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

Summary

EudraCT number	2018-003986-33
Trial protocol	SK BE NL GB EE DE AT CZ FR DK LT BG PT LV HU PL HR ES IT RO
Global end of trial date	07 December 2021

Results information

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

Trial information

Trial identification

Sponsor protocol code	APD334-302

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Arena Pharmaceuticals, Inc.
Sponsor organisation address	6154 Nancy Ridge Drive, San Diego, United States,
Public contact	Fabio Cataldi, Arena Pharmaceuticals, Inc., 001 8584537200, ct.gov@arenapharm.com
Scientific contact	Fabio Cataldi, Arena Pharmaceuticals, Inc., 001 8584537200, ct.gov@arenapharm.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	17 February 2022
Is this the analysis of the primary completion data?	No

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

Notes:

General information about the trial

Main objective of the trial:

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

Protection of trial subjects:

The study was conducted in compliance with the ICH Guidelines for Good Clinical Practice (GCP) and applicable regulatory requirements, the study protocol, and where applicable, Sponsor and/or CRO Standard Operating Procedures.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	18 August 2020
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

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

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

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	2
Adults (18-64 years)	334
From 65 to 84 years	18
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study included a screening period (up to 28 days), a double-blind induction treatment period (12 weeks), and a 2-week and a 4-week follow-up period. The target population consisted of male or female subjects aged between 16 and 80 years (inclusive), with moderately to severely active ulcerative colitis.

Pre-assignment

Screening details:

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

Period 1

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

Blinding implementation details:

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Etrasimod 2 mg

Arm description:

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

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

Dosage and administration details:

1 × 2 mg etrasimod tablet orally QD for 12 weeks

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

Dosage and administration details:

1 × matching etrasimod tablet orally QD for 12 weeks

Arm title	Placebo

Arm description:

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

Arm type	Placebo

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

Dosage and administration details:

1 × matching etrasimod tablet orally QD for 12 weeks

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

Baseline characteristics

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

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

End points

End points reporting groups

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

Primary: Percentage of participants achieving clinical remission at Week 12

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

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

Statistical analyses

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

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

Secondary: Percentage of participants achieving endoscopic improvement at Week 12

End point title	Percentage of participants achieving endoscopic improvement at Week 12

End point description:

Participant reported symptoms using daily e-diary and centrally read endoscopy as follows: stool frequency sub-score 0 or 1 with at least a 1-point change from induction study baseline; and rectal bleeding sub-score of 0; and endoscopic sub-score 0 or 1 (excluding friability).

End point type	Secondary

End point timeframe:

Week 12

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

Statistical analyses

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

Secondary: Percentage of participants achieving symptomatic remission at Week 12

End point title	Percentage of participants achieving symptomatic remission at Week 12

End point description:

Symptomatic remission is a composite score of participant reported symptoms using daily e-diary and centrally read endoscopy as: stool frequency sub-score 0 or 1 with at least a 1-point change from induction study baseline; and rectal bleeding sub-score of 0.

End point type	Secondary

End point timeframe:

Week 12

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

Statistical analyses

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

Secondary: Percentage of participants with mucosal healing at Week 12

End point title	Percentage of participants with mucosal healing at Week 12

End point description:

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

End point type	Secondary

End point timeframe:

Week 12

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

Statistical analyses

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

Secondary: Percentage of participants achieving clinical response at Week 12

End point title	Percentage of participants achieving clinical response at Week 12

End point description:

Clinical response was defined as a greater than equal to (>=) 2-point and >= 30 percent decrease from baseline in modified Mayo score (MMS), and a >= 1-point decrease from Baseline in rectal bleeding (RB) sub-score or an absolute RB sub-score <= 1.

End point type	Secondary

End point timeframe:

Week 12

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

Statistical analyses

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

Secondary: Percentage of participants achieving endoscopic normalization at Week 12

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

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

Statistical analyses

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

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

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

End point title	Percentage of participants achieving symptomatic remission at Weeks 2, 4 and 8

End point description:

Symptomatic remission is a composite score of participant reported symptoms using daily e-diary and centrally read endoscopy as: stool frequency sub-score 0 or 1 with at least a 1-point change from induction study baseline; and rectal bleeding sub-score of 0.

End point type	Secondary

End point timeframe:

Weeks 2, 4 and 8

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

Statistical analyses

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

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

Notes:
[1] - Weeks 2

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

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

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

End point title	Percentage of participants achieving complete symptomatic remission at each study visit at Weeks 2, 4, 8 and 12
End point description:	
Complete symptomatic remission was defined as stool frequency sub-score = 0 and rectal bleeding sub-score = 0.	
End point type	Secondary
End point timeframe:	
Weeks 2, 4, 8 and 12	

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

Statistical analyses

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

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

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

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

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

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

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

End point description:

A noninvasive clinical response was defined as >= 30% decrease from Baseline in composite rectal bleeding and stool frequency sub-scores, and a >= 1-point decrease from Baseline in rectal bleeding sub score or an absolute rectal bleeding sub score =< 1.

End point type	Secondary

End point timeframe:

Weeks 2, 4, 8 and 12

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

Statistical analyses

Statistical analysis title	Statistical Analysis

Statistical analysis description:

Week 2

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

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

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

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

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

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

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

End point title	Percentage of participants achieving symptomatic response at Weeks 2, 4, 8 and 12

End point description:

Symptomatic response was defined as decrease from baseline >= 30% in composite rectal bleeding and Stool frequency sub scores.

End point type	Secondary

End point timeframe:

Weeks 2, 4, 8 and 12

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

Statistical analyses

Statistical analysis title	Statistical Analysis

Statistical analysis description:

Week 2

Comparison groups	Etrasimod 2 mg v Placebo

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

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

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

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

Adverse events

Adverse events information

Timeframe for reporting adverse events:

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

Adverse event reporting additional description:

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

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.1

Reporting groups

Reporting group title	Placebo

Reporting group description:

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

Reporting group title	Etrasimod 2 mg

Reporting group description:

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

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

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

Frequency threshold for reporting non-serious adverse events: 0 %

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

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

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported