



Clinical trial results:

An Extension Study of APD334-003 in Patients with Moderately to Severely Active Ulcerative Colitis

Summary

EudraCT number	2015-002109-12
Trial protocol	LV ES GB HU CZ LT BE BG AT
Global end of trial date	01 November 2018

Results information

Result version number	v1 (current)
This version publication date	28 October 2019
First version publication date	28 October 2019

Trial information

Trial identification

Sponsor protocol code	APD334-005
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02536404
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Arena Pharmaceuticals, Inc.
Sponsor organisation address	6154 Nancy Ridge Drive, San Diego, California, United States, 92121
Public contact	Chris Cabell, Arena Pharmaceuticals, Inc., +1 858-210-3634, ccabell@arenapharm.com
Scientific contact	Chris Cabell, Arena Pharmaceuticals, Inc., +1 858-210-3634, ccabell@arenapharm.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	30 July 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 November 2018
Global end of trial reached?	Yes
Global end of trial date	01 November 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the long-term safety and tolerability of APD334 (etrasimod) in subjects with UC (ulcerative colitis) who have completed the APD334-003 study.

To evaluate the effect of etrasimod on achieving and maintaining clinical response and/or remission in subjects with UC after 46 weeks of treatment (including 12 weeks in APD334-003).

Protection of trial subjects:

The study was conducted in compliance with the ICH Guidelines for Good Clinical Practice (GCP) and applicable regulatory requirements, the study protocol, and where applicable, Sponsor and/or CRO Standard Operating Procedures.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	25 January 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 14
Country: Number of subjects enrolled	Romania: 1
Country: Number of subjects enrolled	Spain: 4
Country: Number of subjects enrolled	United Kingdom: 2
Country: Number of subjects enrolled	Austria: 1
Country: Number of subjects enrolled	Belgium: 3
Country: Number of subjects enrolled	Bulgaria: 4
Country: Number of subjects enrolled	Germany: 10
Country: Number of subjects enrolled	Hungary: 8
Country: Number of subjects enrolled	Latvia: 2
Country: Number of subjects enrolled	United States: 20
Country: Number of subjects enrolled	Canada: 3
Country: Number of subjects enrolled	Korea, Republic of: 3
Country: Number of subjects enrolled	Russian Federation: 20
Country: Number of subjects enrolled	Ukraine: 23
Worldwide total number of subjects	118
EEA total number of subjects	49

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)	112
From 65 to 84 years	6
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

To be eligible, subjects must have completed the APD334-003 study and met the eligibility criteria for APD334-005 at the time of entry.

Pre-assignment

Screening details:

This study was an open-label extension to APD334-003. Eligible subjects from APD334-003 were assigned to receive 2 mg etrasimod QD (once daily) for 34 weeks. Subjects who were enrolled under Protocol Amendment 2 followed a different study design - subjects were randomly assigned to receive placebo or 2 mg QD etrasimod.

Period 1

Period 1 title	Treatment period 1 (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

All eligible subjects were given the option to enroll and receive open-label treatment with 2 mg etrasimod once daily (QD).

Arms

Are arms mutually exclusive?	Yes
Arm title	Etrasimod

Arm description:

Subjects received 2 mg etrasimod tablets orally QD for 34 weeks.

Subjects who were enrolled under Protocol Amendment 2 (28 September 2015) received placebo or 2 mg etrasimod tablets QD for 40 weeks.

Arm type	Experimental
Investigational medicinal product name	Etrasimod
Investigational medicinal product code	APD334
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Study treatment was provided in 40cc, induction sealed, high density polyethylene bottles with child resistant screw caps. Subjects were instructed to take their 2 mg etrasimod tablet QD, in the morning, on an empty stomach (after an overnight fast of approximately 8 hours), and to avoid eating for approximately 1 hour after dosing subjects were advised not to crush, break, chew, or dissolve the tablets and to take study medication with an adequate amount of water.

Arm title	Placebo
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Arm description:

Subjects who were enrolled under Protocol Amendment 2 (28 September 2015) received placebo or 2 mg etrasimod tablets QD for 40 weeks.

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

Dosage and administration details:

Study treatment were provided in 40cc, induction sealed, high density polyethylene bottles with child resistant screw caps. Subjects were instructed to take their 2 mg etrasimod tablet QD (once daily) or placebo, in the morning, on an empty stomach (after an overnight fast of approximately 8 hours), and

to avoid eating for approximately 1 hour after dosing. Subjects were advised not to crush, break, chew, or dissolve the tablets and to take study medication with an adequate amount of water. Subjects enrolled under Protocol Amendment 2 (28 September 2015) were randomly assigned to receive placebo or 2 mg etrasimod QD.

Number of subjects in period 1	Etrasimod	Placebo
Started	112	6
Completed	92	5
Not completed	20	1
Consent withdrawn by subject	4	1
Physician decision	10	-
Adverse event, non-fatal	5	-
Sponsor decision	1	-

Baseline characteristics

Reporting groups

Reporting group title	Treatment period 1
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Reporting group description: -

Reporting group values	Treatment period 1	Total	
Number of subjects	118	118	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	112	112	
From 65-84 years	6	6	
85 years and over	0	0	
Gender categorical			
Units: Subjects			
Female	47	47	
Male	71	71	

End points

End points reporting groups

Reporting group title	Etrasimod
Reporting group description: Subjects received 2 mg etrasimod tablets orally QD for 34 weeks. Subjects who were enrolled under Protocol Amendment 2 (28 September 2015) received placebo or 2 mg etrasimod tablets QD for 40 weeks.	
Reporting group title	Placebo
Reporting group description: Subjects who were enrolled under Protocol Amendment 2 (28 September 2015) received placebo or 2 mg etrasimod tablets QD for 40 weeks.	
Subject analysis set title	Safety
Subject analysis set type	Safety analysis
Subject analysis set description: The Safety population will include all patients who received study medication in the extension study.	
Subject analysis set title	MITT
Subject analysis set type	Modified intention-to-treat
Subject analysis set description: This MITT population consists of all patients, who received at least 1 dose of etrasimod or Placebo, had a baseline measurement, and had a post-enrollment measurement in the extension study for the specific efficacy endpoint being assessed. The MITT evaluable cohort was used for analysis of all proportion-based and all continuous efficacy variables.	

Primary: Number of SAE/AEs

End point title	Number of SAE/AEs
End point description: Treatment-emergent adverse events (AEs) up to 30 days following discontinuation of the study drug. Treatment-emergent serious adverse events (SAEs) up to 30 days following discontinuation of the study drug.	
End point type	Primary
End point timeframe: From first dose in patients participating in APD334-005 study up to 30 days following discontinuation of the study drug - number of serious/treatment-emergent adverse events (AEs).	

End point values	Etrasimod	Placebo	Safety	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	112	6	118	
Units: subjects with TEAEs	67	5	72	

Statistical analyses

Statistical analysis title	Statistical Analysis Plan, Ver 1.2, dated 27Nov18
Statistical analysis description: Descriptive statistics of 90% confidence interval (CI) for change or percent change from baseline of treatment with etrasimod.	

Comparison groups	Etrasimod v Placebo
Number of subjects included in analysis	118
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0
Method	90% confidence interval

Secondary: Clinical response at week 12 and EOT

End point title	Clinical response at week 12 and EOT
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End point description:

Clinical response achieved at Week 12 and maintained at EOT in APD334-005.

Clinical Response is defined as achievement of clinical remission or satisfaction of the following criteria: decrease in the 3-component Mayo Clinic score (consisting of subscores for stool frequency, rectal bleeding and findings of flexible proctosigmoidoscopy) of ≥ 2 points and a decrease of $\geq 30\%$ with either a decrease of rectal bleeding of ≥ 1 or rectal bleeding score of 0 or 1 compared to APD334-003 baseline.

End point type	Secondary
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End point timeframe:

Week 12 and EoT.

End point values	Etrasimod	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	94	5		
Units: number of responders				
arithmetic mean (confidence interval 90%)	35.1 (26.9 to 44.0)	40.0 (7.6 to 81.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical remission at EOT

End point title	Clinical remission at EOT
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End point description:

To evaluate the effect of etrasimod on achieving and maintaining clinical response and/or remission in subjects with UC after 46 weeks of treatment.

Clinical remission is defined as individual subscores of the 3-component Mayo Clinic score as follows: an endoscopy score (using flexible proctosigmoidoscopy) of 0 or 1 (excluding friability), a rectal bleeding score of 0 or 1, and a stool frequency score of 0 or 1 with a decrease of ≥ 1 point] compared to APD334-003 baseline.

End point type	Secondary
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End point timeframe:

EoT

End point values	Etrasimod	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	94	5		
Units: number of observations				
arithmetic mean (confidence interval 90%)	35.1 (26.9 to 44.0)	20.0 (1.0 to 65.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical response at EOT

End point title	Clinical response at EOT
End point description: Clinical Response is defined as achievement of clinical remission or satisfaction of the following criteria: decrease in the 3-component Mayo Clinic score (consisting of subscores for stool frequency, rectal bleeding and findings of flexible proctosigmoidoscopy) of ≥ 2 points and a decrease of $\geq 30\%$ with either a decrease of rectal bleeding of ≥ 1 or rectal bleeding score of 0 or 1 compared to APD334-003 baseline.	
End point type	Secondary
End point timeframe: EoT	

End point values	Etrasimod	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	94	5		
Units: number of responders				
arithmetic mean (confidence interval 90%)	70.2 (61.5 to 77.9)	60.0 (18.9 to 92.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical remission at week 12 and EOT

End point title	Clinical remission at week 12 and EOT
End point description: Clinical remission is defined as individual subscores of the 3-component Mayo Clinic score as follows: an endoscopy score (using flexible proctosigmoidoscopy) of 0 or 1 (excluding friability), a rectal bleeding score of 0 or 1, and a stool frequency score of 0 or 1 with a decrease of ≥ 1 point] compared to APD334-003 baseline.	
End point type	Secondary

End point timeframe:

Week 12 and EoT

End point values	Etrasimod	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	94	5		
Units: number of observations				
arithmetic mean (confidence interval 90%)	12.8 (7.5 to 19.9)	0 (0.0 to 45.1)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were followed up from the beginning of subject`s participation to 30 days following discontinuation of the study drug.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups

Reporting group title	Etrasimod
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Reporting group description: -

Reporting group title	Placebo
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Reporting group description: -

Serious adverse events	Etrasimod	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 112 (6.25%)	0 / 6 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 112 (0.89%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Fine motor skill dysfunction			
subjects affected / exposed	1 / 112 (0.89%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	1 / 112 (0.89%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Iron deficiency anaemia			

subjects affected / exposed	2 / 112 (1.79%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Colitis ulcerative			
subjects affected / exposed	3 / 112 (2.68%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine perforation			
subjects affected / exposed	1 / 112 (0.89%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	1 / 112 (0.89%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Proctitis ulcerative			
subjects affected / exposed	1 / 112 (0.89%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 112 (0.89%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Cystitis haemorrhagic			
subjects affected / exposed	1 / 112 (0.89%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	Etrasimod	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	66 / 112 (58.93%)	5 / 6 (83.33%)	
Investigations			
Gamma-glutamyltransferase increased			
subjects affected / exposed	10 / 112 (8.93%)	0 / 6 (0.00%)	
occurrences (all)	11	0	
Aspartate aminotransferase increased			
subjects affected / exposed	3 / 112 (2.68%)	0 / 6 (0.00%)	
occurrences (all)	3	0	
Faecal calprotectin increased			
subjects affected / exposed	3 / 112 (2.68%)	1 / 6 (16.67%)	
occurrences (all)	3	1	
Hepatic enzyme increased			
subjects affected / exposed	3 / 112 (2.68%)	0 / 6 (0.00%)	
occurrences (all)	3	0	
Nervous system disorders			
Headache			
subjects affected / exposed	5 / 112 (4.46%)	0 / 6 (0.00%)	
occurrences (all)	5	0	
Carpal tunnel syndrome			
subjects affected / exposed	1 / 112 (0.89%)	1 / 6 (16.67%)	
occurrences (all)	1	1	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	10 / 112 (8.93%)	0 / 6 (0.00%)	
occurrences (all)	11	0	
Neutropenia			
subjects affected / exposed	3 / 112 (2.68%)	0 / 6 (0.00%)	
occurrences (all)	3	0	
Eye disorders			
Vitreous detachment			
subjects affected / exposed	0 / 112 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Gastrointestinal disorders			

Colitis ulcerative			
subjects affected / exposed	16 / 112 (14.29%)	1 / 6 (16.67%)	
occurrences (all)	18	1	
Nausea			
subjects affected / exposed	5 / 112 (4.46%)	1 / 6 (16.67%)	
occurrences (all)	5	1	
Dental caries			
subjects affected / exposed	0 / 112 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Gastritis			
subjects affected / exposed	0 / 112 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Glossodynia			
subjects affected / exposed	0 / 112 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Large intestine polyp			
subjects affected / exposed	0 / 112 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Reproductive system and breast disorders			
Premenstrual headache			
subjects affected / exposed	0 / 112 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 112 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Endocrine disorders			
Hyperparathyroidism			
subjects affected / exposed	0 / 112 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	4 / 112 (3.57%)	2 / 6 (33.33%)	
occurrences (all)	4	2	
Musculoskeletal chest pain			

subjects affected / exposed occurrences (all)	0 / 112 (0.00%) 0	1 / 6 (16.67%) 1	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	6 / 112 (5.36%)	2 / 6 (33.33%)	
occurrences (all)	8	2	
Upper respiratory tract infection			
subjects affected / exposed	7 / 112 (6.25%)	0 / 6 (0.00%)	
occurrences (all)	8	0	
Gastroenteritis			
subjects affected / exposed	3 / 112 (2.68%)	0 / 6 (0.00%)	
occurrences (all)	3	0	
Bronchitis			
subjects affected / exposed	0 / 112 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Chronic sinusitis			
subjects affected / exposed	0 / 112 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Herpes zoster			
subjects affected / exposed	1 / 112 (0.89%)	1 / 6 (16.67%)	
occurrences (all)	1	1	
Influenza			
subjects affected / exposed	1 / 112 (0.89%)	1 / 6 (16.67%)	
occurrences (all)	2	1	
Tooth infection			
subjects affected / exposed	0 / 112 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 September 2015	Amendment 02 (28 Sep 2015): - Change in EU Legal representative The EU Legal representative has changed from Covance Clinical and Periapproval Services Limited to Clinical Technology Centre (International) Limited. - Change in applicant for regulatory and ethics committee applications The applicant for regulatory and ethics committee applications has changed. - Change in major responsibilities of the sponsor's trial related duties.
20 October 2016	Amendment 03 (20 Oct 2016) - o Changed study duration from 52 weeks to 46 weeks in total - o Changed study design to single arm, open-label (2 mg once daily [q.d.]) for APD334-003 responders only and removal of Placebo group - o Updated secondary and exploratory outcome measures to reflect study duration of 46 weeks total (including the APD334-003 study) - o Changed time points i.e. removal of 7 and 8 hours post dose electrocardiogram (ECG) and vital signs assessments on Day 1; removal of 8 hours post dose pharmacokinetic (PK) sample on Day 1 and removal of weeks 20, 28, 36, 44 and 52 - o Changed Week 52 to Week 46 as End-of-Treatment - o Removed Primary Safety and Secondary Efficacy hypotheses - o Removed sample size and power calculations - o Changed 'Randomized' to 'Enrolled' and removed treatment groups - o Removed between group differences and removal of formal statistical analysis
27 March 2017	Amendment 04 (27 Mar 2017) - o Updated to add proportion of patients who achieve clinical response to secondary endpoints - o Updated to reflect APD334-003 completers to be eligible for APD334-005 study The following exploratory endpoints have been added to the SAP in comparison with Protocol Amendment 04 to be consistent with the endpoints in the APD334-003 study: • Change from baseline in the following measures: - o PMS#1, 3-component Mayo Clinic score - o PMS#2, 3-component Mayo Clinic score - o 2-component Mayo Clinic score (rectal bleeding and findings on endoscopy) - o Rectal bleeding subscore - o Stool frequency subscore The following exploratory objectives have been added to the SAP in comparison with Protocol Amendment 04 to be consistent with the objectives in the APD334-003 study: • PMS#1, 3-component Mayo Clinic score • PMS#2, 3-component Mayo Clinic score • 2-component Mayo Clinic score The following subgroup analysis has been added to the SAP in comparison with Protocol Amendment 04: • Biologic Agents (Integrin + TNFα antagonists)

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported