



Clinical trial results:

A Phase 2, Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Multi-Center Study to Investigate the Safety and Efficacy of APD334 in Patients with Moderately to Severely Active Ulcerative Colitis Summary

| | |
|--------------------------|-------------------------------------|
| EudraCT number | 2015-001942-28 |
| Trial protocol | CZ GB ES DE LV HU LT FR PL BG BE AT |
| Global end of trial date | 14 February 2018 |

Results information

| | |
|--------------------------------|------------------|
| Result version number | v1 (current) |
| This version publication date | 16 December 2018 |
| First version publication date | 16 December 2018 |

Trial information

Trial identification

| | |
|-----------------------|------------|
| Sponsor protocol code | APD334-003 |
|-----------------------|------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02447302 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Arena Pharmaceuticals, Inc. |
| Sponsor organisation address | 6154 Nancy Ridge Drive, San Diego, United States, CA 92121 |
| Public contact | Chris Cabell, Arena Pharmaceuticals, Inc., ct.gov@arenapharm.com |
| Scientific contact | Chris Cabell, Arena Pharmaceuticals, Inc., ct.gov@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 2018 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 14 February 2018 |
| Global end of trial reached? | Yes |
| Global end of trial date | 14 February 2018 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To determine the effect of treatment with APD334 in inducing clinical remission at 12 weeks.

Protection of trial subjects:

Compliance was assessed using subject data recorded in the drug accountability form of the electronic Case Report Forms (eCRFs). On each day, a subject had to take his or her assigned study drug. The compliance rate for each subject was computed as $100\% \times (\text{actual number of capsules taken over the study period}) / (\text{designated total number of capsules that should have been taken over the study period})$.

There are prohibited medications and medications considered with regard to concomitant procedures.

Background therapy: -

Evidence for comparator:

For all analyses, one model was fitted for the individual treatment comparisons etrasimod 2 mg versus placebo, etrasimod 1 mg versus placebo, and etrasimod 2 mg versus etrasimod 1 mg with the treatment term containing the 3 groups (etrasimod 1 mg, etrasimod 2 mg, and placebo), and the second model was fitted for the pooled treatment comparison (etrasimod 1 mg and etrasimod 2 mg versus placebo) with the treatment term containing 2 treatment groups (pooled 2 mg etrasimod and 1 mg, and placebo).

| | |
|---|--------------|
| Actual start date of recruitment | 01 July 2015 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | Poland: 24 |
| Country: Number of subjects enrolled | Romania: 1 |
| Country: Number of subjects enrolled | Spain: 5 |
| 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: 6 |
| Country: Number of subjects enrolled | Germany: 11 |
| Country: Number of subjects enrolled | Hungary: 10 |
| Country: Number of subjects enrolled | Latvia: 2 |
| Country: Number of subjects enrolled | Lithuania: 1 |
| Country: Number of subjects enrolled | Canada: 5 |
| Country: Number of subjects enrolled | Korea, Republic of: 3 |
| Country: Number of subjects enrolled | Russian Federation: 23 |

| | |
|--------------------------------------|-------------------|
| Country: Number of subjects enrolled | Ukraine: 24 |
| Country: Number of subjects enrolled | United States: 35 |
| Worldwide total number of subjects | 156 |
| EEA total number of subjects | 66 |

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) | 150 |
| From 65 to 84 years | 6 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

The study included a screening period (up to 28 days), a double-blind induction treatment period (12 weeks), and a possible follow-up visit (2 weeks after the last study visit). The target population consisted of male or female subjects aged between 18 and 80 years (inclusive), with moderately to severely active Ulcerative Colitis.

Pre-assignment

Screening details:

During the screening period (Days -28 to -1), subjects were evaluated for study entry based on the inclusion and exclusion criteria. Screening procedures to evaluate subject eligibility for the study were to be conducted within 28 days prior to study drug administration on Day 1.

Period 1

| | |
|------------------------------|---|
| Period 1 title | Induction Treatment Period (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Investigator, Monitor, Assessor, Subject |

Blinding implementation details:

All study personnel directly related to this study (investigators, study site personnel, monitors, and CRO and Sponsor personnel), with the exception of the clinical supply staff, safety staff, and the unblinded statistician supporting the DSMB, were blinded to the identity of study drug. Randomization codes were generated by a CRO statistician not directly involved with the study.

Arms

| | |
|------------------------------|----------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Etrasimod 1 mg |

Arm description:

Etrasimod 1 mg was administered orally once daily (QD) for 12 weeks, administered with approximately 240 mL (8 ounces) of water. The study drug was to be taken on an empty stomach after an overnight fast of approximately 8 hours.

| | |
|--|----------------|
| Arm type | Experimental |
| Investigational medicinal product name | Etrasimod 1 mg |
| Investigational medicinal product code | - |
| Other name | APD334, 1 mg |
| Pharmaceutical forms | Capsule, hard |
| Routes of administration | Oral use |

Dosage and administration details:

1 × 1 mg etrasimod capsule orally QD for 12 weeks

| | |
|------------------|----------------|
| Arm title | Etrasimod 2 mg |
|------------------|----------------|

Arm description:

Etrasimod 2 mg was administered orally once daily (QD) for 12 weeks, administered with approximately 240 mL (8 ounces) of water. The study drug was to be taken on an empty stomach after an overnight fast of approximately 8 hours.

| | |
|--|----------------|
| Arm type | Experimental |
| Investigational medicinal product name | Etrasimod 2 mg |
| Investigational medicinal product code | - |
| Other name | APD334, 2 mg |
| Pharmaceutical forms | Capsule, hard |
| Routes of administration | Oral use |

Dosage and administration details:

1 × 2 mg etrasimod capsule orally QD for 12 weeks

| | |
|------------------|---------|
| Arm title | Placebo |
|------------------|---------|

Arm description:

Placebo was administered orally once daily (QD) for 12 weeks, administered with approximately 240 mL (8 ounces) of water. Placebo was to be taken on an empty stomach after an overnight fast of approximately 8 hours.

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

Dosage and administration details:

1 × matching etrasimod capsule orally QD for 12 weeks

| Number of subjects in period 1 | Etrasimod 1 mg | Etrasimod 2 mg | Placebo |
|---------------------------------------|----------------|----------------|---------|
| Started | 52 | 50 | 54 |
| Completed | 47 | 46 | 48 |
| Not completed | 5 | 4 | 6 |
| Physician decision | 1 | - | - |
| Consent withdrawn by subject | - | 1 | 5 |
| Adverse event, non-fatal | 4 | 3 | - |
| Sponsor Decision | - | - | 1 |

Baseline characteristics

Reporting groups

| | |
|---|----------------|
| Reporting group title | Etrasimod 1 mg |
| Reporting group description: | |
| Etrasimod 1 mg was administered orally once daily (QD) for 12 weeks, administered with approximately 240 mL (8 ounces) of water. The study drug was to be taken on an empty stomach after an overnight fast of approximately 8 hours. | |
| Reporting group title | Etrasimod 2 mg |
| Reporting group description: | |
| Etrasimod 2 mg was administered orally once daily (QD) for 12 weeks, administered with approximately 240 mL (8 ounces) of water. The study drug was to be taken on an empty stomach after an overnight fast of approximately 8 hours. | |
| Reporting group title | Placebo |
| Reporting group description: | |
| Placebo was administered orally once daily (QD) for 12 weeks, administered with approximately 240 mL (8 ounces) of water. Placebo was to be taken on an empty stomach after an overnight fast of approximately 8 hours. | |

| Reporting group values | Etrasimod 1 mg | Etrasimod 2 mg | Placebo |
|------------------------|----------------|----------------|----------|
| Number of subjects | 52 | 50 | 54 |
| Age categorical | | | |
| Units: Subjects | | | |
| Adults (18-64 years) | 52 | 49 | 49 |
| From 65-84 years | 0 | 1 | 5 |
| Age continuous | | | |
| Units: years | | | |
| median | 44.0 | 38.5 | 46.0 |
| full range (min-max) | 21 to 64 | 21 to 67 | 20 to 73 |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 22 | 23 | 22 |
| Male | 30 | 27 | 32 |

| Reporting group values | Total | | |
|------------------------|-------|--|--|
| Number of subjects | 156 | | |
| Age categorical | | | |
| Units: Subjects | | | |
| Adults (18-64 years) | 150 | | |
| From 65-84 years | 6 | | |
| Age continuous | | | |
| Units: years | | | |
| median | - | | |
| full range (min-max) | - | | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 67 | | |
| Male | 89 | | |

Subject analysis sets

| | |
|----------------------------|----------------------------|
| Subject analysis set title | Induction Treatment Period |
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

The 12-week double-blind induction treatment period started at Week 0 (Day 1) immediately after randomly assigning subjects to a treatment group and ended at Week 12. Eligible subjects were randomly assigned in a 1:1:1 ratio to 1 of the 3 treatment groups: etrasimod 1 mg, etrasimod 2 mg, or placebo. Randomization was stratified by presence or absence of current oral corticosteroid usage and prior exposure to tumor necrosis factor alpha (TNFα) antagonists. The study drugs were administered orally once daily (QD) for 12 weeks. All doses were administered with approximately 240 mL (8 ounces) of water. The study drugs were to be taken on an empty stomach after an overnight fast of approximately 8 hours. After the first study drug administration (Week 0 [Day 1]), subjects were to return to the study site for 5 evaluation visits (Weeks 1, 2, 4, 8, and 12) during the double-blind treatment period.

| Reporting group values | Induction Treatment Period | | |
|---------------------------------------|----------------------------|--|--|
| Number of subjects | 156 | | |
| Age categorical Units: Subjects | | | |
| Adults (18-64 years) | 150 | | |
| From 65-84 years | 6 | | |
| Age continuous Units: years | | | |
| median | 42.0 | | |
| full range (min-max) | 20 to 73 | | |
| Gender categorical Units: Subjects | | | |
| Female | 67 | | |
| Male | 89 | | |

End points

End points reporting groups

| | |
|--|----------------------------|
| Reporting group title | Etrasimod 1 mg |
| Reporting group description: Etrasimod 1 mg was administered orally once daily (QD) for 12 weeks, administered with approximately 240 mL (8 ounces) of water. The study drug was to be taken on an empty stomach after an overnight fast of approximately 8 hours. | |
| Reporting group title | Etrasimod 2 mg |
| Reporting group description: Etrasimod 2 mg was administered orally once daily (QD) for 12 weeks, administered with approximately 240 mL (8 ounces) of water. The study drug was to be taken on an empty stomach after an overnight fast of approximately 8 hours. | |
| Reporting group title | Placebo |
| Reporting group description: Placebo was administered orally once daily (QD) for 12 weeks, administered with approximately 240 mL (8 ounces) of water. Placebo was to be taken on an empty stomach after an overnight fast of approximately 8 hours. | |
| Subject analysis set title | Induction Treatment Period |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: The 12-week double-blind induction treatment period started at Week 0 (Day 1) immediately after randomly assigning subjects to a treatment group and ended at Week 12. Eligible subjects were randomly assigned in a 1:1:1 ratio to 1 of the 3 treatment groups: etrasimod 1 mg, etrasimod 2 mg, or placebo. Randomization was stratified by presence or absence of current oral corticosteroid usage and prior exposure to tumor necrosis factor alpha (TNFα) antagonists. The study drugs were administered orally once daily (QD) for 12 weeks. All doses were administered with approximately 240 mL (8 ounces) of water. The study drugs were to be taken on an empty stomach after an overnight fast of approximately 8 hours. After the first study drug administration (Week 0 [Day 1]), subjects were to return to the study site for 5 evaluation visits (Weeks 1, 2, 4, 8, and 12) during the double-blind treatment period. | |

Primary: Adapted Mayo Score (MCS) at Week 12

| | |
|--|-------------------------------------|
| End point title | Adapted Mayo Score (MCS) at Week 12 |
| End point description: Using the multiple imputation method to handle missing data, change from baseline in the adapted MCS at Week 12 was analyzed using ANCOVA on each multiply imputed dataset for the ITT population. | |
| End point type | Primary |
| End point timeframe: The primary efficacy endpoint was the change from baseline in the adapted MCS (stool frequency, rectal bleeding, and findings on endoscopy) at Week 12. | |

| End point values | Etrasimod 1 mg | Etrasimod 2 mg | Placebo | |
|--|------------------------|------------------------|------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 52 | 50 | 54 | |
| Units: mean | | | | |
| least squares mean (confidence interval 90%) | -1.94 (-2.45 to -1.42) | -2.49 (-3.01 to -1.98) | -1.50 (-2.00 to -1.01) | |

Statistical analyses

| | |
|-----------------------------------|-------------------------------|
| Statistical analysis title | ITT Statistical Analysis Plan |
|-----------------------------------|-------------------------------|

Statistical analysis description:

The primary efficacy endpoint was analyzed using an analysis of covariance (ANCOVA) model with terms of treatment, current oral corticosteroid use, prior exposure to TNF α antagonists, and baseline value as covariates. Least-squares (LS) mean by treatment group and its 90% confidence interval (CI), and LS mean difference between treatment group and its 90% CI were reported. Same method was applied to analyze change from baseline at Week 12 for score-based endpoints.

| | |
|---|---|
| Comparison groups | Etrasimod 1 mg v Etrasimod 2 mg v Placebo |
| Number of subjects included in analysis | 156 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[1] |
| P-value | = 0.0091 |
| Method | ANCOVA |
| Parameter estimate | Mean diff. in 2mg etrasimod vs pbo = -.99 |
| Confidence interval | |
| level | 90 % |
| sides | 1-sided |
| lower limit | -1.68 |
| upper limit | -0.3 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.42 |

Notes:

[1] - The proportion of subjects who achieved endoscopic improvement was analyzed individually using the Cochran-Mantel-Haenszel (CMH) test adjusted for the stratification factors of presence or absence of current oral corticosteroid therapy at baseline and previous exposure to TNF α antagonists, to compare the difference of proportions between treatment groups.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events (AEs) were able to be reported by the subject at any time for the duration of the study. All AEs were monitored up to 30 days after the study drug administration.

Adverse event reporting additional description:

The Investigator assessed the severity of each Treatment-Emergent Adverse Event (TEAE) using CTCAE criteria v4.03. Most TEAEs were mild (grade 1) or moderate (grade 2) in severity. An independent Data Safety Monitoring Board (DSMB) was established to review safety data from this study.

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

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|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

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|--------------------|------|
| Dictionary version | 20.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|----------------|
| Reporting group title | Etrasimod 1 mg |
|-----------------------|----------------|

Reporting group description:

Etrasimod 1 mg was administered orally once daily (QD) for 12 weeks, administered with approximately 240 mL (8 ounces) of water. The study drug was to be taken on an empty stomach after an overnight fast of approximately 8 hours.

| | |
|-----------------------|----------------|
| Reporting group title | Etrasimod 2 mg |
|-----------------------|----------------|

Reporting group description:

Etrasimod 2 mg was administered orally once daily (QD) for 12 weeks, administered with approximately 240 mL (8 ounces) of water. The study drug was to be taken on an empty stomach after an overnight fast of approximately 8 hours.

| | |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

Placebo was administered orally once daily (QD) for 12 weeks, administered with approximately 240 mL (8 ounces) of water. Placebo was to be taken on an empty stomach after an overnight fast of approximately 8 hours.

| Serious adverse events | Etrasimod 1 mg | Etrasimod 2 mg | Placebo |
|---|----------------|----------------|-----------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 3 / 52 (5.77%) | 0 / 50 (0.00%) | 6 / 54 (11.11%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 50 (0.00%) | 1 / 54 (1.85%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Colitis ulcerative | | | |
| subjects affected / exposed | 2 / 52 (3.85%) | 0 / 50 (0.00%) | 3 / 54 (5.56%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|----------------|----------------|----------------|
| Duodenal ulcer perforation | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 50 (0.00%) | 1 / 54 (1.85%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Jaundice | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 50 (0.00%) | 1 / 54 (1.85%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Hydronephrosis | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 50 (0.00%) | 1 / 54 (1.85%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Anal abscess | | | |
| subjects affected / exposed | 1 / 52 (1.92%) | 0 / 50 (0.00%) | 0 / 54 (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 | Etrasimod 1 mg | Etrasimod 2 mg | Placebo |
|---|------------------|------------------|------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 29 / 52 (55.77%) | 28 / 50 (56.00%) | 24 / 54 (44.44%) |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 3 / 50 (6.00%) | 1 / 54 (1.85%) |
| occurrences (all) | 0 | 3 | 2 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 2 / 52 (3.85%) | 3 / 50 (6.00%) | 2 / 54 (3.70%) |
| occurrences (all) | 3 | 3 | 3 |
| Gastrointestinal disorders | | | |
| Colitis ulcerative | | | |

| | | | |
|--|---------------------|---------------------|---------------------|
| subjects affected / exposed occurrences (all) | 3 / 52 (5.77%) 3 | 2 / 50 (4.00%) 2 | 1 / 54 (1.85%) 1 |
| Infections and infestations | | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 2 / 52 (3.85%) | 1 / 50 (2.00%) | 4 / 54 (7.41%) |
| occurrences (all) | 2 | 2 | 4 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 4 / 52 (7.69%) | 2 / 50 (4.00%) | 2 / 54 (3.70%) |
| occurrences (all) | 4 | 2 | 2 |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------|--|
| 01 May 2015 | <p>The first amendment to the protocol, dated 01 May 2015, included the following important changes:</p> <ul style="list-style-type: none">• The term partial MCS was changed to 3-component MCS throughout the protocol.• Use of Inflammatory Bowel Disease Questionnaire and corresponding exploratory objective, endpoint, and analysis were added.• Definition of an intolerable AE was added.• A clarification was made to specify that the stool sample collected during the study was used for the analysis of both the fecal calprotectin assay and for culture, ova, and parasite evaluation and C difficile assay.• Requirement for a chest X-ray to be taken at the Week 12 visit was removed for subjects not continuing into the extension study.• Clarified that study medication should be taken after an overnight fast (~8 hours) and food should be avoided for ~1 hour after dosing.• Inclusion criterion pertaining to corticosteroid usage was updated to remove the references pertaining to the allowance of corticosteroid tapering in the study, with the requirement of stable dosage regimen throughout the study duration for corticosteroid usage.• The requirement of capping the number of subjects with prior exposure to TNFα antagonists for randomization into the study was added.• Information about blinding requirements for analysis of total lymphocyte and white blood cell (WBC) counts to be followed during the study was added.• The ECG assessment information was updated to clarify that the ECGs were to be read and interpreted by both the study physician and centrally.• Reference to "continuous telemetry" in the protocol was corrected to "Holter monitoring."• The laboratory parameters were updated to add and remove certain evaluation parameters from the assessments.• "Pharmacodynamic" assessments in the study were replaced with "hematologic" assessments.• Subgroup analyses parameters for fecal calprotectin and CRP were defined. |

| | |
|-------------------|---|
| 17 June 2015 | <p>The second amendment to the protocol, dated 17 Jun 2015, included the following important changes:</p> <ul style="list-style-type: none"> • Analysis time points to the efficacy parameters of rectal bleeding, stool frequency, fecal calprotectin, CRP reduction, and 2-component Mayo Score were added. • The following exploratory endpoints were added: (1) change from baseline in Mayo endoscopic subscore at Week 12; (2) change from baseline in Mayo PGA at Week 12; (3) change from baseline in 2-component Mayo score at Weeks 1, 2, 4, 8, and 12; and (4) change from baseline in lymphocyte counts at Weeks 1, 2, 4, 8, 12, and 14. • A secondary method for the primary efficacy analysis was added, which included a logistic regression analysis with terms of treatment, presence or absence of current oral corticosteroid therapy at baseline, previous exposure to TNFα antagonists, and the interaction between 2 stratification factors (if appropriate). • Requirement of clinical laboratory tests to be performed at screening and Week 12 under fasting conditions was removed. • Inclusion criterion related to colonoscopy for subjects with history of extensive pancolitis or left-sided colitis was clarified. • Exclusion criterion pertaining to the serology requirements was updated to exclude subjects without documented varicella zoster virus (VZV) IgG antibody status. • Addition of 3 exclusion criteria: (1) use of moderate to strong inhibitors of CYP2C9; (2) history of severe renal impairment; and (3) history of severe hepatic impairment. • Dosage instructions for study drug administration were clarified to instruct subjects not to take their study drug dose at home on days with scheduled study visits in order to complete predose study procedures and to remain fasted as instructed on the days of scheduled visits prior to dosing. • Moderate to strong inhibitors of CYP2C9 were added to the excluded (i.e., prohibited) medications list. |
| 30 June 2015 | <p>The third amendment to the protocol, dated 30 Jun 2015, included the following important changes:</p> <ul style="list-style-type: none"> • An exclusion criterion of "previous treatment with 2 or more biologic agents" was added. • Vedolizumab was added to the list of medications that were to be excluded within 60 days prior to randomization. • Consideration for a repeat flexible proctosigmoidoscopy was added. |
| 21 September 2015 | <p>The fourth amendment to the protocol, dated 21 Sep 2015, included the following important changes:</p> <ul style="list-style-type: none"> • Information on retinal photos to be taken at each ophthalmoscopy was added. • Requirement of Week 12 ophthalmoscopy applicable only to subjects who did not enter the extension study was removed. • Inclusion criterion about the permitted use of corticosteroids prior to study entry was updated. • Exclusion criteria related to history or evidence of adenomatous colonic polyps and colonic mucosal dysplasia were updated. |

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|-----------------|---|
| 10 October 2016 | <p>The fifth amendment to the protocol, dated 10 Oct 2016, included the following important changes:</p> <ul style="list-style-type: none"> • Subject entry requirement for participation in the extension Study APD334-005 was updated to include only responders and not both responders and nonresponders. • Blood sample collection at 8 hours postdose for PK assessments was removed. • Added possibility to prolong time window for screening to 35 days. Extended window for specified procedures (proctosigmoidoscopy) to 10 days. Removed all other visit and procedure windows. • The duration within which certain screening procedures were to be completed prior to randomization was updated from 7 to 10 days. • Assessment timings and requirements for heart rate, blood pressure, and ECG measurements were updated. • Exclusion criterion related to use of biologic agents prior to study entry was updated, with subjects who received previous treatment with more than 3 biologics were not to be enrolled. • Additional monitoring considerations for changes in heart rate and ECG parameters were added. • Recipient of notification of SAE was changed from the Sponsor to PPD (contract research organization [CRO]). • Information on extending the screening period window to 35 days and clarification on rescreening procedures was added. • Information about the 2-component May score to be calculated at Weeks 1, 2, 4, and 8 was added. • Added specification that APD334-003 study will remain blinded until completion of the APD334-005 study. • Clarified that clinical laboratory tests and CBC tests should be performed prior to dosing. |
| 27 March 2017 | <p>The sixth amendment to the protocol, dated 27 Mar 2017, included the following important changes:</p> <ul style="list-style-type: none"> • The primary objective was updated to determine the effect of treatment with etrasimod in improving 3-component MCS (score ranging from 0 to 9, including stool frequency, rectal bleeding, and findings on endoscopy) at Week 12. • The following secondary objectives were added: (1) to determine the effect of treatment with etrasimod on a combination of clinical remission and clinical response reflected by a composite endpoint at 12 weeks; and (2) to determine the effect of treatment with etrasimod in inducing clinical remission at 12 weeks. • The following exploratory objectives were added: (1) to determine the effect of etrasimod treatment on total MCS at 12 weeks; and (2) to determine dose response effect of etrasimod on 3-component MCS, combination of clinical remission and clinical response reflected by a composite endpoint, clinical remission, clinical response, and endoscopic improvement, at 12 weeks. • The primary, secondary, and exploratory efficacy endpoints were updated based on the changes made to the study objectives. • The study design information was updated to designate this study as a proof of concept study. • Subject entry requirement for participation in the extension Study APD334-005 was updated to include both responders and nonresponders. • Inclusion criterion about integrin antagonists was updated to include subjects in the study who had discontinued prior treatment with vedolizumab despite clinical benefit. • The exclusion criterion of "a history of primary nonresponse to a treatment regimen of vedolizumab per the current labeling and/or institutional standard of care. • Sample size language was changed to up to 240, with the added statement that the Sponsor can stop enrollment for any reason prior to that. • Sponsor considerations for conducting interim analysis were added. • Added section that outlined reasons to terminate the study. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

None reported

Notes: