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
Physician decision	5	7	5
Consent withdrawn by subject	4	9	7
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 ≤ 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: - 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.

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

Notes: