# Clinical trial results:
# Induction Study #2 - A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study of Oral Ozanimod as Induction Therapy for Moderately to Severely Active Crohn's Disease

## Summary

| | |
|---|---|
| EudraCT number | 2017-004293-33 |
| Trial protocol | HU SK LT DE FR SI AT BG GR ES SE NL PL PT FI |
| Global end of trial date | 21 November 2023 |

### Results information

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 27 November 2024 |
| First version publication date | 27 November 2024 |

## Trial information

### Trial identification

| | |
|---|---|
| Sponsor protocol code | RPC01-3202 |

### Additional study identifiers

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT03440385 |
| WHO universal trial number (UTN) | - |

Notes:

### Sponsors

| | |
|---|---|
| Sponsor organisation name | Bristol-Myers Squibb |
| Sponsor organisation address | Chaussée de la Hulpe 185, Brussels, Belgium, |
| Public contact | EU Study Start-Up Unit, Bristol-Myers Squibb International Corporation, clinical.trials@bms.com |
| Scientific contact | EU Study Start-Up Unit, Bristol-Myers Squibb International Corporation, Clinical.Trials@bms.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 | 18 March 2024 |
| Is this the analysis of the primary completion data? | No |

| | |
|---|---|
| Global end of trial reached? | Yes |
| Global end of trial date | 21 November 2023 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

This is a study to explore the effect of oral ozanimod as an induction treatment for participants with moderately to severely active Crohn's Disease.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization Good Clinical Practice Guidelines. All the local regulatory requirements pertinent to safety of trial participants were followed.

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 07 March 2018 |
| 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 | Canada: 9 |
| Country: Number of subjects enrolled | United States: 71 |
| Country: Number of subjects enrolled | Bulgaria: 12 |
| Country: Number of subjects enrolled | Georgia: 54 |
| Country: Number of subjects enrolled | Hungary: 21 |
| Country: Number of subjects enrolled | Lithuania: 1 |
| Country: Number of subjects enrolled | Poland: 57 |
| Country: Number of subjects enrolled | Russian Federation: 71 |
| Country: Number of subjects enrolled | Serbia: 21 |
| Country: Number of subjects enrolled | Slovakia: 17 |
| Country: Number of subjects enrolled | Slovenia: 2 |
| Country: Number of subjects enrolled | Ukraine: 84 |
| Country: Number of subjects enrolled | Austria: 3 |
| Country: Number of subjects enrolled | France: 13 |
| Country: Number of subjects enrolled | Germany: 34 |
| Country: Number of subjects enrolled | Greece: 1 |
| Country: Number of subjects enrolled | Netherlands: 15 |
| Country: Number of subjects enrolled | Portugal: 5 |
| Country: Number of subjects enrolled | Spain: 3 |
| Country: Number of subjects enrolled | Australia: 17 |

| | |
|---|---|
| Country: Number of subjects enrolled | China: 64 |
| Country: Number of subjects enrolled | Korea, Republic of: 3 |
| Country: Number of subjects enrolled | Taiwan: 7 |
| Country: Number of subjects enrolled | Colombia: 7 |
| Country: Number of subjects enrolled | Israel: 12 |
| Country: Number of subjects enrolled | South Africa: 2 |
| Worldwide total number of subjects | 606 |
| EEA total number of subjects | 184 |

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) | 571 |
| From 65 to 84 years | 35 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

Participants were enrolled in 26 countries.

### Period 1

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

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Ozanimod |

Arm description:

Participants with moderate to severe acute Crohn's disease were administered Ozanimod capsule orally. Participants were administered 0.23 milligram (mg) of Ozanimod capsule (daily) from Day 1 to Day 4 followed by 0.46 mg of Ozanimod (2 capsules of 0.23 mg daily) from Day 5 to Day 7 followed by 0.92 mg of Ozanimod capsule (daily) from Day 8 to Week 12.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Ozanimod |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

0.92 mg capsule

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

Arm description:

Participants with moderate to severely active Crohn's disease were orally administered Placebo (daily) from Day 1 to Week 12.

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

Dosage and administration details:

Administered as capsule

| **Number of subjects in period 1** | Ozanimod | Placebo |
|---|---|---|
| Started | 403 | 203 |
| Completed | 360 | 183 |
| Not completed | 43 | 20 |
| Consent withdrawn by subject | 12 | 6 |
| Site Closed | 1 | - |
| Adverse event, non-fatal | 15 | 11 |
| Other Reason | 4 | 1 |
| Lost to follow-up | 2 | - |
| Lack of efficacy | 9 | 2 |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Ozanimod |
| Reporting group description: | |
| Participants with moderate to severe acute Crohn's disease were administered Ozanimod capsule orally. Participants were administered 0.23 milligram (mg) of Ozanimod capsule (daily) from Day 1 to Day 4 followed by 0.46 mg of Ozanimod (2 capsules of 0.23 mg daily) from Day 5 to Day 7 followed by 0.92 mg of Ozanimod capsule (daily) from Day 8 to Week 12. | |
| Reporting group title | Placebo |
| Reporting group description: | |
| Participants with moderate to severely active Crohn's disease were orally administered Placebo (daily) from Day 1 to Week 12. | |

| Reporting group values | Ozanimod | Placebo | Total |
|---|---|---|---|
| Number of subjects | 403 | 203 | 606 |
| Age categorical<br>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) | 0 | 0 | 0 |
| Adults (18-64 years) | 378 | 193 | 571 |
| From 65-84 years | 25 | 10 | 35 |
| 85 years and over | 0 | 0 | 0 |
| Age Continuous<br>Units: years | | | |
| arithmetic mean | 39.8 | 37.7 | |
| standard deviation | ± 13.69 | ± 13.79 | - |
| Sex: Female, Male<br>Units: Participants | | | |
| Female | 182 | 90 | 272 |
| Male | 221 | 113 | 334 |
| Ethnicity (NIH/OMB)<br>Units: Subjects | | | |
| Hispanic or Latino | 13 | 12 | 25 |
| Not Hispanic or Latino | 378 | 188 | 566 |
| Unknown or Not Reported | 12 | 3 | 15 |
| Race/Ethnicity, Customized<br>Units: Subjects | | | |
| WHITE | 329 | 166 | 495 |
| BLACK OR AFRICAN AMERICAN | 7 | 1 | 8 |
| AMERICAN INDIAN OR ALASKA NATIVE | 1 | 0 | 1 |
| ASIAN | 47 | 29 | 76 |
| NATIVE HAWAIIAN OR OTHER PACIFIC ISLANDER | 1 | 0 | 1 |

| | | | |
|---|---|---|---|
| OTHER | 8 | 4 | 12 |
| NOT REPORTED | 10 | 3 | 13 |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | Ozanimod |
| Reporting group description: | |
| Participants with moderate to severe acute Crohn's disease were administered Ozanimod capsule orally. Participants were administered 0.23 milligram (mg) of Ozanimod capsule (daily) from Day 1 to Day 4 followed by 0.46 mg of Ozanimod (2 capsules of 0.23 mg daily) from Day 5 to Day 7 followed by 0.92 mg of Ozanimod capsule (daily) from Day 8 to Week 12. | |
| Reporting group title | Placebo |
| Reporting group description: | |
| Participants with moderate to severely active Crohn's disease were orally administered Placebo (daily) from Day 1 to Week 12. | |

### Primary: Percentage of Participants with Crohn's Disease Activity Index (CDAI) Score < 150

| | |
|---|---|
| End point title | Percentage of Participants with Crohn's Disease Activity Index (CDAI) Score < 150 |
| End point description: | |
| The CDAI is a composite score that is used to measure the clinical activity of Crohn's disease (CD). The CDAI uses a questionnaire with 8 disease activity variables: number of soft/liquid stools, severity of abdominal pain, general well-being, presence of complications, need for antidiarrheal drugs, presence of an abdominal mass, hematocrit, and deviation in body weight. The sub scores of number of soft/liquid stool, severity of abdominal pain (0 [none] to 3 [Severe]), general well-being (0 [well] to 4 [terrible] were summed over the 7 days prior to each visit. Additionally, the remaining predictors were also noted and weighted to create the total CDAI score which ranged from 0-600 with a higher score indicating a worse outcome. | |
| End point type | Primary |
| End point timeframe: | |
| Week 12 | |

| End point values | Ozanimod | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 403 | 203 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | 29.8 | 30.5 | | |

### Statistical analyses

| | |
|---|---|
| **Statistical analysis title** | Statistical Analysis 1 |
| Comparison groups | Ozanimod v Placebo |

| | |
|---|---|
| Number of subjects included in analysis | 606 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.8125 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 0.96 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.66 |
| upper limit | 1.39 |

## Secondary: Percentage of Participants with Abdominal Pain and Stool Frequency Clinical Remission

| | |
|---|---|
| End point title | Percentage of Participants with Abdominal Pain and Stool Frequency Clinical Remission |

End point description:

Abdominal pain and stool frequency clinical remission was defined as average daily abdominal pain score ≤ 1 point, and average daily stool frequency ≤ 3 times with abdominal pain and stool frequency no worse than baseline at Week 12. Participants entered the responses in diaries daily. The 7 days entries prior to Week 12 visit were considered for calculating average abdominal pain score and stool frequency. The abdominal pain was graded on severity of 0 (none) to 3 (severe) scale and stool frequency was defined number of liquid or soft stools per day. Baseline was defined as the last assessment prior to the start time of the first drug administration if time of measurement is available else the last assessment prior to or on the date of the first drug administration.

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

End point timeframe:

Week 12

| **End point values** | Ozanimod | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 403 | 203 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | 29.0 | 26.6 | | |

## Statistical analyses

| **Statistical analysis title** | Statistical Analysis 1 |
|---|---|
| Comparison groups | Ozanimod v Placebo |

| | |
|---|---|
| Number of subjects included in analysis | 606 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.54 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.13 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.77 |
| upper limit | 1.66 |

## Secondary: Percentage of Participants with Crohn's Disease Activity Index (CDAI) Score Reduction from Baseline of ≥ 100 points or CDAI score < 150 and SES-CD Decrease from Baseline of ≥ 50%

| | |
|---|---|
| End point title | Percentage of Participants with Crohn's Disease Activity Index (CDAI) Score Reduction from Baseline of ≥ 100 points or CDAI score < 150 and SES-CD Decrease from Baseline of ≥ 50% |

End point description:

CDAI include 8 components number of soft/liquid stools, severity of abdominal pain, wellbeing, complications, need antidiarrheal drugs, abdominal mass, hematocrit, deviation in body wt. Subscores of numbers of soft/liquid stool, severity of abdominal pain (0 [none] to 3 [Severe]), general well-being (0 [well] to 4 [terrible] were summed over the 7 days prior to visit. The others weighted to create the total CDAI score ranging 0-600 with higher score indicating worse outcome. The SES-CD has 4 components size of ulcers, ulcerated surface, affected surface, presence of narrowing. Each component was scored on scale of 0 (none) to 3 (worst). In SES-CD, each of 4 components are assessed in the five segments: ileum, right, transverse, left colon, and rectum. The SES-CD was the sum of the individual scores of each of the components across the five segments. The range of SES-CD scores was 0 - 12 for each segment, and 0 - 60 for overall, with larger scores show greater degree of inflammation.

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

End point timeframe:

Week 12

| **End point values** | Ozanimod | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 403 | 203 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | 16.9 | 14.3 | | |

### Statistical analyses

| **Statistical analysis title** | Statistical Analysis 1 |
|---|---|
| Comparison groups | Ozanimod v Placebo |

| | |
|---|---|
| Number of subjects included in analysis | 606 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.4255 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.22 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.75 |
| upper limit | 1.97 |

## Secondary: Percentage of Participants with a Simple Endoscopic Score for Crohn's Disease (SES-CD) Score Decrease from Baseline of ≥ 50%

| | |
|---|---|
| End point title | Percentage of Participants with a Simple Endoscopic Score for Crohn's Disease (SES-CD) Score Decrease from Baseline of ≥ 50% |

End point description:

The SES-CD assessed the degree of inflammation. The SES-CD assesses the following 4 components: size of ulcers, ulcerated surface, affected surface, and presence of narrowing. Each of these components was scored on a scale of 0 (none/unaffected) to 3 (worst). In the SES-CD, each of these 4 components are assessed in the five segments: ileum, right colon, transverse colon, left colon, and rectum. The SES-CD was the sum of the individual scores of each of the components across the five segments. The range of SES-CD scores was 0 - 12 for each segment, and 0 - 60 for the overall SES-CD score, with larger scores indicating greater degree of inflammation. Baseline was defined as the last assessment prior to the start time of the first drug administration if time of measurement is available else the last assessment prior to or on the date of the first drug administration.

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

End point timeframe:

Week 12

| **End point values** | Ozanimod | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 403 | 203 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | 25.6 | 21.2 | | |

## Statistical analyses

| **Statistical analysis title** | Statistical Analysis 1 |
|---|---|
| Comparison groups | Ozanimod v Placebo |

| | |
|---|---|
| Number of subjects included in analysis | 606 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.2411 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.28 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.85 |
| upper limit | 1.95 |

## Secondary: Percentage of Participants with Reduction from Baseline in the Crohn's Disease Activity Index (CDAI) score of >= 100 points or a total CDAI score < 150

| | |
|---|---|
| End point title | Percentage of Participants with Reduction from Baseline in the Crohn's Disease Activity Index (CDAI) score of >= 100 points or a total CDAI score < 150 |

End point description:

The CDAI is a composite score that is used to measure the clinical activity of Crohn's disease (CD). The CDAI uses a questionnaire with 8 disease activity variables: number of soft/liquid stools, severity of abdominal pain, general well-being, presence of complications, need for antidiarrheal drugs, presence of an abdominal mass, hematocrit, and deviation in body weight. The sub scores of number of soft/liquid stool, severity of abdominal pain (0 [none] to 3 [Severe]), general well-being (0 [well] to 4 [terrible] were summed over the 7 days prior to each visit. Additionally, the remaining predictors were also noted and weighted to create the total CDAI score which ranged from 0-600 with a higher score indicating a worse outcome. Baseline was defined as the last assessment prior to the start time of the first drug administration if time of measurement is available else the last assessment prior to or on the date of the first drug administration.

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

End point timeframe:

Week 12

| **End point values** | Ozanimod | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 403 | 203 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | 46.2 | 47.3 | | |

### Statistical analyses

| **Statistical analysis title** | Statistical Analysis 1 |
|---|---|
| Comparison groups | Ozanimod v Placebo |

| | |
|---|---|
| Number of subjects included in analysis | 606 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.7469 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 0.94 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.67 |
| upper limit | 1.34 |

## Secondary: Percentage of Participants with Abdominal Pain and Stool Frequency Clinical Remission and a Simple Endoscopic Score for Crohn's Disease (SES-CD) Score <= 4 Points and Decrease >= 2 Points

| | |
|---|---|
| End point title | Percentage of Participants with Abdominal Pain and Stool Frequency Clinical Remission and a Simple Endoscopic Score for Crohn's Disease (SES-CD) Score <= 4 Points and Decrease >= 2 Points |

End point description:

Abdominal pain (AP) and stool frequency (SF) clinical remission was defined as average daily abdominal pain score ≤ 1 point, and average daily stool frequency ≤ 3 times with AP and SF no worse than baseline at Week 12. Participants entered responses in diaries daily. The 7 days entries prior to visit were considered for calculating average AP score and SF. The AP was graded on severity of 0 (none) to 3 (severe) scale and SF was defined number of liquid or soft stools per day. The SES-CD has 4 components size of ulcers, ulcerated surface, affected surface, presence of narrowing. Each component was scored on scale of 0 (none) to 3 (worst). In SES-CD, each of 4 components are assessed in the five segments: ileum, right, transverse, left colon, and rectum. The SES-CD was the sum of the individual scores of each of the components across the five segments. The range of SES-CD scores was 0 - 12 for each segment, and 0 - 60 for overall, with larger scores show greater degree of inflammation.

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

End point timeframe:

Week 12

| **End point values** | Ozanimod | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 403 | 203 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | 10.4 | 8.4 | | |

### Statistical analyses

| **Statistical analysis title** | Statistical Analysis 1 |
|---|---|
| Comparison groups | Ozanimod v Placebo |

| | |
|---|---|
| Number of subjects included in analysis | 606 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.4339 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.27 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.7 |
| upper limit | 2.31 |

## Secondary: Percentage of Participants with Crohn's Disease Activity Index (CDAI) Score < 150 and Simple Endoscopic Score for Crohn’s Disease (SES-CD) Score Decrease from Baseline of ≥ 50%

| | |
|---|---|
| End point title | Percentage of Participants with Crohn's Disease Activity Index (CDAI) Score < 150 and Simple Endoscopic Score for Crohn’s Disease (SES-CD) Score Decrease from Baseline of ≥ 50% |

End point description:

CDAI include 8 components number of soft/liquid stools, severity of abdominal pain, wellbeing, complications, need antidiarrheal drugs, abdominal mass, hematocrit, deviation in body wt. Subscores of numbers of soft/liquid stool, severity of abdominal pain (0 [none] to 3 [Severe]), general well-being (0 [well] to 4 [terrible] were summed over the 7 days prior to visit. The others weighted to create the total CDAI score ranging 0-600 with higher score indicating worse outcome. The SES-CD has 4 components size of ulcers, ulcerated surface, affected surface, presence of narrowing. Each component was scored on scale of 0 (none) to 3 (worst). In SES-CD, each of 4 components are assessed in the five segments: ileum, right, transverse, left colon, and rectum. The SES-CD was the sum of the individual scores of each of the components across the five segments. The range of SES-CD scores was 0 - 12 for each segment, and 0 - 60 for overall, with larger scores show greater degree of inflammation.

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

End point timeframe:

Week 12

| **End point values** | Ozanimod | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 403 | 203 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | 11.7 | 11.3 | | |

### Statistical analyses

| **Statistical analysis title** | Statistical Analysis 1 |
|---|---|
| Comparison groups | Ozanimod v Placebo |

| | |
|---|---|
| Number of subjects included in analysis | 606 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.9313 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.02 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.6 |
| upper limit | 1.76 |

## Secondary: Percentage of Participants with a Crohn’s Disease Endoscopic Index of Severity (CDEIS) Decrease from Baseline of ≥ 50%

| | |
|---|---|
| End point title | Percentage of Participants with a Crohn’s Disease Endoscopic Index of Severity (CDEIS) Decrease from Baseline of ≥ 50% |

End point description:

CDEIS is an index for determining the severity of Crohn's disease with endoscopic localization to ileum and colon. The CDEIS divides the intestine into 5 segments: rectum, sigmoid and left colon, transverse colon, right colon, and ileum. Four variables are assessed in each segment: the presence of deep ulceration, the presence of superficial ulceration, the percentage of ulcerated surface, and the percentage of surface affected by CD, indicated on 10-cm visual analogue scales. In addition, the presence of ulcerated stenosis and the presence of nonulcerated stenosis are also assessed over the entire intestine. These factors are weighted and summed to calculate the total score ranging from 0- 44, with higher scores indicating more severe disease.

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

End point timeframe:

Week 12

| **End point values** | Ozanimod | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 403 | 203 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | 27.5 | 21.7 | | |

### Statistical analyses

| **Statistical analysis title** | Statistical Analysis 1 |
|---|---|
| Comparison groups | Ozanimod v Placebo |

| | |
|---|---|
| Number of subjects included in analysis | 606 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.1187 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.39 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.92 |
| upper limit | 2.11 |

## Secondary: Percentage of Participants with CDAI Reduction from Baseline of >=70 points

| | |
|---|---|
| End point title | Percentage of Participants with CDAI Reduction from Baseline of >=70 points |

End point description:

The CDAI is a composite score that is used to measure the clinical activity of Crohn's disease (CD). The CDAI uses a questionnaire with 8 disease activity variables: number of soft/liquid stools, severity of abdominal pain, general well-being, presence of complications, need for antidiarrheal drugs, presence of an abdominal mass, hematocrit, and deviation in body weight. The sub scores of number of soft/liquid stool, severity of abdominal pain (0 [none] to 3 [Severe]), general well-being (0 [well] to 4 [terrible] were summed over the 7 days prior to each visit. Additionally, the remaining predictors were also noted and weighted to create the total CDAI score which ranged from 0-600 with a higher score indicating a worse outcome. Baseline was defined as the last assessment prior to the start time of the first drug administration if time of measurement is available else the last assessment prior to or on the date of the first drug administration.

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

End point timeframe:

Week 12

| **End point values** | Ozanimod | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 403 | 203 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | 52.9 | 51.7 | | |

## Statistical analyses

| **Statistical analysis title** | Statistical Analysis 1 |
|---|---|
| Comparison groups | Ozanimod v Placebo |

| | |
|---|---|
| Number of subjects included in analysis | 606 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.82 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.04 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.74 |
| upper limit | 1.47 |

## Secondary: Percentage of Participants with Absence of Ulcers ≥ 0.5 cm with no Segment with any Ulcerated Surface ≥10%

| | |
|---|---|
| End point title | Percentage of Participants with Absence of Ulcers ≥ 0.5 cm with no Segment with any Ulcerated Surface ≥10% |
| End point description: | |
| The ulcerated surface were assessed via endoscopy. | |
| End point type | Secondary |
| End point timeframe: | |
| Week 12 | |

| End point values | Ozanimod | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 403 | 203 | | |
| Units: percentage of partiicpants | | | | |
| number (not applicable) | 25.3 | 24.1 | | |

### Statistical analyses

| Statistical analysis title | Statistical Analysis 1 |
|---|---|
| Comparison groups | Ozanimod v Placebo |
| Number of subjects included in analysis | 606 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.6906 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.06 |

| Confidence interval | |
|---|---|
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.71 |
| upper limit | 1.59 |

## Secondary: Percentage of Participants with Global Histologic Activity Score (GHAS) Remission

| End point title | Percentage of Participants with Global Histologic Activity Score (GHAS) Remission |
|---|---|

End point description:

GHAS assesses the inflammation and mucosal damage. GHAS has 8 components Epithelial damage, Architectural changes, Infiltration of mononuclear cells in the lamina propria, Infiltration of polymorphonuclear cells in the lamina propria, Polymorphonuclear cells in epithelium, Presence of erosion and/or ulcers, Presence of granuloma and number of biopsy specimens affected. Each of these components was scored on a scale of 0 (none/unaffected) to 2 (worst). Each of these 8 components are assessed in the five segments: ileum, right colon, transverse colon, left colon, and rectum. Within each segment, the GHAS score has a range of 0 – 16, and the total GHAS score has a range of 0 – 80. Higher numbers correspond to more inflammation and more mucosal damage. Baseline was defined as the last assessment prior to the start time of the first drug administration if time of measurement is available else the last assessment prior to or on the date of the first drug administration.

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

End point timeframe:

Week 12

| End point values | Ozanimod | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 403 | 203 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | 13.6 | 10.8 | | |

### Statistical analyses

| Statistical analysis title | Statistical Analysis 1 |
|---|---|
| Comparison groups | Ozanimod v Placebo |
| Number of subjects included in analysis | 606 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.333 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.3 |

| Confidence interval | |
|---|---|
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.77 |
| upper limit | 2.2 |

## Secondary: Percentage of Participants with Abdominal Pain (AP) and Stool Frequency (SF) Clinical Remission and an Endoscopic (50%) Response

| End point title | Percentage of Participants with Abdominal Pain (AP) and Stool Frequency (SF) Clinical Remission and an Endoscopic (50%) Response |
|---|---|

End point description:

AP and SF clinical remission is average daily abdominal pain score ≤ 1 point, and average daily stool frequency ≤ 3 times with AP and SF no worse than baseline at Week 12. Participants entered responses in diaries daily. The 7 days entries prior to visit were considered for calculating average AP score and SF. AP was graded on severity of 0 (none) to 3 (severe) scale and SF was defined number of liquid or soft stools per day. SES-CD has 4 components size of ulcers, ulcerated surface, affected surface, presence of narrowing. Each component was scored on scale of 0 (none) to 3 (worst). Endoscopic Response is defined as >= 50% decrease from baseline in SES-CD. In SES-CD, each of 4 components are assessed in five segments: ileum, right, transverse, left colon, and rectum. The SES-CD was sum of individual scores of each of components across five segments. Range of SES-CD scores was 0 - 12 for each segment, and 0 - 60 for overall, with larger scores show greater degree of inflammation.

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

End point timeframe:

Week 12

| **End point values** | Ozanimod | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 403 | 203 | | |
| Units: percentage of particpants | | | | |
| number (not applicable) | 11.7 | 9.4 | | |

### Statistical analyses

| **Statistical analysis title** | Statistical Analysis 1 |
|---|---|
| Comparison groups | Ozanimod v Placebo |
| Number of subjects included in analysis | 606 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.403 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.28 |

| | |
|---|---|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.72 |
| upper limit | 2.26 |

## Secondary: Percentage of Participants with Robarts Histologic Index (RHI) Mucosal Healing at Week 12

| | |
|---|---|
| End point title | Percentage of Participants with Robarts Histologic Index (RHI) Mucosal Healing at Week 12 |

End point description:

RHI mucosal healing was defined as RHI remission combined with SES-CD <= 4 points and a SES-CD decrease from baseline >= 2 points with no SES-CD sub-score >1 point. RHI Remission is defined as no active inflammation in any measured segment. The SES-CD assesses the following 4 components: size of ulcers, ulcerated surface, affected surface, and presence of narrowing. Each of these components was scored on a scale of 0 (none/unaffected) to 3 (worst). In the SES-CD, each of these 4 components are assessed in the five segments: ileum, right colon, transverse colon, left colon, and rectum. The SES-CD was the sum of the individual scores of each of the components across the five segments. The range of SES-CD scores was 0 - 12 for each segment, and 0 - 60 for the overall SES-CD score, with larger scores indicating greater degree of inflammation.

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

End point timeframe:

Week 12

| **End point values** | Ozanimod | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 403 | 203 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | 4.0 | 4.9 | | |

### Statistical analyses

| **Statistical analysis title** | Statistical Analysis 1 |
|---|---|
| Comparison groups | Ozanimod v Placebo |
| Number of subjects included in analysis | 606 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.563 [1] |
| Method | Mantel-Haenszel |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 0.79 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.35 |
| upper limit | 1.78 |

Notes:

[1] - Odds ratio, and p-value are obtained using the CMH test stratified by corticosteroid use at baseline (yes or no), and prior biologic use (yes or no).

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

All cause mortality, non serious adverse events and serious adverse events were collected from the first dose and up to approximately 31 weeks.

Adverse event reporting additional description:

Treated population include all the participants who were treated with at least one dose of study drug. 1 participant earlier randomized or pre-assigned to Placebo arm in error received Ozanimod

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

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 26.1 |

### Reporting groups

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

Reporting group description:

Participants with moderate to severely active Crohn's disease were orally administered Placebo (daily) from Day 1 to Week 12.

| | |
|---|---|
| Reporting group title | Ozanimod 0.92 mg |

Reporting group description:

Participants with moderate to severe acute Crohn's disease were administered Ozanimod capsule orally. Participants were administered 0.23 milligram (mg) of Ozanimod capsule (daily) from Day 1 to Day 4 followed by 0.46 mg of Ozanimod (2 capsules of 0.23 mg daily) from Day 5 to Day 7 followed by 0.92 mg of Ozanimod capsule (daily) from Day 8 to Week 12.

| Serious adverse events | Placebo | Ozanimod 0.92 mg | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 11 / 202 (5.45%) | 24 / 404 (5.94%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Injury, poisoning and procedural complications | | | |
| Femur fracture | | | |
| subjects affected / exposed | 0 / 202 (0.00%) | 1 / 404 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Incision site haematoma | | | |
| subjects affected / exposed | 1 / 202 (0.50%) | 0 / 404 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Postoperative ileus | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 202 (0.00%) | 1 / 404 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Pericarditis | | | |
| subjects affected / exposed | 1 / 202 (0.50%) | 0 / 404 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Syncope | | | |
| subjects affected / exposed | 0 / 202 (0.00%) | 1 / 404 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vertebrobasilar insufficiency | | | |
| subjects affected / exposed | 0 / 202 (0.00%) | 1 / 404 (0.25%) | |
| 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 | 0 / 202 (0.00%) | 1 / 404 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Eye disorders | | | |
| Retinal vein occlusion | | | |
| subjects affected / exposed | 0 / 202 (0.00%) | 1 / 404 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Crohn's disease | | | |
| subjects affected / exposed | 6 / 202 (2.97%) | 10 / 404 (2.48%) | |
| occurrences causally related to treatment / all | 1 / 6 | 2 / 10 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Colonic fistula | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 202 (0.50%) | 0 / 404 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abdominal pain | | | |
| subjects affected / exposed | 0 / 202 (0.00%) | 2 / 404 (0.50%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Small intestinal obstruction | | | |
| subjects affected / exposed | 0 / 202 (0.00%) | 4 / 404 (0.99%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Proctitis | | | |
| subjects affected / exposed | 1 / 202 (0.50%) | 0 / 404 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancreatitis | | | |
| subjects affected / exposed | 0 / 202 (0.00%) | 1 / 404 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intestinal obstruction | | | |
| subjects affected / exposed | 0 / 202 (0.00%) | 1 / 404 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Fistula of small intestine | | | |
| subjects affected / exposed | 0 / 202 (0.00%) | 1 / 404 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Cholecystitis | | | |
| subjects affected / exposed | 0 / 202 (0.00%) | 1 / 404 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin and subcutaneous tissue disorders | | | |

| | | | |
|---|---|---|---|
| Rash papular | | | |
| subjects affected / exposed | 1 / 202 (0.50%) | 0 / 404 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthritis enteropathic | | | |
| subjects affected / exposed | 0 / 202 (0.00%) | 1 / 404 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Abdominal wall abscess | | | |
| subjects affected / exposed | 1 / 202 (0.50%) | 0 / 404 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| COVID-19 | | | |
| subjects affected / exposed | 0 / 202 (0.00%) | 1 / 404 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastroenteritis | | | |
| subjects affected / exposed | 1 / 202 (0.50%) | 0 / 404 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Electrolyte imbalance | | | |
| subjects affected / exposed | 0 / 202 (0.00%) | 1 / 404 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypokalaemia | | | |
| subjects affected / exposed | 0 / 202 (0.00%) | 1 / 404 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Malnutrition | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 202 (0.00%) | 1 / 404 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| **Non-serious adverse events** | Placebo | Ozanimod 0.92 mg | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 11 / 202 (5.45%) | 15 / 404 (3.71%) | |
| Gastrointestinal disorders | | | |
| Crohn's disease | | | |
| subjects affected / exposed | 11 / 202 (5.45%) | 15 / 404 (3.71%) | |
| occurrences (all) | 13 | 18 | |

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 19 December 2017 | The CDEIS is being introduced as an additional secondary endpoint because it is an established endoscopic measure. A change has been made to provide further guidance to investigators on the management of subjects with symptomatic bradycardia, including a reference to local guidelines. |
| 18 June 2018 | Exploratory endpoints updated |
| 10 June 2019 | Revisions to reflect the addition of adolescent subjects. Change to safety follow up from 75 days to 90-day (±10 days) Safety Follow-up Visit to ensure adequate collection of adverse events that could be associated with investigational drug. |
| 03 September 2020 | Adjustment of Sample Size, Refinement of Per-Protocol Population, Update Summary of Clinical Studies in Inflammatory Bowel Disease (IBD), Exploratory, Endoscopic Remission Endpoint, and Exclusion criteria was updated |
| 14 January 2021 | Removal of Adolescent Subjects |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported