



Clinical trial results:

A Phase 3, Randomized, Double Blind, Placebo Controlled, 12 Week Study to Assess the Efficacy and Safety of Etrasimod in Subjects with Moderately to Severely Active Ulcerative Colitis

Summary

| | |
|--------------------------|--|
| EudraCT number | 2018-003986-33 |
| Trial protocol | SK BE NL GB EE DE AT CZ FR DK LT BG PT LV HU PL HR ES IT |
| Global end of trial date | 09 December 2021 |

Results information

| | |
|--------------------------------|--------------|
| Result version number | v1 (current) |
| This version publication date | 22 June 2022 |
| First version publication date | 22 June 2022 |

Trial information

Trial identification

| | |
|-----------------------|------------|
| Sponsor protocol code | APD334-302 |
|-----------------------|------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT03996369 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Arena Pharmaceuticals, Inc. |
| Sponsor organisation address | 6154 Nancy Ridge Drive, San Diego, United States, |
| Public contact | Fabio Cataldi, Arena Pharmaceuticals, Inc., 001 8584537200, ct.gov@arenapharm.com |
| Scientific contact | Fabio Cataldi, Arena Pharmaceuticals, Inc., 001 8584537200, 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 | 17 February 2022 |
| Is this the analysis of the primary completion data? | No |

| | |
|----------------------------------|------------------|
| Global end of trial reached? | Yes |
| Global end of trial date | 07 December 2021 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to assess the efficacy of etrasimod when administered for 12 weeks on clinical remission in subjects with moderately to severely active ulcerative colitis (UC).

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 | 18 August 2020 |
| 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 | United States: 29 |
| Country: Number of subjects enrolled | Belarus: 6 |
| Country: Number of subjects enrolled | Georgia: 11 |
| Country: Number of subjects enrolled | Moldova, Republic of: 6 |
| Country: Number of subjects enrolled | Russian Federation: 35 |
| Country: Number of subjects enrolled | Serbia: 6 |
| Country: Number of subjects enrolled | Ukraine: 25 |
| Country: Number of subjects enrolled | Argentina: 2 |
| Country: Number of subjects enrolled | Australia: 10 |
| Country: Number of subjects enrolled | Chile: 2 |
| Country: Number of subjects enrolled | India: 17 |
| Country: Number of subjects enrolled | Israel: 3 |
| Country: Number of subjects enrolled | Japan: 48 |
| Country: Number of subjects enrolled | Korea, Republic of: 4 |
| Country: Number of subjects enrolled | Lebanon: 1 |
| Country: Number of subjects enrolled | Mexico: 10 |
| Country: Number of subjects enrolled | South Africa: 3 |
| Country: Number of subjects enrolled | Thailand: 1 |
| Country: Number of subjects enrolled | Turkey: 7 |
| Country: Number of subjects enrolled | Poland: 44 |

| | |
|--------------------------------------|-------------------|
| Country: Number of subjects enrolled | Portugal: 2 |
| Country: Number of subjects enrolled | Romania: 6 |
| Country: Number of subjects enrolled | Slovakia: 7 |
| Country: Number of subjects enrolled | Spain: 1 |
| Country: Number of subjects enrolled | United Kingdom: 3 |
| Country: Number of subjects enrolled | Croatia: 1 |
| Country: Number of subjects enrolled | Belgium: 2 |
| Country: Number of subjects enrolled | Bulgaria: 4 |
| Country: Number of subjects enrolled | Czechia: 15 |
| Country: Number of subjects enrolled | Denmark: 1 |
| Country: Number of subjects enrolled | Estonia: 5 |
| Country: Number of subjects enrolled | France: 8 |
| Country: Number of subjects enrolled | Germany: 1 |
| Country: Number of subjects enrolled | Hungary: 15 |
| Country: Number of subjects enrolled | Italy: 9 |
| Country: Number of subjects enrolled | Lithuania: 4 |
| Worldwide total number of subjects | 354 |
| EEA total number of subjects | 125 |

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) | 2 |
| Adults (18-64 years) | 334 |
| From 65 to 84 years | 18 |
| 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 2-week and a 4-week follow-up period. The target population consisted of male or female subjects aged between 16 and 80 years (inclusive), with moderately to severely active ulcerative colitis.

Pre-assignment

Screening details:

During the screening period, 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 - Safety Set (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Monitor, Assessor |

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, some 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 2 mg |

Arm description:

Etrasimod 2 mg was administered orally once daily (QD) for 12 weeks. One tablet is to be taken each day (with water, either with or without food).

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

Dosage and administration details:

1 × 2 mg etrasimod tablet orally QD for 12 weeks

| | |
|--|----------|
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

1 × matching etrasimod tablet orally QD for 12 weeks

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

Arm description:

Placebo was administered orally once daily (QD) for 12 weeks. One tablet is to be taken each day (with water, either with or without food).

| | |
|----------|---------|
| 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:

1 × matching etrasimod tablet orally QD for 12 weeks

| Number of subjects in period 1 | Etrasimod 2 mg | Placebo |
|---------------------------------------|----------------|---------|
| Started | 238 | 116 |
| Completed | 213 | 103 |
| Not completed | 25 | 13 |
| Consent withdrawn by subject | 6 | 8 |
| Physician decision | 4 | 2 |
| Participant decision | - | 1 |
| Adverse event, non-fatal | 9 | - |
| Lost to follow-up | - | 1 |
| Didn't meet I/E criteria | 1 | - |
| Lack of efficacy | 4 | - |
| Protocol deviation | 1 | 1 |

Baseline characteristics

Reporting groups

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

Reporting group description:

Etrasimod 2 mg was administered orally once daily (QD) for 12 weeks. One tablet is to be taken each day (with water, either with or without food).

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

Reporting group description:

Placebo was administered orally once daily (QD) for 12 weeks. One tablet is to be taken each day (with water, either with or without food).

| Reporting group values | Etrasimod 2 mg | Placebo | Total |
|--|----------------|----------|-------|
| Number of subjects | 238 | 116 | 354 |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 1 | 1 | 2 |
| Adults (18-64 years) | 225 | 109 | 334 |
| From 65-84 years | 12 | 6 | 18 |
| 85 years and over | 0 | 0 | 0 |
| Age continuous | | | |
| Units: years | | | |
| median | 37.5 | 38.0 | |
| full range (min-max) | 16 to 73 | 17 to 72 | - |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 103 | 43 | 146 |
| Male | 135 | 73 | 208 |
| Race (NIH/OMB) | | | |
| Units: Subjects | | | |
| American Indian or Alaska Native | 6 | 1 | 7 |
| Asian | 47 | 25 | 72 |
| Black or African American | 2 | 2 | 4 |
| White | 176 | 88 | 264 |
| Multiple | 1 | 0 | 1 |
| Not Reported | 6 | 0 | 6 |

End points

End points reporting groups

| | |
|--|----------------|
| Reporting group title | Etrasimod 2 mg |
| Reporting group description: Etrasimod 2 mg was administered orally once daily (QD) for 12 weeks. One tablet is to be taken each day (with water, either with or without food). | |
| Reporting group title | Placebo |
| Reporting group description: Placebo was administered orally once daily (QD) for 12 weeks. One tablet is to be taken each day (with water, either with or without food). | |

Primary: Percentage of participants achieving clinical remission at Week 12

| | |
|--|--|
| End point title | Percentage of participants achieving clinical remission at Week 12 |
| End point description: Remission is a composite score of participant reported symptoms using daily e-diary and centrally read endoscopy as follows: stool frequency sub-score 0 or 1 with at least a 1-point change from induction study baseline; and rectal bleeding sub-score of 0; and endoscopic sub-score 0 or 1 (modified, excludes friability). The primary efficacy analysis was conducted using the FAS with Baseline MMS 5 to 9. | |
| End point type | Primary |
| End point timeframe: Week 12 | |

| End point values | Etrasimod 2 mg | Placebo | | |
|-----------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 222 | 112 | | |
| Units: Percentage of participants | | | | |
| number (not applicable) | 24.8 | 15.2 | | |

Statistical analyses

| | |
|---|--------------------------|
| Statistical analysis title | Statistical Analysis |
| Comparison groups | Etrasimod 2 mg v Placebo |
| Number of subjects included in analysis | 334 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0264 |
| Method | Mantel-Haenszel |
| Parameter estimate | Risk difference (RD) |
| Point estimate | 9.69 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.14 |
| upper limit | 18.23 |

Secondary: Percentage of participants achieving endoscopic improvement at Week 12

| | |
|---|--|
| End point title | Percentage of participants achieving endoscopic improvement at Week 12 |
| End point description: | |
| Participant reported symptoms using daily e-diary and centrally read endoscopy as follows: stool frequency sub-score 0 or 1 with at least a 1-point change from induction study baseline; and rectal bleeding sub-score of 0; and endoscopic sub-score 0 or 1 (excluding friability). | |
| End point type | Secondary |
| End point timeframe: | |
| Week 12 | |

| End point values | Etrasimod 2 mg | Placebo | | |
|-----------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 222 | 112 | | |
| Units: Percentage of participants | | | | |
| number (not applicable) | 30.6 | 18.8 | | |

Statistical analyses

| | |
|---|--------------------------|
| Statistical analysis title | Statistical Analysis |
| Comparison groups | Etrasimod 2 mg v Placebo |
| Number of subjects included in analysis | 334 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0092 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Risk difference (RD) |
| Point estimate | 12.11 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 3 |
| upper limit | 21.23 |

Secondary: Percentage of participants achieving symptomatic remission at Week 12

| | |
|---|---|
| End point title | Percentage of participants achieving symptomatic remission at Week 12 |
| End point description: Symptomatic remission is a composite score of participant reported symptoms using daily e-diary and centrally read endoscopy as: stool frequency sub-score 0 or 1 with at least a 1-point change from induction study baseline; and rectal bleeding sub-score of 0. | |
| End point type | Secondary |
| End point timeframe: Week 12 | |

| End point values | Etrasimod 2 mg | Placebo | | |
|-----------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 222 | 112 | | |
| Units: Percentage of participants | | | | |
| number (not applicable) | 46.8 | 29.5 | | |

Statistical analyses

| | |
|---|--------------------------|
| Statistical analysis title | Statistical Analysis |
| Comparison groups | Etrasimod 2 mg v Placebo |
| Number of subjects included in analysis | 334 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0013 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Risk difference (RD) |
| Point estimate | 17.48 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 6.81 |
| upper limit | 28.15 |

Secondary: Percentage of participants with mucosal healing at Week 12

| | |
|---|--|
| End point title | Percentage of participants with mucosal healing at Week 12 |
| End point description: Mucosal healing was defined as an endoscopic sub score of less than or equal to 1 (Excluding friability) with histologic remission measured by a Geboes Index score < 2.0). The centrally read endoscopic sub-score of mayo score ranges from 0 to 3 with higher scores indicating more severe disease. Geboes score grading system, was a validated score for evaluating histologic disease activity in UC as follows: grade 0 = structural and architectural changes; grade 1 = chronic inflammatory infiltrate; grade 2 = lamina propria neutrophils and eosinophils; grade 3 = neutrophils in the epithelium; grade 4 = crypt destruction; grade 5 = erosions or ulceration. A higher Geboes score indicates more severe disease. | |
| End point type | Secondary |
| End point timeframe: Week 12 | |

| End point values | Etrasimod 2 mg | Placebo | | |
|-----------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 222 | 112 | | |
| Units: Percentage of participants | | | | |
| number (not applicable) | 16.2 | 8.9 | | |

Statistical analyses

| Statistical analysis title | Statistical Analysis |
|---|--------------------------|
| Comparison groups | Etrasimod 2 mg v Placebo |
| Number of subjects included in analysis | 334 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0358 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Risk difference (RD) |
| Point estimate | 7.44 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.5 |
| upper limit | 14.39 |

Secondary: Percentage of participants achieving clinical response at Week 12

| | |
|--|---|
| End point title | Percentage of participants achieving clinical response at Week 12 |
| End point description: | |
| Clinical response was defined as a greater than equal to (\geq) 2-point and \geq 30 percent decrease from baseline in modified Mayo score (MMS), and a \geq 1-point decrease from Baseline in rectal bleeding (RB) sub-score or an absolute RB sub-score \leq 1. | |
| End point type | Secondary |
| End point timeframe: | |
| Week 12 | |

| End point values | Etrasimod 2 mg | Placebo | | |
|-----------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 222 | 112 | | |
| Units: Percentage of participants | | | | |
| number (not applicable) | 62.2 | 41.1 | | |

Statistical analyses

| | |
|---|--------------------------|
| Statistical analysis title | Statistical Analysis |
| Comparison groups | Etrasimod 2 mg v Placebo |
| Number of subjects included in analysis | 334 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.0002 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Risk difference (RD) |
| Point estimate | 21.23 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 10.18 |
| upper limit | 32.29 |

Secondary: Percentage of participants achieving endoscopic normalization at Week 12

| | |
|---|--|
| End point title | Percentage of participants achieving endoscopic normalization at Week 12 |
| End point description: | |
| Endoscopic normalization was defined as an endoscopic score (ES) = 0. | |
| End point type | Secondary |
| End point timeframe: | |
| Week 12 | |

| | | | | |
|-----------------------------------|-----------------|-----------------|--|--|
| End point values | Etrasimod 2 mg | Placebo | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 222 | 112 | | |
| Units: Percentage of participants | | | | |
| number (not applicable) | 17.1 | 8.0 | | |

Statistical analyses

| | |
|-----------------------------------|--------------------------|
| Statistical analysis title | Statistical Analysis |
| Comparison groups | Etrasimod 2 mg v Placebo |

| | |
|---|-------------------------|
| Number of subjects included in analysis | 334 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0093 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Risk difference (RD) |
| Point estimate | 9.24 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 2.27 |
| upper limit | 16.2 |

Secondary: Percentage of participants achieving symptomatic remission at Weeks 2, 4 and 8

| | |
|------------------------|---|
| End point title | Percentage of participants achieving symptomatic remission at Weeks 2, 4 and 8 |
| End point description: | Symptomatic remission is a composite score of participant reported symptoms using daily e-diary and centrally read endoscopy as: stool frequency sub-score 0 or 1 with at least a 1-point change from induction study baseline; and rectal bleeding sub-score of 0. |
| End point type | Secondary |
| End point timeframe: | Weeks 2, 4 and 8 |

| End point values | Etrasimod 2 mg | Placebo | | |
|-----------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 222 | 112 | | |
| Units: Percentage of participants | | | | |
| number (not applicable) | | | | |
| Week 2 | 16.2 | 10.7 | | |
| Week 4 | 27.5 | 16.1 | | |
| Week 8 | 38.7 | 24.1 | | |

Statistical analyses

| | |
|----------------------------|--------------------------|
| Statistical analysis title | Statistical Analysis |
| Comparison groups | Etrasimod 2 mg v Placebo |

| | |
|---|----------------------------|
| Number of subjects included in analysis | 334 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[1] |
| P-value | = 0.1149 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Risk difference (RD) |
| Point estimate | 5.85 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.42 |
| upper limit | 13.13 |

Notes:

[1] - Weeks 2

| | |
|---|--------------------------|
| Statistical analysis title | Statistical Analysis |
| Statistical analysis description: | |
| Week 4 | |
| Comparison groups | Etrasimod 2 mg v Placebo |
| Number of subjects included in analysis | 334 |
| Analysis specification | Post-hoc |
| Analysis type | superiority |
| P-value | = 0.0073 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Risk difference (RD) |
| Point estimate | 11.83 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 3.19 |
| upper limit | 20.47 |

| | |
|---|--------------------------|
| Statistical analysis title | Statistical Analysis |
| Statistical analysis description: | |
| Week 8 | |
| Comparison groups | Etrasimod 2 mg v Placebo |
| Number of subjects included in analysis | 334 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0032 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Risk difference (RD) |
| Point estimate | 14.84 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 4.98 |
| upper limit | 24.69 |

Secondary: Percentage of participants achieving complete symptomatic remission at each study visit at Weeks 2, 4, 8 and 12

| | |
|-----------------|---|
| End point title | Percentage of participants achieving complete symptomatic remission at each study visit at Weeks 2, 4, 8 and 12 |
|-----------------|---|

End point description:

Complete symptomatic remission was defined as stool frequency sub-score = 0 and rectal bleeding sub-score = 0.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Weeks 2, 4, 8 and 12

| End point values | Etrasimod 2 mg | Placebo | | |
|-----------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 222 | 112 | | |
| Units: Percentage of participants | | | | |
| number (not applicable) | | | | |
| Week 2 | 4.5 | 1.8 | | |
| Week 4 | 11.7 | 3.6 | | |
| Week 8 | 14.0 | 7.1 | | |
| Week 12 | 18.0 | 8.9 | | |

Statistical analyses

| | |
|----------------------------|----------------------|
| Statistical analysis title | Statistical Analysis |
|----------------------------|----------------------|

Statistical analysis description:

Week 2

| | |
|---|--------------------------|
| Comparison groups | Etrasimod 2 mg v Placebo |
| Number of subjects included in analysis | 334 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.1277 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Risk difference (RD) |
| Point estimate | 2.83 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.81 |
| upper limit | 6.48 |

| | |
|---|--------------------------|
| Statistical analysis title | Statistical Analysis |
| Statistical analysis description: | |
| Week 4 | |
| Comparison groups | Etrasimod 2 mg v Placebo |
| Number of subjects included in analysis | 334 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0022 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Risk difference (RD) |
| Point estimate | 8.32 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 3.01 |
| upper limit | 13.64 |

| | |
|---|--------------------------|
| Statistical analysis title | Statistical Analysis |
| Statistical analysis description: | |
| Week 8 | |
| Comparison groups | Etrasimod 2 mg v Placebo |
| Number of subjects included in analysis | 334 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0316 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Risk difference (RD) |
| Point estimate | 7.06 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.62 |
| upper limit | 13.49 |

| | |
|---|--------------------------|
| Statistical analysis title | Statistical Analysis |
| Statistical analysis description: | |
| Week 12 | |
| Comparison groups | Etrasimod 2 mg v Placebo |
| Number of subjects included in analysis | 334 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0145 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Risk difference (RD) |
| Point estimate | 9.18 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.82 |
| upper limit | 16.54 |

Secondary: Percentage of participants achieving noninvasive clinical response at Weeks 2, 4, 8 and 12

| | |
|-----------------|--|
| End point title | Percentage of participants achieving noninvasive clinical response at Weeks 2, 4, 8 and 12 |
|-----------------|--|

End point description:

A noninvasive clinical response was defined as $\geq 30\%$ decrease from Baseline in composite rectal bleeding and stool frequency sub-scores, and a ≥ 1 -point decrease from Baseline in rectal bleeding sub score or an absolute rectal bleeding sub score ≤ 1 .

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Weeks 2, 4, 8 and 12

| End point values | Etrasimod 2 mg | Placebo | | |
|-----------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 222 | 112 | | |
| Units: Percentage of participants | | | | |
| number (not applicable) | | | | |
| Week 2 | 39.2 | 24.1 | | |
| Week 4 | 55.9 | 41.1 | | |
| Week 8 | 68.0 | 45.5 | | |
| Week 12 | 67.6 | 50.0 | | |

Statistical analyses

| | |
|----------------------------|----------------------|
| Statistical analysis title | Statistical Analysis |
|----------------------------|----------------------|

Statistical analysis description:

Week 2

| | |
|---|--------------------------|
| Comparison groups | Etrasimod 2 mg v Placebo |
| Number of subjects included in analysis | 334 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0021 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Risk difference (RD) |
| Point estimate | 15.55 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 5.65 |
| upper limit | 25.46 |

| | |
|---|--------------------------|
| Statistical analysis title | Statistical Analysis |
| Statistical analysis description: | |
| Week 4 | |
| Comparison groups | Etrasimod 2 mg v Placebo |
| Number of subjects included in analysis | 334 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0072 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Risk difference (RD) |
| Point estimate | 14.98 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 4.05 |
| upper limit | 25.91 |

| | |
|---|--------------------------|
| Statistical analysis title | Statistical Analysis |
| Statistical analysis description: | |
| Week 8 | |
| Comparison groups | Etrasimod 2 mg v Placebo |
| Number of subjects included in analysis | 334 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 1 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Risk difference (RD) |
| Point estimate | 22.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 11.95 |
| upper limit | 33.25 |

| | |
|-----------------------------------|------------------------------|
| Statistical analysis title | Copy of Statistical Analysis |
| Statistical analysis description: | |
| Week 12 | |
| Comparison groups | Etrasimod 2 mg v Placebo |

| | |
|---|-------------------------|
| Number of subjects included in analysis | 334 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0015 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Risk difference (RD) |
| Point estimate | 17.58 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 6.7 |
| upper limit | 28.47 |

Secondary: Percentage of participants achieving symptomatic response at Weeks 2, 4, 8 and 12

| | |
|------------------------|--|
| End point title | Percentage of participants achieving symptomatic response at Weeks 2, 4, 8 and 12 |
| End point description: | Symptomatic response was defined as decrease from baseline \geq 30% in composite rectal bleeding and Stool frequency sub scores. |
| End point type | Secondary |
| End point timeframe: | Weeks 2, 4, 8 and 12 |

| End point values | Etrasimod 2 mg | Placebo | | |
|-----------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 222 | 112 | | |
| Units: Percentage of participants | | | | |
| number (not applicable) | | | | |
| Week 2 | 39.6 | 24.1 | | |
| Week 4 | 56.3 | 41.1 | | |
| Week 8 | 68.5 | 46.4 | | |
| Week 12 | 68.5 | 50.0 | | |

Statistical analyses

| | |
|-----------------------------------|--------------------------|
| Statistical analysis title | Statistical Analysis |
| Statistical analysis description: | Week 2 |
| Comparison groups | Etrasimod 2 mg v Placebo |

| | |
|---|-------------------------|
| Number of subjects included in analysis | 334 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0016 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Risk difference (RD) |
| Point estimate | 15.99 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 6.07 |
| upper limit | 25.91 |

| | |
|---|--------------------------|
| Statistical analysis title | Statistical Analysis |
| Statistical analysis description: | |
| Week 4 | |
| Comparison groups | Etrasimod 2 mg v Placebo |
| Number of subjects included in analysis | 334 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0055 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Risk difference (RD) |
| Point estimate | 15.45 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 4.54 |
| upper limit | 26.36 |

| | |
|---|--------------------------|
| Statistical analysis title | Statistical Analysis |
| Statistical analysis description: | |
| Week 8 | |
| Comparison groups | Etrasimod 2 mg v Placebo |
| Number of subjects included in analysis | 334 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 1 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Risk difference (RD) |
| Point estimate | 22.14 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 11.43 |
| upper limit | 32.85 |

| | |
|---|--------------------------|
| Statistical analysis title | Statistical Analysis |
| Statistical analysis description: | |
| Week 12 | |
| Comparison groups | Etrasimod 2 mg v Placebo |
| Number of subjects included in analysis | 334 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0008 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Risk difference (RD) |
| Point estimate | 18.49 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 7.65 |
| upper limit | 29.33 |

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All-cause mortality, non-serious TEAEs and SAEs were collected from the beginning of participant's participation to 30 days following discontinuation of the study drug.

Adverse event reporting additional description:

Safety set population was used to collect the adverse events. The Safety Set includes all randomized participants who received at least 1 dose of study treatment.

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 24.1 |
|--------------------|------|

Reporting groups

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

Reporting group description:

Placebo was administered orally once daily (QD) for 12 weeks. One tablet is to be taken each day (with water, either with or without food).

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

Reporting group description:

Etrasimod 2 mg was administered orally once daily (QD) for 12 weeks. One tablet is to be taken each day (with water, either with or without food).

| Serious adverse events | Placebo | Etrasimod 2 mg | |
|---|-----------------|-----------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 2 / 116 (1.72%) | 6 / 238 (2.52%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | | | |
| Injury, poisoning and procedural complications | | | |
| Hepatobiliary procedural complication | | | |
| subjects affected / exposed | 0 / 116 (0.00%) | 1 / 238 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Coronary artery disease | | | |
| subjects affected / exposed | 0 / 116 (0.00%) | 1 / 238 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Migraine | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 116 (0.00%) | 1 / 238 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | 0 / 238 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Colitis ulcerative | | | |
| subjects affected / exposed | 0 / 116 (0.00%) | 3 / 238 (1.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | 0 / 238 (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: 0 %

| Non-serious adverse events | Placebo | Etrasimod 2 mg | |
|--|-------------------|--------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 54 / 116 (46.55%) | 112 / 238 (47.06%) | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Papilloma | | | |
| subjects affected / exposed | 0 / 116 (0.00%) | 1 / 238 (0.42%) | |
| occurrences (all) | 0 | 1 | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | 3 / 238 (1.26%) | |
| occurrences (all) | 1 | 3 | |
| Venous thrombosis | | | |
| subjects affected / exposed | 0 / 116 (0.00%) | 1 / 238 (0.42%) | |
| occurrences (all) | 0 | 1 | |
| Essential hypertension | | | |

| | | | |
|--|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 116 (0.86%) | 0 / 238 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| General disorders and administration site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 0 / 116 (0.00%) | 3 / 238 (1.26%) | |
| occurrences (all) | 0 | 3 | |
| Pyrexia | | | |
| subjects affected / exposed | 3 / 116 (2.59%) | 8 / 238 (3.36%) | |
| occurrences (all) | 3 | 8 | |
| Chest discomfort | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | 1 / 238 (0.42%) | |
| occurrences (all) | 1 | 1 | |
| Feeling abnormal | | | |
| subjects affected / exposed | 0 / 116 (0.00%) | 1 / 238 (0.42%) | |
| occurrences (all) | 0 | 1 | |
| Injection site reaction | | | |
| subjects affected / exposed | 0 / 116 (0.00%) | 1 / 238 (0.42%) | |
| occurrences (all) | 0 | 1 | |
| Malaise | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | 1 / 238 (0.42%) | |
| occurrences (all) | 1 | 1 | |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | 1 / 238 (0.42%) | |
| occurrences (all) | 1 | 1 | |
| Thirst | | | |
| subjects affected / exposed | 0 / 116 (0.00%) | 1 / 238 (0.42%) | |
| occurrences (all) | 0 | 1 | |
| Asthenia | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | 0 / 238 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Vaccination site pain | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | 0 / 238 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Oedema peripheral | | | |

| | | | |
|--|----------------------|----------------------|--|
| subjects affected / exposed occurrences (all) | 1 / 116 (0.86%) 1 | 0 / 238 (0.00%) 0 | |
| Oedema subjects affected / exposed occurrences (all) | 1 / 116 (0.86%) 1 | 0 / 238 (0.00%) 0 | |
| Immune system disorders Food allergy subjects affected / exposed occurrences (all) | 0 / 116 (0.00%) 0 | 1 / 238 (0.42%) 1 | |
| Reproductive system and breast disorders Testicular torsion subjects affected / exposed occurrences (all) | 0 / 116 (0.00%) 0 | 1 / 238 (0.42%) 1 | |
| Vaginal haemorrhage subjects affected / exposed occurrences (all) | 0 / 116 (0.00%) 0 | 1 / 238 (0.42%) 1 | |
| Respiratory, thoracic and mediastinal disorders Dyspnoea subjects affected / exposed occurrences (all) | 0 / 116 (0.00%) 0 | 2 / 238 (0.84%) 2 | |
| Cough subjects affected / exposed occurrences (all) | 0 / 116 (0.00%) 0 | 1 / 238 (0.42%) 1 | |
| Asthma subjects affected / exposed occurrences (all) | 1 / 116 (0.86%) 1 | 0 / 238 (0.00%) 0 | |
| Nasal congestion subjects affected / exposed occurrences (all) | 0 / 116 (0.00%) 0 | 1 / 238 (0.42%) 1 | |
| Dry throat subjects affected / exposed occurrences (all) | 1 / 116 (0.86%) 1 | 0 / 238 (0.00%) 0 | |
| Psychiatric disorders Initial insomnia subjects affected / exposed occurrences (all) | 0 / 116 (0.00%) 0 | 1 / 238 (0.42%) 1 | |

| | | | |
|---|-----------------|-----------------|--|
| Investigations | | | |
| Gamma-glutamyltransferase increased | | | |
| subjects affected / exposed | 0 / 116 (0.00%) | 5 / 238 (2.10%) | |
| occurrences (all) | 0 | 5 | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 0 / 116 (0.00%) | 3 / 238 (1.26%) | |
| occurrences (all) | 0 | 3 | |
| Blood creatine phosphokinase increased | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | 3 / 238 (1.26%) | |
| occurrences (all) | 1 | 3 | |
| Blood alkaline phosphatase increased | | | |
| subjects affected / exposed | 0 / 116 (0.00%) | 2 / 238 (0.84%) | |
| occurrences (all) | 0 | 2 | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 0 / 116 (0.00%) | 2 / 238 (0.84%) | |
| occurrences (all) | 0 | 2 | |
| Activated partial thromboplastin time prolonged | | | |
| subjects affected / exposed | 0 / 116 (0.00%) | 2 / 238 (0.84%) | |
| occurrences (all) | 0 | 2 | |
| Blood cholesterol increased | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | 2 / 238 (0.84%) | |
| occurrences (all) | 1 | 2 | |
| Blood triglycerides increased | | | |
| subjects affected / exposed | 0 / 116 (0.00%) | 2 / 238 (0.84%) | |
| occurrences (all) | 0 | 2 | |
| Weight decreased | | | |
| subjects affected / exposed | 0 / 116 (0.00%) | 2 / 238 (0.84%) | |
| occurrences (all) | 0 | 2 | |
| Blood glucose increased | | | |
| subjects affected / exposed | 0 / 116 (0.00%) | 1 / 238 (0.42%) | |
| occurrences (all) | 0 | 1 | |
| Blood pressure increased | | | |
| subjects affected / exposed | 0 / 116 (0.00%) | 1 / 238 (0.42%) | |
| occurrences (all) | 0 | 1 | |

| | | |
|---|-----------------|-----------------|
| Blood thyroid stimulating hormone increased | | |
| subjects affected / exposed | 0 / 116 (0.00%) | 1 / 238 (0.42%) |
| occurrences (all) | 0 | 1 |
| Blood thyroid stimulating hormone decreased | | |
| subjects affected / exposed | 1 / 116 (0.86%) | 1 / 238 (0.42%) |
| occurrences (all) | 1 | 1 |
| Heart rate increased | | |
| subjects affected / exposed | 0 / 116 (0.00%) | 1 / 238 (0.42%) |
| occurrences (all) | 0 | 1 |
| Heart rate decreased | | |
| subjects affected / exposed | 0 / 116 (0.00%) | 1 / 238 (0.42%) |
| occurrences (all) | 0 | 1 |
| Hepatic enzyme increased | | |
| subjects affected / exposed | 0 / 116 (0.00%) | 1 / 238 (0.42%) |
| occurrences (all) | 0 | 1 |
| Prothrombin time prolonged | | |
| subjects affected / exposed | 0 / 116 (0.00%) | 1 / 238 (0.42%) |
| occurrences (all) | 0 | 1 |
| Liver function test abnormal | | |
| subjects affected / exposed | 0 / 116 (0.00%) | 1 / 238 (0.42%) |
| occurrences (all) | 0 | 1 |
| International normalised ratio increased | | |
| subjects affected / exposed | 0 / 116 (0.00%) | 1 / 238 (0.42%) |
| occurrences (all) | 0 | 1 |
| Pulmonary function test decreased | | |
| subjects affected / exposed | 0 / 116 (0.00%) | 1 / 238 (0.42%) |
| occurrences (all) | 0 | 1 |
| Transaminases increased | | |
| subjects affected / exposed | 0 / 116 (0.00%) | 1 / 238 (0.42%) |
| occurrences (all) | 0 | 1 |
| Blood creatinine increased | | |
| subjects affected / exposed | 1 / 116 (0.86%) | 0 / 238 (0.00%) |
| occurrences (all) | 1 | 0 |
| FEV1/FVC ratio decreased | | |

| | | | |
|--|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 116 (0.86%) | 0 / 238 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Lipase increased | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | 0 / 238 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Lung diffusion test decreased | | | |
| subjects affected / exposed | 2 / 116 (1.72%) | 0 / 238 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Platelet count increased | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | 0 / 238 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Microcytic anaemia | | | |
| subjects affected / exposed | 0 / 116 (0.00%) | 1 / 238 (0.42%) | |
| occurrences (all) | 0 | 1 | |
| Injury, poisoning and procedural complications | | | |
| Fall | | | |
| subjects affected / exposed | 0 / 116 (0.00%) | 1 / 238 (0.42%) | |
| occurrences (all) | 0 | 1 | |
| Vaccination complication | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | 1 / 238 (0.42%) | |
| occurrences (all) | 1 | 1 | |
| Wound complication | | | |
| subjects affected / exposed | 0 / 116 (0.00%) | 1 / 238 (0.42%) | |
| occurrences (all) | 0 | 1 | |
| Contusion | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | 0 / 238 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Cardiac disorders | | | |
| Sinus bradycardia | | | |
| subjects affected / exposed | 0 / 116 (0.00%) | 4 / 238 (1.68%) | |
| occurrences (all) | 0 | 4 | |
| Tachycardia | | | |
| subjects affected / exposed | 2 / 116 (1.72%) | 2 / 238 (0.84%) | |
| occurrences (all) | 2 | 2 | |
| Atrioventricular block first degree | | | |

| | | | |
|-----------------------------|-----------------|------------------|--|
| subjects affected / exposed | 0 / 116 (0.00%) | 1 / 238 (0.42%) | |
| occurrences (all) | 0 | 1 | |
| Bradycardia | | | |
| subjects affected / exposed | 0 / 116 (0.00%) | 1 / 238 (0.42%) | |
| occurrences (all) | 0 | 1 | |
| Sinus tachycardia | | | |
| subjects affected / exposed | 0 / 116 (0.00%) | 1 / 238 (0.42%) | |
| occurrences (all) | 0 | 1 | |
| Sinus arrhythmia | | | |
| subjects affected / exposed | 0 / 116 (0.00%) | 1 / 238 (0.42%) | |
| occurrences (all) | 0 | 1 | |
| Palpitations | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | 1 / 238 (0.42%) | |
| occurrences (all) | 1 | 1 | |
| Ventricular extrasystoles | | | |
| subjects affected / exposed | 0 / 116 (0.00%) | 1 / 238 (0.42%) | |
| occurrences (all) | 0 | 1 | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 2 / 116 (1.72%) | 11 / 238 (4.62%) | |
| occurrences (all) | 2 | 11 | |
| Somnolence | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | 3 / 238 (1.26%) | |
| occurrences (all) | 1 | 3 | |
| Dizziness | | | |
| subjects affected / exposed | 0 / 116 (0.00%) | 3 / 238 (1.26%) | |
| occurrences (all) | 0 | 3 | |
| Dizziness postural | | | |
| subjects affected / exposed | 0 / 116 (0.00%) | 1 / 238 (0.42%) | |
| occurrences (all) | 0 | 1 | |
| Drug withdrawal headache | | | |
| subjects affected / exposed | 0 / 116 (0.00%) | 1 / 238 (0.42%) | |
| occurrences (all) | 0 | 1 | |
| Migraine | | | |
| subjects affected / exposed | 4 / 116 (3.45%) | 1 / 238 (0.42%) | |
| occurrences (all) | 4 | 1 | |

| | | | |
|---|----------------------|------------------------|--|
| Sinus headache subjects affected / exposed occurrences (all) | 0 / 116 (0.00%) 0 | 1 / 238 (0.42%) 1 | |
| Presyncope subjects affected / exposed occurrences (all) | 0 / 116 (0.00%) 0 | 1 / 238 (0.42%) 1 | |
| Blood and lymphatic system disorders | | | |
| Anaemia subjects affected / exposed occurrences (all) | 8 / 116 (6.90%) 8 | 14 / 238 (5.88%) 14 | |
| Iron deficiency anaemia subjects affected / exposed occurrences (all) | 3 / 116 (2.59%) 3 | 3 / 238 (1.26%) 3 | |
| Blood loss anaemia subjects affected / exposed occurrences (all) | 0 / 116 (0.00%) 0 | 1 / 238 (0.42%) 1 | |
| Thrombocytosis subjects affected / exposed occurrences (all) | 0 / 116 (0.00%) 0 | 1 / 238 (0.42%) 1 | |
| Ear and labyrinth disorders | | | |
| Ear pain subjects affected / exposed occurrences (all) | 0 / 116 (0.00%) 0 | 1 / 238 (0.42%) 1 | |
| Tinnitus subjects affected / exposed occurrences (all) | 0 / 116 (0.00%) 0 | 1 / 238 (0.42%) 1 | |
| Eye disorders | | | |
| Uveitis subjects affected / exposed occurrences (all) | 0 / 116 (0.00%) 0 | 2 / 238 (0.84%) 2 | |
| Vision blurred subjects affected / exposed occurrences (all) | 0 / 116 (0.00%) 0 | 2 / 238 (0.84%) 2 | |
| Blepharitis subjects affected / exposed occurrences (all) | 0 / 116 (0.00%) 0 | 1 / 238 (0.42%) 1 | |
| Conjunctival haemorrhage | | | |

| | | |
|-----------------------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 116 (0.00%) | 1 / 238 (0.42%) |
| occurrences (all) | 0 | 1 |
| Eye pain | | |
| subjects affected / exposed | 0 / 116 (0.00%) | 1 / 238 (0.42%) |
| occurrences (all) | 0 | 1 |
| Conjunctivitis allergic | | |
| subjects affected / exposed | 0 / 116 (0.00%) | 1 / 238 (0.42%) |
| occurrences (all) | 0 | 1 |
| Eyelid margin crusting | | |
| subjects affected / exposed | 0 / 116 (0.00%) | 1 / 238 (0.42%) |
| occurrences (all) | 0 | 1 |
| Glaucoma | | |
| subjects affected / exposed | 1 / 116 (0.86%) | 1 / 238 (0.42%) |
| occurrences (all) | 1 | 1 |
| Meibomian gland dysfunction | | |
| subjects affected / exposed | 0 / 116 (0.00%) | 1 / 238 (0.42%) |
| occurrences (all) | 0 | 1 |
| Macular oedema | | |
| subjects affected / exposed | 1 / 116 (0.86%) | 1 / 238 (0.42%) |
| occurrences (all) | 1 | 1 |
| Macular hole | | |
| subjects affected / exposed | 0 / 116 (0.00%) | 1 / 238 (0.42%) |
| occurrences (all) | 0 | 1 |
| Visual impairment | | |
| subjects affected / exposed | 0 / 116 (0.00%) | 1 / 238 (0.42%) |
| occurrences (all) | 0 | 1 |
| Pigment dispersion syndrome | | |
| subjects affected / exposed | 0 / 116 (0.00%) | 1 / 238 (0.42%) |
| occurrences (all) | 0 | 1 |
| Metamorphopsia | | |
| subjects affected / exposed | 0 / 116 (0.00%) | 1 / 238 (0.42%) |
| occurrences (all) | 0 | 1 |
| Visual snow syndrome | | |
| subjects affected / exposed | 0 / 116 (0.00%) | 1 / 238 (0.42%) |
| occurrences (all) | 0 | 1 |
| Chorioretinopathy | | |

| | | | |
|-----------------------------|-----------------|------------------|--|
| subjects affected / exposed | 1 / 116 (0.86%) | 0 / 238 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Exudative retinopathy | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | 0 / 238 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Ocular hypertension | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | 0 / 238 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Gastrointestinal disorders | | | |
| Nausea | | | |
| subjects affected / exposed | 2 / 116 (1.72%) | 10 / 238 (4.20%) | |
| occurrences (all) | 2 | 10 | |
| Colitis ulcerative | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | 8 / 238 (3.36%) | |
| occurrences (all) | 1 | 8 | |
| Vomiting | | | |
| subjects affected / exposed | 0 / 116 (0.00%) | 5 / 238 (2.10%) | |
| occurrences (all) | 0 | 5 | |
| Abdominal pain | | | |
| subjects affected / exposed | 3 / 116 (2.59%) | 3 / 238 (1.26%) | |
| occurrences (all) | 3 | 3 | |
| Diarrhoea | | | |
| subjects affected / exposed | 0 / 116 (0.00%) | 3 / 238 (1.26%) | |
| occurrences (all) | 0 | 3 | |
| Flatulence | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | 2 / 238 (0.84%) | |
| occurrences (all) | 1 | 2 | |
| Abdominal tenderness | | | |
| subjects affected / exposed | 0 / 116 (0.00%) | 2 / 238 (0.84%) | |
| occurrences (all) | 0 | 2 | |
| Abdominal pain lower | | | |
| subjects affected / exposed | 0 / 116 (0.00%) | 1 / 238 (0.42%) | |
| occurrences (all) | 0 | 1 | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | 1 / 238 (0.42%) | |
| occurrences (all) | 1 | 1 | |

| | | |
|--------------------------------|-----------------|-----------------|
| Anal eczema | | |
| subjects affected / exposed | 0 / 116 (0.00%) | 1 / 238 (0.42%) |
| occurrences (all) | 0 | 1 |
| Frequent bowel movements | | |
| subjects affected / exposed | 0 / 116 (0.00%) | 1 / 238 (0.42%) |
| occurrences (all) | 0 | 1 |
| Gingival bleeding | | |
| subjects affected / exposed | 0 / 116 (0.00%) | 1 / 238 (0.42%) |
| occurrences (all) | 0 | 1 |
| Irritable bowel syndrome | | |
| subjects affected / exposed | 0 / 116 (0.00%) | 1 / 238 (0.42%) |
| occurrences (all) | 0 | 1 |
| Toothache | | |
| subjects affected / exposed | 2 / 116 (1.72%) | 1 / 238 (0.42%) |
| occurrences (all) | 2 | 1 |
| Chronic gastritis | | |
| subjects affected / exposed | 1 / 116 (0.86%) | 0 / 238 (0.00%) |
| occurrences (all) | 1 | 0 |
| Gastritis | | |
| subjects affected / exposed | 1 / 116 (0.86%) | 0 / 238 (0.00%) |
| occurrences (all) | 1 | 0 |
| Gastrointestinal hypermotility | | |
| subjects affected / exposed | 1 / 116 (0.86%) | 0 / 238 (0.00%) |
| occurrences (all) | 1 | 0 |
| Gastrointestinal pain | | |
| subjects affected / exposed | 1 / 116 (0.86%) | 0 / 238 (0.00%) |
| occurrences (all) | 1 | 0 |
| Haemorrhoids | | |
| subjects affected / exposed | 1 / 116 (0.86%) | 0 / 238 (0.00%) |
| occurrences (all) | 1 | 0 |
| Hyperaesthesia teeth | | |
| subjects affected / exposed | 1 / 116 (0.86%) | 0 / 238 (0.00%) |
| occurrences (all) | 1 | 0 |
| Lip blister | | |
| subjects affected / exposed | 1 / 116 (0.86%) | 0 / 238 (0.00%) |
| occurrences (all) | 1 | 0 |

| | | | |
|--|-----------------|-----------------|--|
| Stomatitis | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | 0 / 238 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Abdominal distension | | | |
| subjects affected / exposed | 0 / 116 (0.00%) | 5 / 238 (2.10%) | |
| occurrences (all) | 0 | 5 | |
| Dyspepsia | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | 0 / 238 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Hepatobiliary disorders | | | |
| Liver disorder | | | |
| subjects affected / exposed | 0 / 116 (0.00%) | 3 / 238 (1.26%) | |
| occurrences (all) | 0 | 3 | |
| Hepatic function abnormal | | | |
| subjects affected / exposed | 0 / 116 (0.00%) | 1 / 238 (0.42%) | |
| occurrences (all) | 0 | 1 | |
| Hepatic cytolysis | | | |
| subjects affected / exposed | 0 / 116 (0.00%) | 1 / 238 (0.42%) | |
| occurrences (all) | 0 | 1 | |
| Cholestasis | | | |
| subjects affected / exposed | 0 / 116 (0.00%) | 1 / 238 (0.42%) | |
| occurrences (all) | 0 | 1 | |
| Skin and subcutaneous tissue disorders | | | |
| Rash | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | 2 / 238 (0.84%) | |
| occurrences (all) | 1 | 2 | |
| Alopecia | | | |
| subjects affected / exposed | 0 / 116 (0.00%) | 1 / 238 (0.42%) | |
| occurrences (all) | 0 | 1 | |
| Cutaneous vasculitis | | | |
| subjects affected / exposed | 0 / 116 (0.00%) | 1 / 238 (0.42%) | |
| occurrences (all) | 0 | 1 | |
| Dermatitis contact | | | |
| subjects affected / exposed | 0 / 116 (0.00%) | 1 / 238 (0.42%) | |
| occurrences (all) | 0 | 1 | |
| Dry skin | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 116 (0.00%) | 1 / 238 (0.42%) | |
| occurrences (all) | 0 | 1 | |
| Night sweats | | | |
| subjects affected / exposed | 0 / 116 (0.00%) | 1 / 238 (0.42%) | |
| occurrences (all) | 0 | 1 | |
| Nail bed bleeding | | | |
| subjects affected / exposed | 0 / 116 (0.00%) | 1 / 238 (0.42%) | |
| occurrences (all) | 0 | 1 | |
| Miliaria | | | |
| subjects affected / exposed | 0 / 116 (0.00%) | 1 / 238 (0.42%) | |
| occurrences (all) | 0 | 1 | |
| Pruritus | | | |
| subjects affected / exposed | 0 / 116 (0.00%) | 1 / 238 (0.42%) | |
| occurrences (all) | 0 | 1 | |
| Photosensitivity reaction | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | 0 / 238 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Blister | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | 0 / 238 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Renal and urinary disorders | | | |
| Haematuria | | | |
| subjects affected / exposed | 0 / 116 (0.00%) | 1 / 238 (0.42%) | |
| occurrences (all) | 0 | 1 | |
| Nephrolithiasis | | | |
| subjects affected / exposed | 0 / 116 (0.00%) | 1 / 238 (0.42%) | |
| occurrences (all) | 0 | 1 | |
| Endocrine disorders | | | |
| Hyperthyroidism | | | |
| subjects affected / exposed | 0 / 116 (0.00%) | 1 / 238 (0.42%) | |
| occurrences (all) | 0 | 1 | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthritis | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | 2 / 238 (0.84%) | |
| occurrences (all) | 1 | 2 | |
| Back pain | | | |

| | | | |
|-----------------------------------|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 116 (0.00%) | 4 / 238 (1.68%) | |
| occurrences (all) | 0 | 4 | |
| Muscular weakness | | | |
| subjects affected / exposed | 0 / 116 (0.00%) | 1 / 238 (0.42%) | |
| occurrences (all) | 0 | 1 | |
| Arthralgia | | | |
| subjects affected / exposed | 3 / 116 (2.59%) | 4 / 238 (1.68%) | |
| occurrences (all) | 3 | 4 | |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 0 / 116 (0.00%) | 1 / 238 (0.42%) | |
| occurrences (all) | 0 | 1 | |
| Myalgia | | | |
| subjects affected / exposed | 0 / 116 (0.00%) | 1 / 238 (0.42%) | |
| occurrences (all) | 0 | 1 | |
| Osteochondrosis | | | |
| subjects affected / exposed | 0 / 116 (0.00%) | 1 / 238 (0.42%) | |
| occurrences (all) | 0 | 1 | |
| Pain in extremity | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | 1 / 238 (0.42%) | |
| occurrences (all) | 1 | 1 | |
| Spinal pain | | | |
| subjects affected / exposed | 0 / 116 (0.00%) | 1 / 238 (0.42%) | |
| occurrences (all) | 0 | 1 | |
| Infections and infestations | | | |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 116 (0.00%) | 4 / 238 (1.68%) | |
| occurrences (all) | 0 | 4 | |
| COVID-19 | | | |
| subjects affected / exposed | 3 / 116 (2.59%) | 3 / 238 (1.26%) | |
| occurrences (all) | 3 | 3 | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | 2 / 238 (0.84%) | |
| occurrences (all) | 1 | 2 | |
| Sinusitis | | | |
| subjects affected / exposed | 0 / 116 (0.00%) | 2 / 238 (0.84%) | |
| occurrences (all) | 0 | 2 | |

| | | |
|---------------------------------|-----------------|-----------------|
| Nasopharyngitis | | |
| subjects affected / exposed | 2 / 116 (1.72%) | 3 / 238 (1.26%) |
| occurrences (all) | 2 | 3 |
| Anal abscess | | |
| subjects affected / exposed | 0 / 116 (0.00%) | 1 / 238 (0.42%) |
| occurrences (all) | 0 | 1 |
| Campylobacter infection | | |
| subjects affected / exposed | 0 / 116 (0.00%) | 1 / 238 (0.42%) |
| occurrences (all) | 0 | 1 |
| Clostridium difficile colitis | | |
| subjects affected / exposed | 0 / 116 (0.00%) | 1 / 238 (0.42%) |
| occurrences (all) | 0 | 1 |
| Clostridium difficile infection | | |
| subjects affected / exposed | 0 / 116 (0.00%) | 1 / 238 (0.42%) |
| occurrences (all) | 0 | 1 |
| Cytomegalovirus infection | | |
| subjects affected / exposed | 0 / 116 (0.00%) | 1 / 238 (0.42%) |
| occurrences (all) | 0 | 1 |
| Cystitis | | |
| subjects affected / exposed | 0 / 116 (0.00%) | 1 / 238 (0.42%) |
| occurrences (all) | 0 | 1 |
| Conjunctivitis | | |
| subjects affected / exposed | 0 / 116 (0.00%) | 1 / 238 (0.42%) |
| occurrences (all) | 0 | 1 |
| Gastroenteritis | | |
| subjects affected / exposed | 0 / 116 (0.00%) | 1 / 238 (0.42%) |
| occurrences (all) | 0 | 1 |
| Genitourinary tract infection | | |
| subjects affected / exposed | 0 / 116 (0.00%) | 1 / 238 (0.42%) |
| occurrences (all) | 0 | 1 |
| Hordeolum | | |
| subjects affected / exposed | 0 / 116 (0.00%) | 1 / 238 (0.42%) |
| occurrences (all) | 0 | 1 |
| Infected dermal cyst | | |
| subjects affected / exposed | 1 / 116 (0.86%) | 1 / 238 (0.42%) |
| occurrences (all) | 1 | 1 |

| | | | |
|------------------------------------|-----------------|-----------------|--|
| Influenza | | | |
| subjects affected / exposed | 0 / 116 (0.00%) | 1 / 238 (0.42%) | |
| occurrences (all) | 0 | 1 | |
| Localised infection | | | |
| subjects affected / exposed | 0 / 116 (0.00%) | 1 / 238 (0.42%) | |
| occurrences (all) | 0 | 1 | |
| Rhinitis | | | |
| subjects affected / exposed | 0 / 116 (0.00%) | 1 / 238 (0.42%) | |
| occurrences (all) | 0 | 1 | |
| Oral herpes | | | |
| subjects affected / exposed | 0 / 116 (0.00%) | 1 / 238 (0.42%) | |
| occurrences (all) | 0 | 1 | |
| Herpes zoster | | | |
| subjects affected / exposed | 2 / 116 (1.72%) | 0 / 238 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Enterocolitis bacterial | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | 0 / 238 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Laryngitis | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | 0 / 238 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Rash pustular | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | 0 / 238 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Tooth infection | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | 0 / 238 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Viral infection | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | 0 / 238 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Blood bilirubin increased | | | |
| subjects affected / exposed | 0 / 116 (0.00%) | 2 / 238 (0.84%) | |
| occurrences (all) | 0 | 2 | |
| Metabolism and nutrition disorders | | | |
| Hypophosphataemia | | | |

| | | |
|-----------------------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 116 (0.00%) | 4 / 238 (1.68%) |
| occurrences (all) | 0 | 4 |
| Iron deficiency | | |
| subjects affected / exposed | 0 / 116 (0.00%) | 3 / 238 (1.26%) |
| occurrences (all) | 0 | 3 |
| Hypercholesterolaemia | | |
| subjects affected / exposed | 0 / 116 (0.00%) | 2 / 238 (0.84%) |
| occurrences (all) | 0 | 2 |
| Folate deficiency | | |
| subjects affected / exposed | 0 / 116 (0.00%) | 1 / 238 (0.42%) |
| occurrences (all) | 0 | 1 |
| Gout | | |
| subjects affected / exposed | 0 / 116 (0.00%) | 1 / 238 (0.42%) |
| occurrences (all) | 0 | 1 |
| Hypertriglyceridaemia | | |
| subjects affected / exposed | 0 / 116 (0.00%) | 1 / 238 (0.42%) |
| occurrences (all) | 0 | 1 |
| Hyperkalaemia | | |
| subjects affected / exposed | 0 / 116 (0.00%) | 1 / 238 (0.42%) |
| occurrences (all) | 0 | 1 |
| Hypoalbuminaemia | | |
| subjects affected / exposed | 0 / 116 (0.00%) | 1 / 238 (0.42%) |
| occurrences (all) | 0 | 1 |
| Hypomagnesaemia | | |
| subjects affected / exposed | 0 / 116 (0.00%) | 1 / 238 (0.42%) |
| occurrences (all) | 0 | 1 |
| Hypokalaemia | | |
| subjects affected / exposed | 0 / 116 (0.00%) | 1 / 238 (0.42%) |
| occurrences (all) | 0 | 1 |
| Hypoproteinaemia | | |
| subjects affected / exposed | 0 / 116 (0.00%) | 1 / 238 (0.42%) |
| occurrences (all) | 0 | 1 |
| Hypovolaemia | | |
| subjects affected / exposed | 0 / 116 (0.00%) | 1 / 238 (0.42%) |
| occurrences (all) | 0 | 1 |
| Underweight | | |

| | | | |
|-----------------------------|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 116 (0.00%) | 1 / 238 (0.42%) | |
| occurrences (all) | 0 | 1 | |
| Increased appetite | | | |
| subjects affected / exposed | 0 / 116 (0.00%) | 1 / 238 (0.42%) | |
| occurrences (all) | 0 | 1 | |
| Vitamin D deficiency | | | |
| subjects affected / exposed | 0 / 116 (0.00%) | 1 / 238 (0.42%) | |
| occurrences (all) | 0 | 1 | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | 0 / 238 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Hypoglycaemia | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | 0 / 238 (0.00%) | |
| occurrences (all) | 1 | 0 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|--|
| 05 March 2019 | Amendment 1 - provides additional guidance for the cardiac monitoring procedures required on Day 1 after the first dose of study treatment. These additional monitoring procedures are based feedback from the Food and Drug Administration. In particular, post-dose safety vital signs, 12-lead ECGs, monitoring of subjects who do not meet the discharge criteria, and discontinuation rules have been revised. |
| 07 February 2020 | Amendment 2 - update eligibility criteria (eg, contraception use). Additional instructions for safety monitoring related to ophthalmoscopy and optical coherence tomography testing were included. The prohibition of concomitant use of QT prolonging drugs was removed based on the results of the QT study (Study APD334-008). In addition, a 4-Week Safety Follow-Up visit was added. Clarification and further instructions for tuberculosis testing were added and the tuberculosis screening questionnaire was updated. |
| 22 February 2021 | Amendment 3 - includes guidance for conducting virtual and offsite visits. Also, information on anti-arrhythmic drugs was added to prohibited concomitant therapies. Language was updated regarding timing of screening optical coherence tomography (OCTs) and pulmonary function tests (PFTs). Additionally, an exclusion criterion was added regarding treatment with topical rectal Chinese medicine, enemas or suppositories prior to randomization. Minor corrections were made for consistency within the protocol. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported