



Clinical trial results:

A Double-Blind, Placebo-Controlled, Phase 2a Study to Assess the Safety, Tolerability, and Efficacy of ION-827359 in Patients with Mild to Moderate COPD with Chronic Bronchitis

Summary

EudraCT number	2020-000210-15
Trial protocol	GB DE HU CZ PL IT
Global end of trial date	09 August 2021

Results information

Result version number	v1 (current)
This version publication date	05 January 2023
First version publication date	05 January 2023

Trial information

Trial identification

Sponsor protocol code	ION-827359-CS2
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04441788
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Ionis Pharmaceuticals, Inc.
Sponsor organisation address	2855 Gazelle Court, Carlsbad, CA, United States,
Public contact	Ionis Clinical Trial, Ionis Pharmaceuticals, Inc., +1 760 603 3890, ClinicalTrials@ionisph.com
Scientific contact	Ionis Clinical Trial, Ionis Pharmaceuticals, Inc., +1 760 603 3890, ClinicalTrials@ionisph.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	09 August 2021
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	09 August 2021
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study was to evaluate the effect of ION-827359 on forced expiratory volume in 1 second (FEV1) in subjects with mild to moderate chronic obstructive pulmonary disease (COPD) with chronic bronchitis (CB).

Protection of trial subjects:

All study subjects were required to read and sign an Informed Consent Form.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	22 December 2020
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 5
Country: Number of subjects enrolled	Czechia: 5
Country: Number of subjects enrolled	Germany: 45
Country: Number of subjects enrolled	Hungary: 5
Worldwide total number of subjects	60
EEA total number of subjects	55

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)	40
From 65 to 84 years	20

85 years and over	0
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Subject disposition

Recruitment

Recruitment details:

60 subjects were randomised at 11 study centres in Czech Republic, Germany, Hungary and the United Kingdom.

Pre-assignment

Screening details:

Of the 60 randomised subjects, one was randomised but did not receive study treatment as the subject was ineligible. The study included an 8-week screening period (including a diet-stabilisation period), a 52-week treatment period, and a 13-week post-treatment evaluation period.

Pre-assignment period milestones

Number of subjects started	60
Number of subjects completed	59

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Ineligibility: 1
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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
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Arm title	Placebo
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Arm description:

Single-dose of placebo was administered by oral inhalation via nebuliser, once every week for up to 13 weeks.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

Placebo was administered once weekly for 13 weeks.

Arm title	ION-827359 37.5 milligrams (mg)
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Arm description:

Single-dose of ION-827359 37.5 mg was administered by oral inhalation via nebuliser, once every week for up to 13 weeks.

Arm type	Experimental
Investigational medicinal product name	ION-827359
Investigational medicinal product code	
Other name	Antisense Inhibitor of Epithelial Sodium Channel (ENaCRx)
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

ION-827359 37.5 mg was administered once weekly for 13 weeks.

Arm title	ION-827359 75 mg
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Arm description:

Single-dose of ION-827359 75 mg was administered by oral inhalation via nebuliser, once every week for up to 13 weeks.

Arm type	Experimental
Investigational medicinal product name	ION-827359
Investigational medicinal product code	
Other name	ENaCRx
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

ION-827359 75 mg was administered once weekly for 13 weeks.

Number of subjects in period 1^[1]	Placebo	ION-827359 37.5 milligrams (mg)	ION-827359 75 mg
Started	19	21	19
Completed	17	20	18
Not completed	2	1	1
Voluntary Withdrawal	1	1	-
Reason not specified	1	-	1

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: Of the 60 randomised subjects, one was randomised but did not receive study treatment due to ineligibility.

Baseline characteristics

Reporting groups

Reporting group title	Placebo
Reporting group description:	
Single-dose of placebo was administered by oral inhalation via nebuliser, once every week for up to 13 weeks.	
Reporting group title	ION-827359 37.5 milligrams (mg)
Reporting group description:	
Single-dose of ION-827359 37.5 mg was administered by oral inhalation via nebuliser, once every week for up to 13 weeks.	
Reporting group title	ION-827359 75 mg
Reporting group description:	
Single-dose of ION-827359 75 mg was administered by oral inhalation via nebuliser, once every week for up to 13 weeks.	

Reporting group values	Placebo	ION-827359 37.5 milligrams (mg)	ION-827359 75 mg
Number of subjects	19	21	19
Age categorical			
Units: Subjects			

Age continuous			
Units: years			
arithmetic mean	61.3	61.8	61.8
standard deviation	± 4.54	± 5.86	± 5.39
Gender categorical			
Units: Subjects			
Female	9	7	5
Male	10	14	14
Ethnicity			
Units: Subjects			
Not Hispanic or Latino	19	21	19
Race			
Units: Subjects			
White	19	21	18
More than one race	0	0	1
Forced Expiratory Volume in 1 second (FEV1)			
FEV1 is the amount of air which can be forcibly exhaled from the lungs in the first second of a forced exhalation.			
Units: litres			
arithmetic mean	1.8317	1.9311	1.6536
standard deviation	± 0.4670	± 0.6608	± 0.3498

Reporting group values	Total		
Number of subjects	59		
Age categorical			
Units: Subjects			

Age continuous Units: years arithmetic mean standard deviation	-		
Gender categorical Units: Subjects			
Female	21		
Male	38		
Ethnicity Units: Subjects			
Not Hispanic or Latino	59		
Race Units: Subjects			
White	58		
More than one race	1		
Forced Expiratory Volume in 1 second (FEV1)			
FEV1 is the amount of air which can be forcibly exhaled from the lungs in the first second of a forced exhalation.			
Units: litres arithmetic mean standard deviation	-		

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description: Single-dose of placebo was administered by oral inhalation via nebuliser, once every week for up to 13 weeks.	
Reporting group title	ION-827359 37.5 milligrams (mg)
Reporting group description: Single-dose of ION-827359 37.5 mg was administered by oral inhalation via nebuliser, once every week for up to 13 weeks.	
Reporting group title	ION-827359 75 mg
Reporting group description: Single-dose of ION-827359 75 mg was administered by oral inhalation via nebuliser, once every week for up to 13 weeks.	

Primary: Change From Baseline to the Primary Time Point in Forced Expiratory Volume in 1 Second (FEV1) Compared to Placebo

End point title	Change From Baseline to the Primary Time Point in Forced Expiratory Volume in 1 Second (FEV1) Compared to Placebo ^[1]
End point description: FEV1 is the amount of air which can be forcibly exhaled from the lungs in the first second of a forced exhalation. Baseline was defined as the last non-missing measurement prior to the first study drug administration. The primary time point was defined as the average of Weeks 13 and 14. The change to the primary time point was calculated as the average values of assessments at Weeks 13 and 14. Full Analysis Set (FAS) included all randomised subjects who received at least 1 dose of study drug (ION827359 or placebo) and who had at least 1 post-Baseline efficacy assessment (i.e., post-Baseline FEV1 assessment, Exacerbations of Chronic pulmonary Disease Tool [EXACT] Respiratory Symptoms (E-RS) score, Chronic Obstructive Pulmonary Disease [COPD] Assessment Test (CAT) score, or St. George's Respiratory Questionnaire - COPD Specific (SGRQ-C score), post-bronchodilator FEV1 assessment. Number of subjects analysed is the number of subjects with data available for analyses in this end point.	
End point type	Primary
End point timeframe: Baseline, Weeks 13 and 14	
Notes: [1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point. Justification: Only descriptive statistics were planned to be reported for this end point.	

End point values	Placebo	ION-827359 37.5 milligrams (mg)	ION-827359 75 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	5	5	4	
Units: litres				
arithmetic mean (standard deviation)	0.0642 (± 0.2506)	-0.0240 (± 0.3581)	0.1336 (± 0.1087)	

Statistical analyses

Secondary: Change From Baseline in the Exacerbations of Chronic Pulmonary Disease Tool [EXACT] Respiratory Symptoms (E-RS) Daily Symptom Diary Total Score to the Primary Time Point

End point title	Change From Baseline in the Exacerbations of Chronic Pulmonary Disease Tool [EXACT] Respiratory Symptoms (E-RS) Daily Symptom Diary Total Score to the Primary Time Point
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End point description:

The E-RS scale is a patient-reported outcome (PRO) designed to measure the symptoms of subjects with chronic obstructive pulmonary disease (COPD). It utilizes 11 respiratory symptom items from the 14-item EXACT, which measures symptoms of exacerbation. The E-RS total score quantifies respiratory symptom severity, and 3 domains assess breathlessness (comprised of 5 items, score range [0-17]), cough and sputum (comprised of 3 items, score range [0-11]), and chest symptoms (comprised of 3 items, score range [0-12]). The total score was derived by summing the 11-item scores and ranged between 0-40 with higher values indicating severe respiratory symptoms. The primary time point was defined as the average of Weeks 13 and 14. The change to the primary time point was calculated as the average values of assessments at Weeks 13 and 14. FAS population was used in this end point.

End point type	Secondary
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End point timeframe:

Baseline, Weeks 13 and 14

End point values	Placebo	ION-827359 37.5 milligrams (mg)	ION-827359 75 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	4	5	4	
Units: score on a scale				
arithmetic mean (standard deviation)	-1.08 (± 1.171)	-1.41 (± 2.486)	-1.99 (± 4.217)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in the Chronic Obstructive Pulmonary Disease [COPD] Assessment Test (CAT) to the Week 14 Time Point

End point title	Change From Baseline in the Chronic Obstructive Pulmonary Disease [COPD] Assessment Test (CAT) to the Week 14 Time Point
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End point description:

The CAT is an eight-item questionnaire that will be completed by the subject and is designed to quantify the impact of COPD symptoms on the health status of subjects. Each item is rated on a 6-point scale ranging from 0 (no impairment) to 5 (maximum impairment). The total CAT score is calculated by summing the scores of all items and ranges from 0 to 40. Higher scores indicate a severe condition (more severe impact of COPD on a subject's life). FAS included all randomised subjects who received at least 1 dose of study drug (ION827359 or placebo) and who had at least 1 post-Baseline efficacy assessment (i.e., post-Baseline FEV1 assessment, E-RS score, CAT score, or SGRQ-C score). Number of subjects analysed is the number of subjects with data available for analyses in this end point.

End point type	Secondary
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End point timeframe:

From Baseline to Week 14

End point values	Placebo	ION-827359 37.5 milligrams (mg)	ION-827359 75 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	5	5	3	
Units: score on a scale				
arithmetic mean (standard deviation)	-2.6 (\pm 2.51)	-0.6 (\pm 3.78)	0.0 (\pm 1.73)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in St. George's Respiratory Questionnaire - COPD Specific (SGRQ-C) Total Score to the Week 14 Time Point

End point title	Change From Baseline in St. George's Respiratory Questionnaire - COPD Specific (SGRQ-C) Total Score to the Week 14 Time Point
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End point description:

The SGRQ is a subject completed, a disease-specific instrument designed to measure impact on overall health, daily life, and perceived well-being in subjects with obstructive airway disease. The shorter 40-item version (SGRQ-C) specifically for COPD subjects was used in this study. It consists of 40 items each weighted from 0 to a possible maximum of 100. Items 1-7 produced the symptoms score, 9-12 the activity score, and items 8, 10, 11, 13 and 14 the impacts score. Higher scores indicated a worse outcome (more limitations). FAS included all randomised subjects who received at least 1 dose of study drug (ION827359 or placebo) and who had at least 1 post-Baseline efficacy assessment (i.e., post-Baseline FEV1 assessment, E-RS score, CAT score, or SGRQ-C score). Number of subjects analysed is the number of subjects with data available for analyses in this end point.

End point type	Secondary
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End point timeframe:

From Baseline to Week 14

End point values	Placebo	ION-827359 37.5 milligrams (mg)	ION-827359 75 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	5	5	3	
Units: score on a scale				
arithmetic mean (standard deviation)	-15.93 (\pm 19.515)	-1.74 (\pm 3.839)	-0.76 (\pm 2.350)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Post-Bronchodilator FEV1

End point title	Change From Baseline in Post-Bronchodilator FEV1
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End point description:

Post-bronchodilator FEV1 is the amount of air which can be forcibly exhaled from the lungs in the first second of a forced exhalation after administration of bronchodilator. Baseline was defined as the last non-missing measurement prior to the first study drug administration. FAS included all randomised subjects who received at least 1 dose of study drug (ION827359 or placebo) and who had at least 1 post-Baseline efficacy assessment (i.e., post-Baseline FEV1 assessment, E-RS score, CAT score, or SGRQ-C score). Number of subjects analysed is the number of subjects with data available for analyses in this end point.

End point type	Secondary
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End point timeframe:

From Baseline to end of treatment (EOT) [Up to Week 14]

End point values	Placebo	ION-827359 37.5 milligrams (mg)	ION-827359 75 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	3	5	3	
Units: litres				
arithmetic mean (standard deviation)	0.0663 (± 0.0685)	0.0320 (± 0.2379)	0.1180 (± 0.1006)	

Statistical analyses

No statistical analyses for this end point

Secondary: Cmax: Maximum Observed Plasma Concentration for ION-827359

End point title	Cmax: Maximum Observed Plasma Concentration for ION-827359 ^[2]
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End point description:

PK population included all subjects who were randomised and received at least 1 dose of active study drug (ION-827359) and had at least 1 evaluable PK sample collected and analysed with reportable result. n=number of subjects with data available for analysis at the specified time point. 99999 denotes that the geometric coefficient of variation was not estimable due to lower number of subjects.

End point type	Secondary
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End point timeframe:

Days 1 and 85

Notes:

[2] - 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: This end point was planned to be analysed only in the ION-827359 37.5 mg and ION-827359 75 mg reporting groups.

End point values	ION-827359 37.5 milligrams (mg)	ION-827359 75 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	6		
Units: nanogram per millilitre (ng/mL)				
geometric mean (geometric coefficient				

of variation)				
Day 1 (n=6,6)	85.6 (± 198)	203 (± 52.6)		
Day 85 (n=1,2)	53.5 (± 99999)	195 (± 124)		

Statistical analyses

No statistical analyses for this end point

Secondary: Tmax: Time to Reach the Maximum Plasma Concentration for ION-827359

End point title	Tmax: Time to Reach the Maximum Plasma Concentration for ION-827359 ^[3]
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End point description:

PK population included all subjects who were randomised and received at least 1 dose of active study drug (ION-827359) and had at least 1 evaluable PK sample collected and analysed with reportable result. n=number of subjects with data available for analysis at the specified time point.

End point type	Secondary
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End point timeframe:

Days 1 and 85

Notes:

[3] - 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: This end point was planned to be analysed only in the ION-827359 37.5 mg and ION-827359 75 mg reporting groups.

End point values	ION-827359 37.5 milligrams (mg)	ION-827359 75 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	6		
Units: hours				
median (full range (min-max))				
Day 1 (n=6,6)	1.54 (0.567 to 2.05)	1.64 (0.667 to 2.12)		
Day 85 (n=1,2)	1.98 (1.98 to 1.98)	3.11 (1.73 to 4.48)		

Statistical analyses

No statistical analyses for this end point

Secondary: AUC[0-24h]: Area Under the Plasma Concentration-Time Curve From Time Zero to 24 Hours for ION-827359

End point title	AUC[0-24h]: Area Under the Plasma Concentration-Time Curve From Time Zero to 24 Hours for ION-827359 ^[4]
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End point description:

PK population included all subjects who were randomised and received at least 1 dose of active study drug (ION-827359) and had at least 1 evaluable PK sample collected and analysed with reportable result. n=number of subjects with data available for analysis at the specified time point. 99999 denotes that the geometric coefficient of variation was not estimable due to lower number of subjects.

End point type	Secondary
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End point timeframe:

Days 1 and 85

Notes:

[4] - 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: This end point was planned to be analysed only in the ION-827359 37.5 mg and ION-827359 75 mg reporting groups.

End point values	ION-827359 37.5 milligrams (mg)	ION-827359 75 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	6		
Units: hours*nanogram per millilitre (h*ng/mL)				
geometric mean (geometric coefficient of variation)				
Day 1 (n=6,6)	528 (± 190)	1323 (± 66.0)		
Day 85 (n=1,2)	312 (± 99999)	2416 (± 252)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With at Least One Treatment-Emergent Adverse Event (TEAE) Based on Severity

End point title	Percentage of Subjects With at Least One Treatment-Emergent Adverse Event (TEAE) Based on Severity
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End point description:

An adverse event (AE) can be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of medicinal (investigational) product, whether or not the AE is considered related to the medicinal (investigational) product. A TEAE is defined as any AE starting or getting worse on or after the first dose of the study drug. The severity of a TEAE was assessed by the investigator and classified into one of the following: mild, moderate, and severe. Safety population included all subjects who were randomised and received at least 1 dose of study drug.

End point type	Secondary
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End point timeframe:

Up to Week 24

End point values	Placebo	ION-827359 37.5 milligrams (mg)	ION-827359 75 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	19	21	19	
Units: percentage of subjects				
number (not applicable)				
Mild	10.5	14.3	15.8	
Moderate	52.6	38.1	63.2	
Severe	10.5	0	5.3	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Clinically Significant Change in Laboratory Values

End point title	Percentage of Subjects With Clinically Significant Change in Laboratory Values
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End point description:

Laboratory parameters for serum chemistry, haematology, urinalysis, coagulation, complement, and lipids were assessed. Safety population included all subjects who were randomised and received at least 1 dose of study drug.

End point type	Secondary
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End point timeframe:

Up to Week 24

End point values	Placebo	ION-827359 37.5 milligrams (mg)	ION-827359 75 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	19	21	19	
Units: percentage of subjects				
number (not applicable)	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Clinically Significant Change in Vital Signs

End point title	Percentage of Subjects With Clinically Significant Change in Vital Signs
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End point description:

Vital signs included assessment of heart rate, blood pressure, respiratory rate, and temperature. Safety population included all subjects who were randomised and received at least 1 dose of study drug.

End point type	Secondary
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End point timeframe:

Up to Week 24

End point values	Placebo	ION-827359 37.5 milligrams (mg)	ION-827359 75 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	19	21	19	
Units: percentage of subjects				
number (not applicable)	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Clinically Significant Change in Electrocardiogram (ECG) Findings

End point title	Percentage of Subjects With Clinically Significant Change in Electrocardiogram (ECG) Findings
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End point description:

ECG parameters of ventricular rate, PR interval, QRS duration, QT, or QTc were assessed. Safety population included all subjects who were randomised and received at least 1 dose of study drug.

End point type	Secondary
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End point timeframe:

Up to Week 24

End point values	Placebo	ION-827359 37.5 milligrams (mg)	ION-827359 75 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	19	21	19	
Units: percentage of subjects				
number (not applicable)	0	0	0	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to Week 24

Adverse event reporting additional description:

Safety population included all subjects who were randomised and received at least 1 dose of study drug.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	23.0
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Reporting groups

Reporting group title	Placebo
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Reporting group description:

Single-dose of placebo was administered by oral inhalation via nebuliser, once every week for up to 13 weeks

Reporting group title	ION-827359 37.5 mg
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Reporting group description:

Single-dose of ION-827359 37.5 mg was administered by oral inhalation via nebuliser, once every week for up to 13 weeks.

Reporting group title	ION-827359 75 mg
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Reporting group description:

Single-dose of ION-827359 75 mg was administered by oral inhalation via nebuliser, once every week for up to 13 weeks.

Serious adverse events	Placebo	ION-827359 37.5 mg	ION-827359 75 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 19 (5.26%)	1 / 21 (4.76%)	1 / 19 (5.26%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Cardiac disorders			
Atrial flutter			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	0 / 19 (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
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 19 (0.00%)	1 / 21 (4.76%)	0 / 19 (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
Respiratory, thoracic and mediastinal disorders			

Bronchospasm			
subjects affected / exposed	0 / 19 (0.00%)	0 / 21 (0.00%)	1 / 19 (5.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	0 / 19 (0.00%)	0 / 21 (0.00%)	1 / 19 (5.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Placebo	ION-827359 37.5 mg	ION-827359 75 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	14 / 19 (73.68%)	8 / 21 (38.10%)	16 / 19 (84.21%)
Vascular disorders			
Arteriosclerosis			
subjects affected / exposed	0 / 19 (0.00%)	0 / 21 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Peripheral vascular disorder			
subjects affected / exposed	0 / 19 (0.00%)	0 / 21 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
Burning sensation			
subjects affected / exposed	0 / 19 (0.00%)	2 / 21 (9.52%)	0 / 19 (0.00%)
occurrences (all)	0	6	0
Chest discomfort			
subjects affected / exposed	0 / 19 (0.00%)	0 / 21 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Cyst			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Pyrexia			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Immune system disorders			

Vaccination complication subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1	0 / 21 (0.00%) 0	0 / 19 (0.00%) 0
Respiratory, thoracic and mediastinal disorders			
Sputum increased subjects affected / exposed occurrences (all)	0 / 19 (0.00%) 0	0 / 21 (0.00%) 0	2 / 19 (10.53%) 4
Cough subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1	5 / 21 (23.81%) 11	7 / 19 (36.84%) 23
Chronic obstructive pulmonary disease subjects affected / exposed occurrences (all)	5 / 19 (26.32%) 6	0 / 21 (0.00%) 0	4 / 19 (21.05%) 5
Dyspnoea subjects affected / exposed occurrences (all)	0 / 19 (0.00%) 0	2 / 21 (9.52%) 4	5 / 19 (26.32%) 5
Chest pain subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1	0 / 21 (0.00%) 0	1 / 19 (5.26%) 1
Throat irritation subjects affected / exposed occurrences (all)	2 / 19 (10.53%) 5	0 / 21 (0.00%) 0	0 / 19 (0.00%) 0
Bronchial irritation subjects affected / exposed occurrences (all)	0 / 19 (0.00%) 0	0 / 21 (0.00%) 0	1 / 19 (5.26%) 1
Bronchospasm subjects affected / exposed occurrences (all)	0 / 19 (0.00%) 0	0 / 21 (0.00%) 0	1 / 19 (5.26%) 1
Dysphonia subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1	0 / 21 (0.00%) 0	0 / 19 (0.00%) 0
Nasal congestion subjects affected / exposed occurrences (all)	0 / 19 (0.00%) 0	0 / 21 (0.00%) 0	1 / 19 (5.26%) 1
Oropharyngeal pain			

subjects affected / exposed occurrences (all)	0 / 19 (0.00%) 0	0 / 21 (0.00%) 0	1 / 19 (5.26%) 1
Rhinitis subjects affected / exposed occurrences (all)	0 / 19 (0.00%) 0	0 / 21 (0.00%) 0	1 / 19 (5.26%) 3
Rhinorrhoea subjects affected / exposed occurrences (all)	0 / 19 (0.00%) 0	0 / 21 (0.00%) 0	1 / 19 (5.26%) 1
Sputum discoloured subjects affected / exposed occurrences (all)	0 / 19 (0.00%) 0	0 / 21 (0.00%) 0	1 / 19 (5.26%) 1
Psychiatric disorders Sleep disorder subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1	0 / 21 (0.00%) 0	0 / 19 (0.00%) 0
Product issues Product taste abnormal subjects affected / exposed occurrences (all)	0 / 19 (0.00%) 0	0 / 21 (0.00%) 0	1 / 19 (5.26%) 7
Investigations Blood creatine phosphokinase increased subjects affected / exposed occurrences (all)	0 / 19 (0.00%) 0	0 / 21 (0.00%) 0	1 / 19 (5.26%) 1
Blood glucose decreased subjects affected / exposed occurrences (all)	0 / 19 (0.00%) 0	0 / 21 (0.00%) 0	1 / 19 (5.26%) 1
FEV1/FVC ratio decreased subjects affected / exposed occurrences (all)	0 / 19 (0.00%) 0	0 / 21 (0.00%) 0	1 / 19 (5.26%) 2
SARS-CoV-2 test positive subjects affected / exposed occurrences (all)	0 / 19 (0.00%) 0	0 / 21 (0.00%) 0	1 / 19 (5.26%) 1
Injury, poisoning and procedural complications Skin laceration subjects affected / exposed occurrences (all)	0 / 19 (0.00%) 0	0 / 21 (0.00%) 0	1 / 19 (5.26%) 1

Cardiac disorders Cyanosis subjects affected / exposed occurrences (all)	0 / 19 (0.00%) 0	0 / 21 (0.00%) 0	1 / 19 (5.26%) 1
Nervous system disorders Headache subjects affected / exposed occurrences (all)	0 / 19 (0.00%) 0	1 / 21 (4.76%) 1	2 / 19 (10.53%) 2
Eye disorders Eye irritation subjects affected / exposed occurrences (all)	0 / 19 (0.00%) 0	0 / 21 (0.00%) 0	1 / 19 (5.26%) 1
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all) Abdominal pain subjects affected / exposed occurrences (all) Dyspepsia subjects affected / exposed occurrences (all) Gastritis subjects affected / exposed occurrences (all) Tongue dry subjects affected / exposed occurrences (all)	2 / 19 (10.53%) 2 1 / 19 (5.26%) 1 0 / 19 (0.00%) 0 0 / 19 (0.00%) 0 0 / 19 (0.00%) 0 0 / 19 (0.00%) 0	4 / 21 (19.05%) 4 0 / 21 (0.00%) 0 0 / 21 (0.00%) 0 0 / 21 (0.00%) 0 0 / 21 (0.00%) 0	0 / 19 (0.00%) 0 0 / 19 (0.00%) 0 1 / 19 (5.26%) 1 1 / 19 (5.26%) 1 1 / 19 (5.26%) 5
Hepatobiliary disorders Cholecystitis subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1	0 / 21 (0.00%) 0	0 / 19 (0.00%) 0
Musculoskeletal and connective tissue disorders Muscle spasms subjects affected / exposed occurrences (all) Neck pain	0 / 19 (0.00%) 0	0 / 21 (0.00%) 0	1 / 19 (5.26%) 1

subjects affected / exposed occurrences (all)	0 / 19 (0.00%) 0	0 / 21 (0.00%) 0	1 / 19 (5.26%) 1
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	3 / 19 (15.79%)	1 / 21 (4.76%)	0 / 19 (0.00%)
occurrences (all)	3	1	0
Urinary tract infection			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	1 / 19 (5.26%)
occurrences (all)	1	0	1
Bronchitis			
subjects affected / exposed	0 / 19 (0.00%)	0 / 21 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Oral candidiasis			
subjects affected / exposed	0 / 19 (0.00%)	0 / 21 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 May 2020	The primary purpose of Amendment 1 was to mitigate any potential effects of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) on study subjects and study site personnel.
10 August 2020	The primary purpose of Amendment 2 was addition of contraceptive requirements in the United Kingdom.
02 February 2021	The primary purpose of Amendment 3 was to help prevent any potential bronchospasm after inhalation of study drug.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
09 August 2021	The study was terminated based on the toxicology findings from a 9-month study and subjects who had not completed the treatment period were instructed to terminate dosing and return for an end of study visit, followed by the 10-week follow-up period.	-

Notes:

Limitations and caveats

None reported