (27.27%)
occurrences (all)	3	4	3
Skin and subcutaneous tissue disorders			
Eczema			
subjects affected / exposed	1 / 83 (1.20%)	2 / 80 (2.50%)	1 / 11 (9.09%)
occurrences (all)	1	2	1
Pruritus			

subjects affected / exposed occurrences (all)	0 / 83 (0.00%) 0	2 / 80 (2.50%) 2	1 / 11 (9.09%) 1
Rash subjects affected / exposed occurrences (all)	1 / 83 (1.20%) 1	1 / 80 (1.25%) 1	1 / 11 (9.09%) 1
Renal and urinary disorders Haematuria subjects affected / exposed occurrences (all)	0 / 83 (0.00%) 0	0 / 80 (0.00%) 0	1 / 11 (9.09%) 1
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all)	0 / 83 (0.00%) 0	3 / 80 (3.75%) 5	0 / 11 (0.00%) 0
Arthralgia subjects affected / exposed occurrences (all)	5 / 83 (6.02%) 6	6 / 80 (7.50%) 7	1 / 11 (9.09%) 1
Osteochondrosis subjects affected / exposed occurrences (all)	1 / 83 (1.20%) 1	0 / 80 (0.00%) 0	1 / 11 (9.09%) 1
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	7 / 83 (8.43%) 8	8 / 80 (10.00%) 11	2 / 11 (18.18%) 2
Upper respiratory tract infection subjects affected / exposed occurrences (all)	4 / 83 (4.82%) 4	4 / 80 (5.00%) 5	0 / 11 (0.00%) 0
Gastroenteritis subjects affected / exposed occurrences (all)	3 / 83 (3.61%) 3	3 / 80 (3.75%) 3	1 / 11 (9.09%) 1
Influenza subjects affected / exposed occurrences (all)	2 / 83 (2.41%) 2	3 / 80 (3.75%) 4	1 / 11 (9.09%) 1
Periodontitis subjects affected / exposed occurrences (all)	1 / 83 (1.20%) 1	0 / 80 (0.00%) 0	1 / 11 (9.09%) 1
Pneumonia			

subjects affected / exposed occurrences (all)	1 / 83 (1.20%) 1	1 / 80 (1.25%) 1	1 / 11 (9.09%) 1
Sinusitis subjects affected / exposed occurrences (all)	4 / 83 (4.82%) 4	0 / 80 (0.00%) 0	1 / 11 (9.09%) 3
Metabolism and nutrition disorders			
Decreased appetite subjects affected / exposed occurrences (all)	2 / 83 (2.41%) 2	3 / 80 (3.75%) 3	1 / 11 (9.09%) 1
Iron deficiency subjects affected / exposed occurrences (all)	0 / 83 (0.00%) 0	2 / 80 (2.50%) 2	1 / 11 (9.09%) 1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 August 2014	<ul style="list-style-type: none">• The planned sample size was reduced from 249 to 165 after an internal decision to keep the Study CC-10004-UC-001 design in line with standard proof-of-concept Phase 2 trials.• The assessment of the primary endpoint was changed from Week 8 to Week 12 because cumulative clinical experience in other indications suggests that apremilast may take a longer time to induce a clinical response than initially anticipated in the approved protocol. Clinical remission at Week 8 was planned to be evaluated as one of the key secondary endpoints.• Secondary endpoints based on a modified Mayo score (without inclusion of PGA) were added based on a recommendation by the Food and Drug Administration during review of the original Investigational New Drug application.• Nonresponder criteria were revised to allow patients with an incomplete response (partial responders) at Week 12 to continue blinded treatment, to assess the potential late response of apremilast in this population.• Exclusion criterion 15 was added to clarify the psychiatric conditions that were exclusionary.
13 April 2015	<ul style="list-style-type: none">• A treatment extension phase was added to provide all subjects the opportunity to receive active apremilast during the 40-week Blinded Active-treatment Phase.• Concomitant medication restrictions were changed from a prohibition of background oral corticosteroid treatment to instead allow subjects to receive stable doses of prednisone ≤ 20 mg/day or equivalent or budesonide ≤ 9 mg/day.• Stratification was added based on use of oral corticosteroids. Stratification based on use of aminosalicylates was deleted.• The requirement for chest radiograph was removed.• The psychiatric evaluation was updated based on feedback from the Health Authorities.• Several efficacy-related exploratory endpoints were deleted and time points in the secondary and exploratory endpoints were modified due to the change in study duration.• The definition of clinical remission based on the PMS was changed: "The proportion of subjects achieving clinical remission at Week 12, defined as a PMS of ≤ 2, with no individual subscore ≥ 1". Changed to > 1.• The description in the sparse PK section was updated for clarity.
20 July 2016	<ul style="list-style-type: none">• An Extension Phase was added for subjects who met the criteria for endoscopic response at Week 52 to allow these subjects to receive blinded, active treatment (apremilast) for an additional 52 weeks (Weeks 52 to 104).• Safety information was updated to reflect the most recent version of the Investigator's Brochure.• The following exploratory endpoints were added:<ul style="list-style-type: none">- The proportion of subjects with endoscopic remission, defined as a Mayo endoscopic subscore ≤ 1, and histological remission at Week 12- The proportion of subjects achieving a clinical remission in the TMS at Week 12, defined as a TMS ≤ 2 with no individual subscore > 1 and no evidence of friability on the Mayo endoscopic subscore- The exposure-adjusted incidence of UC-related health outcomes (eg, UC-related hospitalizations, emergency room visits, and surgeries)

08 August 2018	<ul style="list-style-type: none"> • The apremilast dose in the Extension Phase was adjusted so that all subjects participating in that phase of the study would receive apremilast 30 mg BID (rather than either apremilast 30 mg BID or 40 mg BID). • Overdose for subjects receiving open-label 30 mg BID in the Extension Phase was defined as 4 or more 30-mg tablets in any 24-hour period (on a per-dose basis) or dosing more than 4 times in 24 hours (on a schedule or frequency basis). • The DMC was decommissioned. After a meeting with the external DMC on 27 Oct 2017, Celgene determined that the DMC was no longer needed to support CC-10004-UC-001, as described in Section 6. • Safety information was updated to reflect the most current information in the Investigator's Brochure. • Clarification was added that subjects who experienced UC-related symptoms after corticosteroid tapering were permitted to receive the same treatment taken prior to tapering, provided that the dose was the same.
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Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported