Clinical trial results:
A Phase 2, proof-of-concept, multicentre, double-blind, randomised, dose-ascending, sequential group, placebo-controlled study to evaluate the mechanistic effect, safety, and tolerability of 12 weeks twice daily oral administration of alvelestat (MPH966) in participants with alpha-1 antitrypsin deficiency.

Summary

EudraCT number	2018-001309-95
Trial protocol	GB SE DK ES PL BE
Global end of trial date	30 March 2022

Results information

Result version number	v1 (current)
This version publication date	27 September 2024
First version publication date	27 September 2024

Trial information

Trial identification

Sponsor protocol code	MPH966-2-01

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03636347
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Mereo BioPharma
Sponsor organisation address	1 Cavendish Place, London, United Kingdom, W1G 0QF
Public contact	Mereo BioPharma, Mereo BioPharma, enquiries@mereobiopharma.com
Scientific contact	Mereo BioPharma, Mereo BioPharma, enquiries@mereobiopharma.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 March 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	30 March 2022
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was to evaluate the mechanistic effect of two doses of alvelestat administered twice daily (bid) for 12 weeks on blood markers of Neutrophil Elastase (NE) activity and safety in individuals with alpha-1 antitrypsin deficiency-associated emphysema.

Protection of trial subjects:

This study was conducted in accordance with the accepted version of the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines and/or all relevant federal regulations as set forth in Parts 50, 56, 312, Subpart D, of Title 21 of the United States Code of Federal Regulations (CFR), in compliance with International Council for Harmonisation (ICH) good clinical practice (GCP) guidelines, and according to the appropriate regulatory requirements in the countries where the study was conducted.

Background therapy:

Standard of Care for Chronic Obstructive Pulmonary Disease

Evidence for comparator: -

Actual start date of recruitment	03 September 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	United Kingdom: 39
Country: Number of subjects enrolled	Denmark: 23
Country: Number of subjects enrolled	Sweden: 14
Country: Number of subjects enrolled	Belgium: 7
Country: Number of subjects enrolled	Canada: 6
Country: Number of subjects enrolled	United States: 6
Country: Number of subjects enrolled	Poland: 3
Country: Number of subjects enrolled	Spain: 1
Worldwide total number of subjects	99
EEA total number of subjects	48

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)	77
From 65 to 84 years	22
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Participants were enrolled at 26 sites in the United States, Canada, Belgium, Denmark, Poland, Spain, Sweden and the United Kingdom. 1 participant was randomized to alvelestat 240 milligram (mg) but did not receive study treatment.

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	Alvelestat 120 mg

Arm description:

4 × 30 mg alvelestat and 4 × 30 mg placebo oral tablets taken twice daily (BID) 12 hours apart with water for 12 weeks.

Arm type	Experimental
Investigational medicinal product name	Alvelestat
Investigational medicinal product code	
Other name	MPH966
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Alvelestat tablets were administered orally

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

Dosage and administration details:

Placebo tablets were administered orally

Arm title	Alvelestat 240 mg

Arm description:

8 × 30 mg alvelestat oral tablets BID 12 hours apart with water for 12 weeks.

Arm type	Experimental
Investigational medicinal product name	Alvelestat
Investigational medicinal product code	
Other name	MPH966
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Alvelestat tablets were administered orally

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

Dosage and administration details:

Placebo tablets were administered orally

Arm title	Placebo

Arm description:

8 × oral placebo tablets BID 12 hours apart with water for 12 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:

Placebo tablets were administered orally

Number of subjects in period 1[1]	Alvelestat 120 mg	Alvelestat 240 mg	Placebo
Started	22	40	36
Received at least 1 dose of study drug	22	40	36
Completed	14	29	33
Not completed	8	11	3
Adverse event, non-fatal	2	11	-
Withdrew due to COVID-19 restrictions	6	-	3

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: 1 participant was randomized to alvelestat 240 mg but did not receive study treatment.

Baseline characteristics

Reporting groups	
Reporting group title	Alvelestat 120 mg
Reporting group description:	
4 × 30 mg alvelestat and 4 × 30 mg placebo oral tablets taken twice daily (BID) 12 hours apart with water for 12 weeks.	
Reporting group title	Alvelestat 240 mg
Reporting group description:	
8 × 30 mg alvelestat oral tablets BID 12 hours apart with water for 12 weeks.	
Reporting group title	Placebo
Reporting group description:	
8 × oral placebo tablets BID 12 hours apart with water for 12 weeks.	

Reporting group values	Alvelestat 120 mg	Alvelestat 240 mg	Placebo
Number of subjects	22	40	36
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	55.5	59.8	55.3
standard deviation	± 9.67	± 9.25	± 8.05
Sex: Female, Male Units: participants			
Female	18	27	14
Male	4	13	22
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	0	0
White	22	40	36
More than one race	0	0	0
Unknown or Not Reported	0	0	0

Reporting group values	Total		
Number of subjects	98		

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 standard deviation	- 		
Sex: Female, Male Units: participants			
Female Male	59 39		
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native Asian Native Hawaiian or Other Pacific Islander Black or African American White More than one race Unknown or Not Reported	0 0 0 0 98 0 0		

End points

End points reporting groups

Reporting group title	Alvelestat 120 mg
Reporting group description:	
4 × 30 mg alvelestat and 4 × 30 mg placebo oral tablets taken twice daily (BID) 12 hours apart with water for 12 weeks.	
Reporting group title	Alvelestat 240 mg
Reporting group description:	
8 × 30 mg alvelestat oral tablets BID 12 hours apart with water for 12 weeks.	
Reporting group title	Placebo
Reporting group description:	
8 × oral placebo tablets BID 12 hours apart with water for 12 weeks.	

Primary: Percent Change from Baseline to End of Treatment in Blood Neutrophil Elastase Activity

End point title	Percent Change from Baseline to End of Treatment in Blood Neutrophil Elastase Activity
End point description:	
Percent change of Blood Neutrophil Elastase (NE) Activity is reported. To fulfil the residual normality assumptions of the model for NE serum, a log transformation was applied. The log ratio defined as log (visit value or EndPoint value / baseline value) was used as the dependent variable in place of the percentage change in the MMRM model. Therefore, the back-transformed least squares mean (LSM) values were obtained by applying the formula [exp(LSM) -1]×100%.	
End point type	Primary
End point timeframe:	
Baseline, Weeks 4, 8, and 12	

End point values	Alvelestat 120 mg	Alvelestat 240 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	17	28	32	
Units: Percent change from Baseline				
least squares mean (standard error)				
Week 4	-90.0 (± 0.68)	-90.0 (± 0.54)	-18.1 (± 0.42)	
Week 8	-86.5 (± 0.80)	-93.3 (± 0.52)	-25.9 (± 0.44)	
Week 12	-83.5 (± 0.83)	-93.3 (± 0.53)	-18.1 (± 0.38)	

Statistical analyses

Statistical analysis title	Alvelestat 120mg vs Placebo at Week 12
Statistical analysis description:	
Analysis was performed on the Per-Protocol analysis set. 42 participants were evaluable at the Week 12 time point.	
Comparison groups	Alvelestat 120 mg v Placebo

Number of subjects included in analysis	49
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001
Method	Mixed Models Repeated Measures

Statistical analysis title	Alvelestat 240mg vs Placebo at Week 12

Statistical analysis description:

Analysis was performed on the Per-Protocol analysis set. 52 participants were evaluable at the Week 12 time point.

Comparison groups	Alvelestat 240 mg v Placebo
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed Models Repeated Measures

Primary: Percent Change From Baseline to End of Treatment in Plasma Aα-Val360

End point title	Percent Change From Baseline to End of Treatment in Plasma Aα-Val360

End point description:

Percent change of Plasma Aα-Val360 is reported as [(measure at time t - measure at baseline)/measure at baseline * 100%]

End point type	Primary

End point timeframe:

Baseline, Weeks 4, 8, and 12

End point values	Alvelestat 120 mg	Alvelestat 240 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	15	25	31	
Units: Percent change from Baseline				
least squares mean (standard error)				
Week 4	-18.7 (± 8.98)	-2.0 (± 8.36)	10.3 (± 6.96)	
Week 8	-11.3 (± 8.84)	-15.0 (± 7.85)	17.0 (± 9.57)	
Week 12	4.1 (± 13.60)	-22.7 (± 7.46)	11.7 (± 8.24)	

Statistical analyses

Statistical analysis title	Alvelestat 120mg vs Placebo at Week 12

Statistical analysis description:

Analysis was performed on the Per-Protocol analysis set. 41 participants were evaluable at the Week 12 time point.

Comparison groups	Alvelestat 120 mg v Placebo
Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.533
Method	Mixed Models Repeated Measures

Statistical analysis title	Alvelestat 240mg vs Placebo at Week 12
Statistical analysis description:	
Analysis was performed on the Per-Protocol analysis set. 49 participants were evaluable at the Week 12 time point.	
Comparison groups	Alvelestat 240 mg v Placebo
Number of subjects included in analysis	56
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001
Method	Mixed Models Repeated Measures

Primary: Percent Change From Baseline to End of Treatment in Plasma Desmosine

End point title	Percent Change From Baseline to End of Treatment in Plasma Desmosine
End point description:	
Percent change of Plasma Desmosine is reported as [(measure at time t - measure at baseline)/measure at baseline * 100%]	
End point type	Primary
End point timeframe:	
Baseline, Weeks 4, 8, and 12	

End point values	Alvelestat 120 mg	Alvelestat 240 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	17	28	32	
Units: Percent change from Baseline				
least squares mean (standard error)				
Week 4	9.3 (± 10.47)	-11.0 (± 7.65)	10.1 (± 5.77)	
Week 8	23.2 (± 11.93)	-14.0 (± 7.65)	17.9 (± 6.65)	
Week 12	29.2 (± 11.59)	-13.2 (± 7.42)	18.1 (± 6.64)	

Statistical analyses

Statistical analysis title	Alvelestat 120mg vs Placebo at Week 12

Statistical analysis description:

Analysis was performed on the Per-Protocol analysis set. 43 participants were evaluable at the Week 12 time point.

Comparison groups	Alvelestat 120 mg v Placebo
Number of subjects included in analysis	49
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.922
Method	Mixed Models Repeated Measures

Statistical analysis title	Alvelestat 240mg vs Placebo at Week 12

Statistical analysis description:

Analysis was performed on the Per-Protocol analysis set. 53 participants were evaluable at the Week 12 time point.

Comparison groups	Alvelestat 240 mg v Placebo
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.041
Method	Mixed Models Repeated Measures

Secondary: Alvelestat Plasma Concentrations by Visit

End point title	Alvelestat Plasma Concentrations by Visit[1]

End point description:

End point type	Secondary

End point timeframe:

Up to Week 12

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only study-drug arms were analyzed for this measure.

End point values	Alvelestat 120 mg	Alvelestat 240 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	40		
Units: nanogram per milliliter (ng/mL)				
geometric mean (geometric coefficient of variation)				
Baseline - Predose	4.5494 (± 136.1)	0.5410 (± 99999)		
Baseline - Post-dose 1-2 hours(h)	904.4804 (± 40.3)	1126.7272 (± 56.3)		
Week 4 - Predose	356.83 (± 79.5)	661.31 (± 53.4)		
Week 4 - Post-dose 1-2 h	1241.03 (± 40.4)	2242.14 (± 37.2)		
Week 8 - Predose	402.5 (± 43.1)	670.1 (± 50.9)		

Week 8 - Post-dose 1-2 h	1327.7 (± 32.3)	2342.9 (± 35.2)		
Week 12 - Predose	350.0140 (± 57.3)	120.2227 (± 100.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Active Neutrophil Elastase Concentration Below the Limit of Detection (<LLOQ)

End point title	Number of Participants with Active Neutrophil Elastase Concentration Below the Limit of Detection (<LLOQ)
End point description:	
End point type	Secondary
End point timeframe:	
Up to week 12	

End point values	Alvelestat 120 mg	Alvelestat 240 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	18	34	32	
Units: Participants				
Baseline	1	2	3	
Week 4	8	14	8	
Week 8	6	15	8	
Week 12	5	15	5	

Statistical analyses

Statistical analysis title	Alvelestat 120mg vs Placebo at Week 12
Comparison groups	Alvelestat 120 mg v Placebo
Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.729
Method	Mixed Models Repeated Measures

Statistical analysis title	Alvelestat 240mg vs Placebo at Week 12
Comparison groups	Alvelestat 240 mg v Placebo

Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.002
Method	Mixed Models Repeated Measures

Secondary: Numbers of Participants Who Experienced At Least 1 Treatment-emergent Adverse Event (TEAE)

End point title	Numbers of Participants Who Experienced At Least 1 Treatment-emergent Adverse Event (TEAE)

End point description:

An Adverse Event (AE) was defined as any untoward medical occurrence in a participant or clinical investigation participant administered a pharmaceutical (investigational) product and which did not necessarily have to have a causal relationship with this treatment. TEAEs were events with start dates on or after the date of the first dose of study treatment and up to 28 days after the date of the last dose of study treatment or events with start dates prior to the date of the first dose of study treatment whose severity worsened on or after the date of the first dose of study treatment. A summary of serious and all other non-serious adverse events regardless of causality is located in the Reported Adverse Events module.

End point type	Secondary

End point timeframe:

Up to Week 16

End point values	Alvelestat 120 mg	Alvelestat 240 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	22	40	36	
Units: Participants	22	37	32	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Adverse Events of Special Interest (AESI)

End point title	Number of Participants with Adverse Events of Special Interest (AESI)

End point description:

Adverse events of special interest (AESIs) were defined as AEs associated with liver function abnormalities, corrected QT interval (QTc)/cardiac, infections, and neutropenia.

End point type	Secondary

End point timeframe:

Up to Week 16

End point values	Alvelestat 120 mg	Alvelestat 240 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	22	40	36	
Units: Participants	5	11	7	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: From first dose to 28 days after date of last dose (Up to Week 16)	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	24.1

Reporting groups	
Reporting group title	Alvelestat 120 mg
Reporting group description: 4 × 30 mg alvelestat and 4 × 30 mg placebo oral tablets taken twice daily (BID) 12 hours apart with water for 12 weeks.	
Reporting group title	Placebo
Reporting group description: 8 × oral placebo tablets BID 12 hours apart with water for 12 weeks.	
Reporting group title	Alvelestat 240 mg
Reporting group description: 8 × 30 mg alvelestat oral tablets BID 12 hours apart with water for 12 weeks.	

Serious adverse events	Alvelestat 120 mg	Placebo	Alvelestat 240 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 22 (4.55%)	0 / 36 (0.00%)	3 / 40 (7.50%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 22 (4.55%)	0 / 36 (0.00%)	2 / 40 (5.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	0 / 22 (0.00%)	0 / 36 (0.00%)	1 / 40 (2.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 22 (0.00%)	0 / 36 (0.00%)	1 / 40 (2.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Infections and infestations			
Gastroenteritis			
subjects affected / exposed	0 / 22 (0.00%)	0 / 36 (0.00%)	1 / 40 (2.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Alvelestat 120 mg	Placebo	Alvelestat 240 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	22 / 22 (100.00%)	32 / 36 (88.89%)	37 / 40 (92.50%)
Vascular disorders			
Hot flush			
subjects affected / exposed	1 / 22 (4.55%)	1 / 36 (2.78%)	2 / 40 (5.00%)
occurrences (all)	1	1	2
Hypertension			
subjects affected / exposed	0 / 22 (0.00%)	1 / 36 (2.78%)	1 / 40 (2.50%)
occurrences (all)	0	1	1
Varicose vein			
subjects affected / exposed	0 / 22 (0.00%)	1 / 36 (2.78%)	0 / 40 (0.00%)
occurrences (all)	0	1	0
General disorders and administration site conditions			
Non-cardiac chest pain			
subjects affected / exposed	0 / 22 (0.00%)	0 / 36 (0.00%)	1 / 40 (2.50%)
occurrences (all)	0	0	1
Asthenia			
subjects affected / exposed	0 / 22 (0.00%)	1 / 36 (2.78%)	0 / 40 (0.00%)
occurrences (all)	0	2	0
Fatigue			
subjects affected / exposed	1 / 22 (4.55%)	1 / 36 (2.78%)	2 / 40 (5.00%)
occurrences (all)	1	1	2
Feeling hot			
subjects affected / exposed	1 / 22 (4.55%)	0 / 36 (0.00%)	1 / 40 (2.50%)
occurrences (all)	1	0	1
Influenza like illness			

subjects affected / exposed	0 / 22 (0.00%)	2 / 36 (5.56%)	0 / 40 (0.00%)
occurrences (all)	0	2	0
Malaise			
subjects affected / exposed	0 / 22 (0.00%)	1 / 36 (2.78%)	0 / 40 (0.00%)
occurrences (all)	0	2	0
Oedema peripheral			
subjects affected / exposed	0 / 22 (0.00%)	0 / 36 (0.00%)	1 / 40 (2.50%)
occurrences (all)	0	0	1
Sensation of foreign body			
subjects affected / exposed	1 / 22 (4.55%)	0 / 36 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Swelling face			
subjects affected / exposed	0 / 22 (0.00%)	1 / 36 (2.78%)	0 / 40 (0.00%)
occurrences (all)	0	1	0
Thirst			
subjects affected / exposed	0 / 22 (0.00%)	0 / 36 (0.00%)	1 / 40 (2.50%)
occurrences (all)	0	0	1
Vaccination site pain			
subjects affected / exposed	0 / 22 (0.00%)	0 / 36 (0.00%)	1 / 40 (2.50%)
occurrences (all)	0	0	1
Pyrexia			
subjects affected / exposed	0 / 22 (0.00%)	0 / 36 (0.00%)	1 / 40 (2.50%)
occurrences (all)	0	0	1
Reproductive system and breast disorders			
Erectile dysfunction			
subjects affected / exposed	1 / 22 (4.55%)	0 / 36 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Amenorrhoea			
subjects affected / exposed	0 / 22 (0.00%)	0 / 36 (0.00%)	1 / 40 (2.50%)
occurrences (all)	0	0	1
Breast calcifications			
subjects affected / exposed	0 / 22 (0.00%)	1 / 36 (2.78%)	0 / 40 (0.00%)
occurrences (all)	0	1	0
Uterine haemorrhage			

subjects affected / exposed	0 / 22 (0.00%)	0 / 36 (0.00%)	1 / 40 (2.50%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 22 (4.55%)	3 / 36 (8.33%)	4 / 40 (10.00%)
occurrences (all)	1	3	4
Cough			
subjects affected / exposed	0 / 22 (0.00%)	2 / 36 (5.56%)	1 / 40 (2.50%)
occurrences (all)	0	3	1
Cough decreased			
subjects affected / exposed	0 / 22 (0.00%)	0 / 36 (0.00%)	1 / 40 (2.50%)
occurrences (all)	0	0	1
Dyspnoea			
subjects affected / exposed	2 / 22 (9.09%)	1 / 36 (2.78%)	3 / 40 (7.50%)
occurrences (all)	2	1	3
Epistaxis			
subjects affected / exposed	0 / 22 (0.00%)	1 / 36 (2.78%)	1 / 40 (2.50%)
occurrences (all)	0	2	1
Hypoxia			
subjects affected / exposed	0 / 22 (0.00%)	1 / 36 (2.78%)	0 / 40 (0.00%)
occurrences (all)	0	1	0
Lung disorder			
subjects affected / exposed	1 / 22 (4.55%)	0 / 36 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Nasal congestion			
subjects affected / exposed	0 / 22 (0.00%)	1 / 36 (2.78%)	0 / 40 (0.00%)
occurrences (all)	0	1	0
Oropharyngeal pain			
subjects affected / exposed	0 / 22 (0.00%)	0 / 36 (0.00%)	1 / 40 (2.50%)
occurrences (all)	0	0	1
Pulmonary embolism			
subjects affected / exposed	0 / 22 (0.00%)	0 / 36 (0.00%)	1 / 40 (2.50%)
occurrences (all)	0	0	1
Rhinorrhoea			

subjects affected / exposed	0 / 22 (0.00%)	0 / 36 (0.00%)	1 / 40 (2.50%)
occurrences (all)	0	0	1
Sinus congestion			
subjects affected / exposed	0 / 22 (0.00%)	1 / 36 (2.78%)	0 / 40 (0.00%)
occurrences (all)	0	1	0
Sputum decreased			
subjects affected / exposed	0 / 22 (0.00%)	0 / 36 (0.00%)	1 / 40 (2.50%)
occurrences (all)	0	0	1
Sputum increased			
subjects affected / exposed	0 / 22 (0.00%)	2 / 36 (5.56%)	2 / 40 (5.00%)
occurrences (all)	0	2	2
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 22 (0.00%)	1 / 36 (2.78%)	1 / 40 (2.50%)
occurrences (all)	0	1	1
Insomnia			
subjects affected / exposed	1 / 22 (4.55%)	0 / 36 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Sleep disorder			
subjects affected / exposed	0 / 22 (0.00%)	0 / 36 (0.00%)	1 / 40 (2.50%)
occurrences (all)	0	0	1
Investigations			
Platelet count increased			
subjects affected / exposed	0 / 22 (0.00%)	0 / 36 (0.00%)	1 / 40 (2.50%)
occurrences (all)	0	0	1
Alanine aminotransferase increased			
subjects affected / exposed	1 / 22 (4.55%)	0 / 36 (0.00%)	2 / 40 (5.00%)
occurrences (all)	1	0	2
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 22 (4.55%)	0 / 36 (0.00%)	1 / 40 (2.50%)
occurrences (all)	1	0	1
Bilirubin conjugated increased			
subjects affected / exposed	1 / 22 (4.55%)	0 / 36 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Blood bilirubin increased			

subjects affected / exposed	1 / 22 (4.55%)	0 / 36 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Blood cholesterol increased			
subjects affected / exposed	0 / 22 (0.00%)	0 / 36 (0.00%)	1 / 40 (2.50%)
occurrences (all)	0	0	1
Blood creatine phosphokinase increased			
subjects affected / exposed	1 / 22 (4.55%)	1 / 36 (2.78%)	0 / 40 (0.00%)
occurrences (all)	1	1	0
Blood triglycerides increased			
subjects affected / exposed	0 / 22 (0.00%)	0 / 36 (0.00%)	1 / 40 (2.50%)
occurrences (all)	0	0	1
Creatinine renal clearance decreased			
subjects affected / exposed	0 / 22 (0.00%)	1 / 36 (2.78%)	0 / 40 (0.00%)
occurrences (all)	0	1	0
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 22 (0.00%)	0 / 36 (0.00%)	1 / 40 (2.50%)
occurrences (all)	0	0	1
Eosinophil count increased			
subjects affected / exposed	1 / 22 (4.55%)	0 / 36 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Escherichia test positive			
subjects affected / exposed	0 / 22 (0.00%)	1 / 36 (2.78%)	0 / 40 (0.00%)
occurrences (all)	0	1	0
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 22 (4.55%)	0 / 36 (0.00%)	1 / 40 (2.50%)
occurrences (all)	1	0	1
Glomerular filtration rate decreased			
subjects affected / exposed	0 / 22 (0.00%)	0 / 36 (0.00%)	1 / 40 (2.50%)
occurrences (all)	0	0	1
Prothrombin time prolonged			
subjects affected / exposed	1 / 22 (4.55%)	0 / 36 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Injury, poisoning and procedural complications			

Animal bite			
subjects affected / exposed	0 / 22 (0.00%)	0 / 36 (0.00%)	1 / 40 (2.50%)
occurrences (all)	0	0	1
Arthropod bite			
subjects affected / exposed	0 / 22 (0.00%)	1 / 36 (2.78%)	0 / 40 (0.00%)
occurrences (all)	0	1	0
Foreign body in respiratory tract			
subjects affected / exposed	0 / 22 (0.00%)	0 / 36 (0.00%)	1 / 40 (2.50%)
occurrences (all)	0	0	1
Post procedural haematoma			
subjects affected / exposed	0 / 22 (0.00%)	1 / 36 (2.78%)	0 / 40 (0.00%)
occurrences (all)	0	1	0
Tendon injury			
subjects affected / exposed	0 / 22 (0.00%)	1 / 36 (2.78%)	0 / 40 (0.00%)
occurrences (all)	0	1	0
Tooth fracture			
subjects affected / exposed	0 / 22 (0.00%)	0 / 36 (0.00%)	1 / 40 (2.50%)
occurrences (all)	0	0	1
Nervous system disorders			
Dizziness			
subjects affected / exposed	2 / 22 (9.09%)	0 / 36 (0.00%)	4 / 40 (10.00%)
occurrences (all)	4	0	5
Dizziness postural			
subjects affected / exposed	0 / 22 (0.00%)	0 / 36 (0.00%)	1 / 40 (2.50%)
occurrences (all)	0	0	1
Head discomfort			
subjects affected / exposed	1 / 22 (4.55%)	0 / 36 (0.00%)	0 / 40 (0.00%)
occurrences (all)	2	0	0
Headache			
subjects affected / exposed	7 / 22 (31.82%)	11 / 36 (30.56%)	20 / 40 (50.00%)
occurrences (all)	13	32	35
Migraine			
subjects affected / exposed	0 / 22 (0.00%)	0 / 36 (0.00%)	2 / 40 (5.00%)
occurrences (all)	0	0	2
Syncope			

subjects affected / exposed	0 / 22 (0.00%)	0 / 36 (0.00%)	1 / 40 (2.50%)
occurrences (all)	0	0	1
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	0 / 22 (0.00%)	1 / 36 (2.78%)	1 / 40 (2.50%)
occurrences (all)	0	1	1
Ear pain			
subjects affected / exposed	0 / 22 (0.00%)	1 / 36 (2.78%)	0 / 40 (0.00%)
occurrences (all)	0	1	0
Eye disorders			
Blepharitis			
subjects affected / exposed	1 / 22 (4.55%)	0 / 36 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Glaucoma			
subjects affected / exposed	1 / 22 (4.55%)	0 / 36 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Eye swelling			
subjects affected / exposed	0 / 22 (0.00%)	1 / 36 (2.78%)	0 / 40 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 22 (4.55%)	0 / 36 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Abdominal pain upper			
subjects affected / exposed	0 / 22 (0.00%)	3 / 36 (8.33%)	0 / 40 (0.00%)
occurrences (all)	0	3	0
Constipation			
subjects affected / exposed	0 / 22 (0.00%)	1 / 36 (2.78%)	0 / 40 (0.00%)
occurrences (all)	0	1	0
Diarrhoea			
subjects affected / exposed	2 / 22 (9.09%)	1 / 36 (2.78%)	0 / 40 (0.00%)
occurrences (all)	2	1	0
Dry mouth			
subjects affected / exposed	0 / 22 (0.00%)	1 / 36 (2.78%)	0 / 40 (0.00%)
occurrences (all)	0	1	0
Dyspepsia			

subjects affected / exposed	0 / 22 (0.00%)	2 / 36 (5.56%)	2 / 40 (5.00%)
occurrences (all)	0	2	2
Enteritis			
subjects affected / exposed	0 / 22 (0.00%)	1 / 36 (2.78%)	0 / 40 (0.00%)
occurrences (all)	0	1	0
Eructation			
subjects affected / exposed	0 / 22 (0.00%)	2 / 36 (5.56%)	0 / 40 (0.00%)
occurrences (all)	0	2	0
Flatulence			
subjects affected / exposed	0 / 22 (0.00%)	1 / 36 (2.78%)	1 / 40 (2.50%)
occurrences (all)	1	3	1
Frequent bowel movements			
subjects affected / exposed	0 / 22 (0.00%)	1 / 36 (2.78%)	0 / 40 (0.00%)
occurrences (all)	0	1	0
Gastritis			
subjects affected / exposed	2 / 22 (9.09%)	0 / 36 (0.00%)	0 / 40 (0.00%)
occurrences (all)	2	0	0
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 22 (0.00%)	1 / 36 (2.78%)	1 / 40 (2.50%)
occurrences (all)	0	1	5
Nausea			
subjects affected / exposed	4 / 22 (18.18%)	1 / 36 (2.78%)	5 / 40 (12.50%)
occurrences (all)	4	1	8
Vomiting			
subjects affected / exposed	1 / 22 (4.55%)	0 / 36 (0.00%)	2 / 40 (5.00%)
occurrences (all)	1	0	2
Skin and subcutaneous tissue disorders			
Erythema			
subjects affected / exposed	0 / 22 (0.00%)	0 / 36 (0.00%)	1 / 40 (2.50%)
occurrences (all)	0	0	2
Pruritus			
subjects affected / exposed	0 / 22 (0.00%)	1 / 36 (2.78%)	2 / 40 (5.00%)
occurrences (all)	0	2	3
Rash			
subjects affected / exposed	1 / 22 (4.55%)	0 / 36 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0

Acne			
subjects affected / exposed	0 / 22 (0.00%)	0 / 36 (0.00%)	1 / 40 (2.50%)
occurrences (all)	0	0	1
Alopecia			
subjects affected / exposed	0 / 22 (0.00%)	1 / 36 (2.78%)	1 / 40 (2.50%)
occurrences (all)	0	1	1
Renal and urinary disorders			
Glycosuria			
subjects affected / exposed	0 / 22 (0.00%)	0 / 36 (0.00%)	1 / 40 (2.50%)
occurrences (all)	0	0	1
Pollakiuria			
subjects affected / exposed	0 / 22 (0.00%)	2 / 36 (5.56%)	0 / 40 (0.00%)
occurrences (all)	0	2	0
Polyuria			
subjects affected / exposed	0 / 22 (0.00%)	0 / 36 (0.00%)	1 / 40 (2.50%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 22 (4.55%)	1 / 36 (2.78%)	1 / 40 (2.50%)
occurrences (all)	1	1	1
Back pain			
subjects affected / exposed	1 / 22 (4.55%)	0 / 36 (0.00%)	2 / 40 (5.00%)
occurrences (all)	1	0	2
Costochondritis			
subjects affected / exposed	1 / 22 (4.55%)	0 / 36 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Flank pain			
subjects affected / exposed	0 / 22 (0.00%)	1 / 36 (2.78%)	0 / 40 (0.00%)
occurrences (all)	0	3	0
Myalgia			
subjects affected / exposed	0 / 22 (0.00%)	1 / 36 (2.78%)	1 / 40 (2.50%)
occurrences (all)	0	1	1
Pain in extremity			
subjects affected / exposed	0 / 22 (0.00%)	1 / 36 (2.78%)	1 / 40 (2.50%)
occurrences (all)	0	1	1
Infections and infestations			

Tooth abscess			
subjects affected / exposed	1 / 22 (4.55%)	0 / 36 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
COVID-19			
subjects affected / exposed	0 / 22 (0.00%)	4 / 36 (11.11%)	2 / 40 (5.00%)
occurrences (all)	0	4	2
Cystitis			
subjects affected / exposed	1 / 22 (4.55%)	0 / 36 (0.00%)	1 / 40 (2.50%)
occurrences (all)	1	0	1
Erysipelas			
subjects affected / exposed	1 / 22 (4.55%)	0 / 36 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Escherichia urinary tract infection			
subjects affected / exposed	0 / 22 (0.00%)	1 / 36 (2.78%)	0 / 40 (0.00%)
occurrences (all)	0	1	0
Folliculitis			
subjects affected / exposed	0 / 22 (0.00%)	1 / 36 (2.78%)	0 / 40 (0.00%)
occurrences (all)	0	1	0
Gastroenteritis			
subjects affected / exposed	0 / 22 (0.00%)	0 / 36 (0.00%)	1 / 40 (2.50%)
occurrences (all)	0	0	1
Gastroenteritis bacterial			
subjects affected / exposed	0 / 22 (0.00%)	0 / 36 (0.00%)	1 / 40 (2.50%)
occurrences (all)	0	0	1
Gastroenteritis viral			
subjects affected / exposed	0 / 22 (0.00%)	1 / 36 (2.78%)	0 / 40 (0.00%)
occurrences (all)	0	1	0
Infective exacerbation of chronic obstructive airways disease			
subjects affected / exposed	0 / 22 (0.00%)	1 / 36 (2.78%)	3 / 40 (7.50%)
occurrences (all)	0	1	4
Lower respiratory tract infection			
subjects affected / exposed	2 / 22 (9.09%)	0 / 36 (0.00%)	0 / 40 (0.00%)
occurrences (all)	2	0	0
Lower respiratory tract infection bacterial			

subjects affected / exposed	0 / 22 (0.00%)	1 / 36 (2.78%)	0 / 40 (0.00%)
occurrences (all)	0	1	0
Nasopharyngitis			
subjects affected / exposed	0 / 22 (0.00%)	4 / 36 (11.11%)	4 / 40 (10.00%)
occurrences (all)	0	4	4
Oral candidiasis			
subjects affected / exposed	1 / 22 (4.55%)	0 / 36 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Pneumonia			
subjects affected / exposed	0 / 22 (0.00%)	2 / 36 (5.56%)	0 / 40 (0.00%)
occurrences (all)	0	2	0
Respiratory tract infection			
subjects affected / exposed	2 / 22 (9.09%)	0 / 36 (0.00%)	2 / 40 (5.00%)
occurrences (all)	2	0	2
Rhinitis			
subjects affected / exposed	0 / 22 (0.00%)	1 / 36 (2.78%)	1 / 40 (2.50%)
occurrences (all)	0	1	1
Upper respiratory tract infection			
subjects affected / exposed	0 / 22 (0.00%)	1 / 36 (2.78%)	1 / 40 (2.50%)
occurrences (all)	0	1	1
Viral infection			
subjects affected / exposed	1 / 22 (4.55%)	0 / 36 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 22 (0.00%)	0 / 36 (0.00%)	1 / 40 (2.50%)
occurrences (all)	0	0	1
Urinary tract infection			
subjects affected / exposed	1 / 22 (4.55%)	1 / 36 (2.78%)	1 / 40 (2.50%)
occurrences (all)	1	1	1
Metabolism and nutrition disorders			
Type 2 diabetes mellitus			
subjects affected / exposed	0 / 22 (0.00%)	1 / 36 (2.78%)	0 / 40 (0.00%)
occurrences (all)	0	1	0
Decreased appetite			
subjects affected / exposed	0 / 22 (0.00%)	1 / 36 (2.78%)	1 / 40 (2.50%)
occurrences (all)	0	2	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 May 2018	Clarifications and corrections.
02 July 2018	Amendments to inclusion/exclusion criteria and treatment discontinuation criteria for liver function tests at request of FDA.
15 August 2018	Amendments to the exclusion criteria and description of a potential non-clinical safety risk of phototoxicity and the protective measures for participants to minimize exposure to UV radiation at the request of the FDA.
30 July 2019	Clarifications and corrections. Amendments to remove the procedures for phototoxicity and the protective measures for participants to minimize exposure to UV radiation.
05 December 2019	Introduction of within participant dose escalation to improve participant tolerability of the 240 mg bid dose. Simplifications of the protocol.
07 June 2021	Clarifications and corrections. Amendments to inclusion/exclusion criteria and Concomitant Therapy information
16 November 2021	Clarifications and corrections. Change to study design from single primary endpoint proof of concept design to multiple (3 mechanistic) primary endpoint, signal-seeking, weight of evidence design with related changes throughout.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
30 March 2022	Trial terminated early due to recruitment difficulties during COVID-19.	-

Notes:

Limitations and caveats

None reported