



Clinical trial results:

A Phase 2 Multi-center, Randomized, Double-blind, Placebo-controlled, Parallel-group Study to Evaluate the Efficacy and Safety of Induction Therapy with 2 Doses of TD-1473 in Subjects with Moderately-to-Severely Active Crohn's Disease

Summary

| | |
|--------------------------|-------------------------------------|
| EudraCT number | 2018-001272-37 |
| Trial protocol | FR DE PT ES HU BG AT GB PL GR HR RO |
| Global end of trial date | 30 December 2021 |

Results information

| | |
|--------------------------------|-----------------|
| Result version number | v1 (current) |
| This version publication date | 16 January 2023 |
| First version publication date | 16 January 2023 |

Trial information

Trial identification

| | |
|-----------------------|------|
| Sponsor protocol code | 0173 |
|-----------------------|------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT03635112 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Theravance Biopharma Ireland Limited |
| Sponsor organisation address | Ten Earlsfort Terrace, Dublin, Ireland, D02 T380 |
| Public contact | Medical Monitor, Theravance Biopharma, +1 855-633-8479, medinfo@theravance.com |
| Scientific contact | Medical Monitor, Theravance Biopharma, +1 855-633-8479, medinfo@theravance.com |

Notes:

Paediatric regulatory details

| | |
|--|----|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

Results analysis stage

| | |
|--|------------------|
| Analysis stage | Final |
| Date of interim/final analysis | 30 December 2021 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 30 December 2021 |
| Was the trial ended prematurely? | Yes |

Notes:

General information about the trial

Main objective of the trial:

The primary objectives of the study are as follows:

- To assess the effect of TD-1473 compared to placebo in improving Crohn's Disease Activity Index (CDAI) score at Week 12 in subjects with moderately-to-severely active CD
- To assess the safety and tolerability of TD-1473

Protection of trial subjects:

This trial was conducted in accordance with the ethical principles of Good Clinical Practice, according to the International Council for Harmonisation (ICH) Harmonised Tripartite Guideline.

Background therapy: -

Evidence for comparator: -

| | |
|---|--------------|
| Actual start date of recruitment | 19 July 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 | Austria: 3 |
| Country: Number of subjects enrolled | Spain: 3 |
| Country: Number of subjects enrolled | Australia: 5 |
| Country: Number of subjects enrolled | South Africa: 4 |
| Country: Number of subjects enrolled | Poland: 26 |
| Country: Number of subjects enrolled | Russian Federation: 20 |
| Country: Number of subjects enrolled | Ukraine: 20 |
| Country: Number of subjects enrolled | Serbia: 9 |
| Country: Number of subjects enrolled | Bulgaria: 8 |
| Country: Number of subjects enrolled | Croatia: 4 |
| Country: Number of subjects enrolled | Georgia: 2 |
| Country: Number of subjects enrolled | Hungary: 2 |
| Country: Number of subjects enrolled | United States: 28 |
| Country: Number of subjects enrolled | France: 11 |
| Country: Number of subjects enrolled | Germany: 7 |
| Country: Number of subjects enrolled | Israel: 2 |
| Country: Number of subjects enrolled | Romania: 3 |
| Country: Number of subjects enrolled | New Zealand: 2 |

| | |
|------------------------------------|-----|
| Worldwide total number of subjects | 159 |
| EEA total number of subjects | 67 |

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) | 152 |
| From 65 to 84 years | 7 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 167 participants were randomized, of which 159 participants were eligible for analysis at sites in Australia, Asia/Pacific, Israel, Russia, the United States and South Africa between 19 November 2018 and 30 December 2021.

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 | Placebo |

Arm description:

Participants were randomized to receive once-daily oral administrations of placebo for 12 weeks during the Induction Period. Participants who completed the Induction Period received once-daily oral administrations of TD-1473 80 mg in the Active Treatment Extension period for up to 48 additional weeks.

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

Dosage and administration details:

Received orally.

| | |
|------------------|---------------|
| Arm title | TD-1473 80 mg |
|------------------|---------------|

Arm description:

Participants were randomized to receive once-daily oral administrations of TD-1473 80 mg for 12 weeks during the Induction Period. Participants who completed the Induction Period received once-daily oral administrations of TD-1473 80 mg in the Active Treatment Extension period for up to 48 additional weeks.

| | |
|--|--------------|
| Arm type | Experimental |
| Investigational medicinal product name | TD-1473 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Received orally.

| | |
|------------------|----------------|
| Arm title | TD-1473 200 mg |
|------------------|----------------|

Arm description:

Participants were randomized to receive once-daily oral administrations of TD-1473 200 mg for 12 weeks during the Induction Period. Participants who completed the Induction Period received once-daily oral administrations of TD-1473 200 mg in the Active Treatment Extension period for up to 48 additional weeks.

| | |
|--|--------------|
| Arm type | Experimental |
| Investigational medicinal product name | TD-1473 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Received orally.

| Number of subjects in period 1 | Placebo | TD-1473 80 mg | TD-1473 200 mg |
|---------------------------------------|---------|---------------|----------------|
| Started | 38 | 58 | 63 |
| Completed Week 12 Visit | 33 | 48 | 49 |
| Completed | 12 | 16 | 13 |
| Not completed | 26 | 42 | 50 |
| Consent withdrawn by subject | 4 | 9 | 7 |
| Physician decision | 5 | 7 | 5 |
| Adverse event, non-fatal | 5 | 9 | 14 |
| Miscellaneous | - | - | 1 |
| Study Terminated by Sponsor | 11 | 17 | 21 |
| Lost to follow-up | 1 | - | 1 |
| Protocol deviation | - | - | 1 |

Baseline characteristics

Reporting groups

| | |
|--|----------------|
| Reporting group title | Placebo |
| Reporting group description: | |
| Participants were randomized to receive once-daily oral administrations of placebo for 12 weeks during the Induction Period. Participants who completed the Induction Period received once-daily oral administrations of TD-1473 80 mg in the Active Treatment Extension period for up to 48 additional weeks. | |
| Reporting group title | TD-1473 80 mg |
| Reporting group description: | |
| Participants were randomized to receive once-daily oral administrations of TD-1473 80 mg for 12 weeks during the Induction Period. Participants who completed the Induction Period received once-daily oral administrations of TD-1473 80 mg in the Active Treatment Extension period for up to 48 additional weeks. | |
| Reporting group title | TD-1473 200 mg |
| Reporting group description: | |
| Participants were randomized to receive once-daily oral administrations of TD-1473 200 mg for 12 weeks during the Induction Period. Participants who completed the Induction Period received once-daily oral administrations of TD-1473 200 mg in the Active Treatment Extension period for up to 48 additional weeks. | |

| Reporting group values | Placebo | TD-1473 80 mg | TD-1473 200 mg |
|--|---------|---------------|----------------|
| Number of subjects | 38 | 58 | 63 |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | | | |
| Preterm newborn infants (gestational age < 37 wks) | | | |
| Newborns (0-27 days) | | | |
| Infants and toddlers (28 days-23 months) | | | |
| Children (2-11 years) | | | |
| Adolescents (12-17 years) | | | |
| Adults (18-64 years) | | | |
| From 65-84 years | | | |
| 85 years and over | | | |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 39.5 | 37.1 | 40.0 |
| standard deviation | ± 14.85 | ± 12.45 | ± 13.64 |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 18 | 28 | 31 |
| Male | 20 | 30 | 32 |
| Ethnicity | | | |
| Units: Subjects | | | |
| Hispanic or Latino | 2 | 1 | 0 |
| Not Hispanic or Latino | 36 | 57 | 60 |
| Unknown | 0 | 0 | 2 |
| Not Reported | 0 | 0 | 1 |

| | | | |
|---|-------|--|--|
| Reporting group values | Total | | |
| Number of subjects | 159 | | |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | 0 | | |
| Preterm newborn infants (gestational age < 37 wks) | 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) | 0 | | |
| From 65-84 years | 0 | | |
| 85 years and over | 0 | | |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | | | |
| standard deviation | - | | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 77 | | |
| Male | 82 | | |
| Ethnicity | | | |
| Units: Subjects | | | |
| Hispanic or Latino | 3 | | |
| Not Hispanic or Latino | 153 | | |
| Unknown | 2 | | |
| Not Reported | 1 | | |

End points

End points reporting groups

| | |
|--|----------------|
| Reporting group title | Placebo |
| Reporting group description: Participants were randomized to receive once-daily oral administrations of placebo for 12 weeks during the Induction Period. Participants who completed the Induction Period received once-daily oral administrations of TD-1473 80 mg in the Active Treatment Extension period for up to 48 additional weeks. | |
| Reporting group title | TD-1473 80 mg |
| Reporting group description: Participants were randomized to receive once-daily oral administrations of TD-1473 80 mg for 12 weeks during the Induction Period. Participants who completed the Induction Period received once-daily oral administrations of TD-1473 80 mg in the Active Treatment Extension period for up to 48 additional weeks. | |
| Reporting group title | TD-1473 200 mg |
| Reporting group description: Participants were randomized to receive once-daily oral administrations of TD-1473 200 mg for 12 weeks during the Induction Period. Participants who completed the Induction Period received once-daily oral administrations of TD-1473 200 mg in the Active Treatment Extension period for up to 48 additional weeks. | |

Primary: Change From Baseline in Crohn's Disease Activity Index (CDAI) Score

| | |
|---|---|
| End point title | Change From Baseline in Crohn's Disease Activity Index (CDAI) Score |
| End point description: The CDAI score was generated using regression coefficients for 8 predictors of disease activity: severity of abdominal pain, general well-being, very soft/liquid stool frequency, extra-intestinal symptoms, need for antidiarrheal drugs, presence of an abdominal mass, body weight & hematocrit. The subscores of abdominal pain (0-3), general well-being (0-4), & number of very soft or liquid stools were then summed over the 7 days prior to each visit. The remaining predictors were also noted & weighted to create the total CDAI score. Benchmarks for disease activity were: <150, clinical remission; 150 to 219, mildly active disease; 220-450, moderately active disease; >450, very severe disease. Modified Intent-to-Treat Analysis Set: Comprised all randomized evaluable participants who received at least 1 dose of study drug and had at least one postbaseline CDAI score. Only participants with non-missing values at both baseline and postbaseline visit were included. | |
| End point type | Primary |
| End point timeframe: Baseline to Week 12 | |

| End point values | Placebo | TD-1473 80 mg | TD-1473 200 mg | |
|-------------------------------------|--------------------|--------------------|--------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 33 | 47 | 50 | |
| Units: score on a scale | | | | |
| least squares mean (standard error) | -104.86 (± 15.496) | -105.62 (± 12.713) | -117.99 (± 12.423) | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | TD-1473 80 mg Versus Placebo |
| Comparison groups | Placebo v TD-1473 80 mg |
| Number of subjects included in analysis | 80 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.97 |
| Method | Mixed Model Repeated Measures Analysis |
| Parameter estimate | Least Square Mean Difference |
| Point estimate | -0.76 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -40.62 |
| upper limit | 39.11 |

| | |
|---|--|
| Statistical analysis title | TD-1473 200 mg Versus Placebo |
| Comparison groups | Placebo v TD-1473 200 mg |
| Number of subjects included in analysis | 83 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.51 |
| Method | Mixed Model Repeated Measures Analysis |
| Parameter estimate | Least Square Mean Difference |
| Point estimate | -13.13 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -52.46 |
| upper limit | 26.19 |

Secondary: Number of Participants Who Demonstrated a Clinical Response as Measured by CDAI

| | |
|-----------------|---|
| End point title | Number of Participants Who Demonstrated a Clinical Response as Measured by CDAI |
|-----------------|---|

End point description:

The CDAI score was generated using regression coefficients for 8 predictors of disease activity: severity of abdominal pain, general well-being, very soft/liquid stool frequency, extra-intestinal symptoms, need for antidiarrheal drugs, presence of an abdominal mass, body weight & hematocrit. The subscores of abdominal pain (0-3), general well-being (0-4), & number of very soft or liquid stools were then summed over the 7 days prior to each visit. The remaining predictors were also noted & weighted to

create the total CDAI score.

Benchmarks for disease activity were: <150, clinical remission; 150 to 219, mildly active disease; 220-450, moderately active disease; >450, very severe disease.

Clinical response was defined as a reduction from baseline of ≥ 100 points or CDAI <150.

The analysis set used was the Modified Intent-to-Treat Analysis Set.

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Week 12 | |

| End point values | Placebo | TD-1473 80 mg | TD-1473 200 mg | |
|-----------------------------|-----------------|-----------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 35 | 54 | 56 | |
| Units: participants | 19 | 28 | 34 | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | TD-1473 80 mg Versus Placebo |
| Comparison groups | Placebo v TD-1473 80 mg |
| Number of subjects included in analysis | 89 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.5102 |
| Method | Cochran-Mantel-Haenszel Chi-square Test |
| Parameter estimate | Difference in Proportion |
| Point estimate | -0.07 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.277 |
| upper limit | 0.135 |

| | |
|---|---|
| Statistical analysis title | TD-1473 200 mg Versus Placebo |
| Comparison groups | Placebo v TD-1473 200 mg |
| Number of subjects included in analysis | 91 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.8591 |
| Method | Cochran-Mantel-Haenszel Chi-square Test |
| Parameter estimate | Difference in Proportion |
| Point estimate | 0.02 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.181 |
| upper limit | 0.218 |

Secondary: Number of Participants Who Demonstrated CDAI Clinical Remission

| | |
|-----------------|---|
| End point title | Number of Participants Who Demonstrated CDAI Clinical Remission |
|-----------------|---|

End point description:

The CDAI score was generated using regression coefficients for 8 predictors of disease activity: severity of abdominal pain, general well-being, very soft/liquid stool frequency, extra-intestinal symptoms, need for antidiarrheal drugs, presence of an abdominal mass, body weight & hematocrit. The subscores of abdominal pain (0-3), general well-being (0-4), & number of very soft or liquid stools were then summed over the 7 days prior to each visit. The remaining predictors were also noted & weighted to create the total CDAI score.

Benchmarks for disease activity were: <150, clinical remission; 150 to 219, mildly active disease; 220-450, moderately active disease; >450, very severe disease. CDAI clinical remission was defined as a CDAI score less than 150 at Week 12.

The analysis set used was the Modified Intent-to-Treat Analysis Set.

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

End point timeframe:

Week 12

| End point values | Placebo | TD-1473 80 mg | TD-1473 200 mg | |
|-----------------------------|-----------------|-----------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 35 | 54 | 56 | |
| Units: participants | 13 | 13 | 22 | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | TD-1473 80 mg Versus Placebo |
| Comparison groups | Placebo v TD-1473 80 mg |
| Number of subjects included in analysis | 89 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.1805 |
| Method | Cochran-Mantel-Haenszel Chi-square Test |
| Parameter estimate | Difference in Proportion |
| Point estimate | -0.13 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.322 |
| upper limit | 0.061 |

| | |
|---|---|
| Statistical analysis title | TD-1473 200 mg Versus Placebo |
| Comparison groups | Placebo v TD-1473 200 mg |
| Number of subjects included in analysis | 91 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.9215 |
| Method | Cochran-Mantel-Haenszel Chi-square Test |
| Parameter estimate | Difference in Proportion |
| Point estimate | -0.01 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.204 |
| upper limit | 0.184 |

Secondary: Change From Baseline in Simple Endoscopic Score for Crohn's Disease (SES-CD) at Week 12

| | |
|-----------------|---|
| End point title | Change From Baseline in Simple Endoscopic Score for Crohn's Disease (SES-CD) at Week 12 |
|-----------------|---|

End point description:

The SES-CD incorporated 4 descriptors: the ulcer size, the proportion of surface covered by ulcer, the proportion of surface covered by other lesions, and the presence of stenosis. Each descriptor was graded from 0-3 and was scored in 5 segments (ileum, right colon, transverse colon, left colon, and rectum). The total score was calculated as the sum of all the items in each segment and ranged from 0 to 56, with higher scores indicating a worse outcome.

The analysis set used was the Modified Intent-to-Treat Analysis Set including only participants who had non-missing values at both baseline and postbaseline visit.

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

End point timeframe:

Baseline to Week 12

| End point values | Placebo | TD-1473 80 mg | TD-1473 200 mg | |
|-------------------------------------|-----------------|-----------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 20 | 35 | 37 | |
| Units: score on a scale | | | | |
| least squares mean (standard error) | -1.9 (± 1.27) | -0.2 (± 0.96) | -1.9 (± 0.95) | |

Statistical analyses

| | |
|---|------------------------------|
| Statistical analysis title | TD-1473 80 mg Versus Placebo |
| Comparison groups | Placebo v TD-1473 80 mg |
| Number of subjects included in analysis | 55 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.316 |
| Method | ANCOVA |
| Parameter estimate | Least Square Mean Difference |
| Point estimate | 1.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.6 |
| upper limit | 4.8 |

| | |
|---|-------------------------------|
| Statistical analysis title | TD-1473 200 mg Versus Placebo |
| Comparison groups | Placebo v TD-1473 200 mg |
| Number of subjects included in analysis | 57 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.988 |
| Method | ANCOVA |
| Parameter estimate | Least Square Mean Difference |
| Point estimate | 0 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.2 |
| upper limit | 3.2 |

Secondary: Number of Participants With Endoscopic Response at Week 12

| | |
|---|--|
| End point title | Number of Participants With Endoscopic Response at Week 12 |
| End point description: | |
| Endoscopic Response was defined as a reduction of SES-CD score or Endoscopic Remission (defined as SES-CD \leq 2) at Week 12. | |
| The analysis set used was the Modified Intent-to-Treat Analysis Set. | |
| End point type | Secondary |

End point timeframe:

Week 12

| End point values | Placebo | TD-1473 80 mg | TD-1473 200 mg | |
|-----------------------------|-----------------|-----------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 31 | 53 | 54 | |
| Units: participants | 6 | 5 | 15 | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | TD-1473 80 mg Versus Placebo |
| Comparison groups | Placebo v TD-1473 80 mg |
| Number of subjects included in analysis | 84 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.1828 |
| Method | Cochran-Mantel-Haenszel Chi-square Test |
| Parameter estimate | Difference in Proportion |
| Point estimate | -0.11 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.27 |
| upper limit | 0.059 |

| | |
|---|---|
| Statistical analysis title | TD-1473 200 mg Versus Placebo |
| Comparison groups | Placebo v TD-1473 200 mg |
| Number of subjects included in analysis | 85 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.5785 |
| Method | Cochran-Mantel-Haenszel Chi-square Test |
| Parameter estimate | Difference in Proportion |
| Point estimate | 0.06 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.133 |
| upper limit | 0.244 |

Secondary: Number of Participants With Stool Frequency and Abdominal Pain (SFAP) Clinical Remission

| | |
|-----------------|--|
| End point title | Number of Participants With Stool Frequency and Abdominal Pain (SFAP) Clinical Remission |
|-----------------|--|

End point description:

SFAP clinical remission was defined as an abdominal pain score ≤ 1 (on a scale of 0-3 with 0 representing 'no pain' and 3 representing 'severe pain'), stool frequency ≤ 2.8 , and both not worse than baseline at Week 12.

The analysis set used was the Modified Intent-to-Treat Analysis Set.

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

End point timeframe:

Week 12

| End point values | Placebo | TD-1473 80 mg | TD-1473 200 mg | |
|-----------------------------|-----------------|-----------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 35 | 54 | 56 | |
| Units: participants | 6 | 6 | 10 | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | TD-1473 80 mg Versus Placebo |
| Comparison groups | Placebo v TD-1473 80 mg |
| Number of subjects included in analysis | 89 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.3776 |
| Method | Cochran-Mantel-Haenszel Chi-square Test |
| Parameter estimate | Difference in Proportion |
| Point estimate | -0.07 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.225 |
| upper limit | 0.095 |

| | |
|-----------------------------------|-------------------------------|
| Statistical analysis title | TD-1473 200 mg Versus Placebo |
| Comparison groups | Placebo v TD-1473 200 mg |

| | |
|---|---|
| Number of subjects included in analysis | 91 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.6063 |
| Method | Cochran-Mantel-Haenszel Chi-square Test |
| Parameter estimate | Difference in Proportion |
| Point estimate | -0.04 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.189 |
| upper limit | 0.111 |

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From Day 1 up to 28 days after the last dose (up to 64 weeks)

Adverse event reporting additional description:

The safety analysis set comprised all participants who received at least 1 dose of study drug.

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

Dictionary used

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

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

Reporting groups

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

Reporting group description:

Participants were randomized to receive once-daily oral administrations of placebo for 12 weeks during the Induction Period. Participants who completed the Induction Period received once-daily oral administrations of TD-1473 80 mg in the Active Treatment Extension period for up to 48 additional weeks.

| | |
|-----------------------|---------------|
| Reporting group title | TD-1473 80 mg |
|-----------------------|---------------|

Reporting group description:

Participants were randomized to receive once-daily oral administrations of TD-1473 80 mg for 12 weeks during the Induction Period. Participants who completed the Induction Period received once-daily oral administrations of TD-1473 80 mg in the Active Treatment Extension period for up to 48 additional weeks.

| | |
|-----------------------|---------------------------|
| Reporting group title | TD-1473 80mg Post-Placebo |
|-----------------------|---------------------------|

Reporting group description:

Participants who were treated with placebo in Induction Period and switched to TD-1473 80mg in Active Treatment Extension period.

| | |
|-----------------------|----------------|
| Reporting group title | TD-1473 200 mg |
|-----------------------|----------------|

Reporting group description:

Participants were randomized to receive once-daily oral administrations of TD-1473 200 mg for 12 weeks during the Induction Period. Participants who completed the Induction Period received once-daily oral administrations of TD-1473 200 mg in the Active Treatment Extension period for up to 48 additional weeks.

| Serious adverse events | Placebo | TD-1473 80 mg | TD-1473 80mg Post-Placebo |
|---|----------------|-----------------|---------------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 3 / 38 (7.89%) | 9 / 58 (15.52%) | 3 / 33 (9.09%) |
| number of deaths (all causes) | 1 | 0 | 0 |
| number of deaths resulting from adverse events | 1 | 0 | 0 |
| Investigations | | | |
| Transaminases increased | | | |
| subjects affected / exposed | 1 / 38 (2.63%) | 0 / 58 (0.00%) | 0 / 33 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |

| | | | |
|--|----------------|-----------------|----------------|
| Intentional overdose | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 58 (0.00%) | 0 / 33 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |
| Vasculitis | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 1 / 58 (1.72%) | 0 / 33 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Granuloma | | | |
| subjects affected / exposed | 1 / 38 (2.63%) | 0 / 58 (0.00%) | 0 / 33 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Immune system disorders | | | |
| Drug hypersensitivity | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 58 (0.00%) | 1 / 33 (3.03%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Crohn's Disease | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 6 / 58 (10.34%) | 1 / 33 (3.03%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 6 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intestinal perforation | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 1 / 58 (1.72%) | 0 / 33 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intussusception | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 58 (0.00%) | 1 / 33 (3.03%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pancreatitis acute | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 1 / 38 (2.63%) | 0 / 58 (0.00%) | 0 / 33 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psychiatric disorders | | | |
| Anxiety | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 1 / 58 (1.72%) | 0 / 33 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Depression | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 1 / 58 (1.72%) | 0 / 33 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| COVID-19 pneumonia | | | |
| subjects affected / exposed | 1 / 38 (2.63%) | 0 / 58 (0.00%) | 0 / 33 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Rectal abscess | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 58 (0.00%) | 0 / 33 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|--|------------------|--|--|
| Serious adverse events | TD-1473 200 mg | | |
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 10 / 63 (15.87%) | | |
| number of deaths (all causes) | 0 | | |
| number of deaths resulting from adverse events | 0 | | |
| Investigations | | | |
| Transaminases increased | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Injury, poisoning and procedural complications | | | |
| Intentional overdose | | | |

| | | | |
|--|-----------------|--|--|
| subjects affected / exposed | 1 / 63 (1.59%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vascular disorders | | | |
| Vasculitis | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| General disorders and administration site conditions | | | |
| Granuloma | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Immune system disorders | | | |
| Drug hypersensitivity | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |
| Crohn's Disease | | | |
| subjects affected / exposed | 8 / 63 (12.70%) | | |
| occurrences causally related to treatment / all | 0 / 8 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Intestinal perforation | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Intussusception | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pancreatitis acute | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 0 / 63 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Psychiatric disorders | | | |
| Anxiety | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Depression | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| COVID-19 pneumonia | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Rectal abscess | | | |
| subjects affected / exposed | 1 / 63 (1.59%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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

| Non-serious adverse events | Placebo | TD-1473 80 mg | TD-1473 80mg Post-Placebo |
|---|------------------|------------------|---------------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 11 / 38 (28.95%) | 23 / 58 (39.66%) | 7 / 33 (21.21%) |
| Investigations | | | |
| SARS-CoV-2 test positive | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 1 / 58 (1.72%) | 0 / 33 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 3 / 38 (7.89%) | 3 / 58 (5.17%) | 1 / 33 (3.03%) |
| occurrences (all) | 3 | 3 | 3 |

| | | | |
|---|----------------|-----------------|----------------|
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 4 / 58 (6.90%) | 0 / 33 (0.00%) |
| occurrences (all) | 0 | 4 | 0 |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 1 / 38 (2.63%) | 1 / 58 (1.72%) | 1 / 33 (3.03%) |
| occurrences (all) | 1 | 1 | 1 |
| Crohn's disease | | | |
| subjects affected / exposed | 3 / 38 (7.89%) | 8 / 58 (13.79%) | 2 / 33 (6.06%) |
| occurrences (all) | 3 | 8 | 2 |
| Diarrhoea | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 3 / 58 (5.17%) | 0 / 33 (0.00%) |
| occurrences (all) | 0 | 3 | 0 |
| Nausea | | | |
| subjects affected / exposed | 1 / 38 (2.63%) | 1 / 58 (1.72%) | 2 / 33 (6.06%) |
| occurrences (all) | 1 | 1 | 2 |
| Vomiting | | | |
| subjects affected / exposed | 1 / 38 (2.63%) | 1 / 58 (1.72%) | 2 / 33 (6.06%) |
| occurrences (all) | 1 | 1 | 2 |
| Skin and subcutaneous tissue disorders | | | |
| Rash | | | |
| subjects affected / exposed | 2 / 38 (5.26%) | 4 / 58 (6.90%) | 0 / 33 (0.00%) |
| occurrences (all) | 2 | 4 | 0 |
| Psychiatric disorders | | | |
| Anxiety | | | |
| subjects affected / exposed | 2 / 38 (5.26%) | 1 / 58 (1.72%) | 1 / 33 (3.03%) |
| occurrences (all) | 2 | 1 | 1 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 3 / 58 (5.17%) | 0 / 33 (0.00%) |
| occurrences (all) | 0 | 4 | 0 |
| Back pain | | | |
| subjects affected / exposed | 2 / 38 (5.26%) | 1 / 58 (1.72%) | 0 / 33 (0.00%) |
| occurrences (all) | 2 | 1 | 0 |
| Infections and infestations | | | |

| | | | |
|-----------------------------|----------------|----------------|----------------|
| Nasopharyngitis | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 58 (0.00%) | 1 / 33 (3.03%) |
| occurrences (all) | 0 | 0 | 1 |
| Urinary tract infection | | | |
| subjects affected / exposed | 1 / 38 (2.63%) | 4 / 58 (6.90%) | 0 / 33 (0.00%) |
| occurrences (all) | 1 | 6 | 0 |

| | | | |
|---|------------------|--|--|
| Non-serious adverse events | TD-1473 200 mg | | |
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 22 / 63 (34.92%) | | |
| Investigations | | | |
| SARS-CoV-2 test positive | | | |
| subjects affected / exposed | 4 / 63 (6.35%) | | |
| occurrences (all) | 5 | | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 5 / 63 (7.94%) | | |
| occurrences (all) | 7 | | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 1 / 63 (1.59%) | | |
| occurrences (all) | 1 | | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 4 / 63 (6.35%) | | |
| occurrences (all) | 5 | | |
| Crohn's disease | | | |
| subjects affected / exposed | 7 / 63 (11.11%) | | |
| occurrences (all) | 9 | | |
| Diarrhoea | | | |
| subjects affected / exposed | 1 / 63 (1.59%) | | |
| occurrences (all) | 1 | | |
| Nausea | | | |
| subjects affected / exposed | 4 / 63 (6.35%) | | |
| occurrences (all) | 4 | | |
| Vomiting | | | |

| | | | |
|--|--|--|--|
| subjects affected / exposed occurrences (all) | 1 / 63 (1.59%) 1 | | |
| Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all) | 1 / 63 (1.59%) 1 | | |
| Psychiatric disorders Anxiety subjects affected / exposed occurrences (all) | 1 / 63 (1.59%) 2 | | |
| Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Back pain subjects affected / exposed occurrences (all) | 1 / 63 (1.59%) 2 3 / 63 (4.76%) 3 | | |
| Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) Urinary tract infection subjects affected / exposed occurrences (all) | 5 / 63 (7.94%) 6 1 / 63 (1.59%) 1 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---------------|--|
| 20 April 2018 | Amendment 1 included the following changes: <ul style="list-style-type: none">- Theravance Biopharma Ireland Limited telephone number was removed- Stratification factors were updated- Minor adjustment in the targeted proportion of biologics-naïve participants- Treatment regimen updated- Inclusion and exclusion criteria updated- Fecal lactoferrin added to the fecal testing- Statistical analysis section updated- Schedule of study procedures updated- Fistula Drainage Assessment was added for applicable participants- Risk and Benefits section updated- Treatment failure definition added- Rationale for study design updated- Rationale for dose assignment updated- Treatment compliance definition updated- Medical history data collection updated- Biopsy location information added- Participant diaries updated- Prohibited and permitted medications sections updated- Adverse event of special interest (AESI) definition updated- References and appendices updated. |
| 13 July 2018 | Amendment 2 included updates to the following sections: Cover Page and Protocol Synopsis; Background and Rationale; Risks and Benefits; Inclusion and Exclusion Criteria; Schedule of Study Procedures; Screening Stage 1; Fecal Sampling; Ileocolonoscopy and Biopsies; Prohibited Medications; Subject Discontinuation; AESI; serious adverse event (SAE) and AESI reporting timeline; Clinical Laboratory Abnormalities and Other Abnormal Assessments as Adverse Events or SAEs; Major Analysis Protocol Deviations; and Appendices. |
| 28 June 2019 | Amendment 3 included updates to the following sections: Protocol Synopsis; Background and Rationale; Clinical Experience; Selection of Dose and Duration of Treatment; Study Design Overview; Study Population; Overview; Procedures by Visit; Inclusion and Exclusion Criteria; Schedule of Study Procedures; Coexisting Medical Conditions or Past Medical History; Concomitant Medications; Statistical Methods; Sample Size and Power; Study Procedures; Objectives; Study Endpoints; Blinding; Treatment Assignment; Females of Childbearing Potential and Acceptable Birth Control; Screening Stage 2; Medication History; Vital Signs; Physical Examination; Viral Hepatitis and Human Immunodeficiency Virus Serology Panel; Tuberculosis (TB) Test; Ileocolonoscopy and Biopsies; Fecal Samples; Subject Daily Diary; Permitted Medications; Subject Discontinuation; Informed Consent; Confidentiality; Access to Data and Documents; SAE; Clinical Laboratory Abnormalities and Other Abnormal Assessments as Adverse Events or SAEs; and Appendices. |
| 09 June 2020 | Amendment 4 included updates to the following sections: Protocol Synopsis; Clinical Experience; Inclusion and Exclusion Criteria; Schedule of Study Procedures; TB Test; Permitted Medications; Subject Replacement; Pregnancy; AESI; Clinical Laboratory Abnormalities and Other Abnormal Assessments as Adverse Events or SAEs; Clinical Events Committee; Electrocardiogram Data; References; and Appendices. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

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|--|
| The study was terminated by the sponsor on 16 November 2021 after a planned review by the Independent Data Monitoring Committee. |
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Notes: