

**Clinical trial results:****A Phase 3 Study Evaluating the Safety, Tolerability, and Pharmacokinetics of Elexacaftor/Tezacaftor/Ivacaftor Triple Combination Therapy in Cystic Fibrosis Subjects 2 Through 5 Years of Age****Summary**

EudraCT number	2020-002251-38
Trial protocol	DE
Global end of trial date	03 June 2022

Results information

Result version number	v2 (current)
This version publication date	15 July 2023
First version publication date	17 December 2022
Version creation reason	• New data added to full data set Update as per CT.gov final results submission

Trial information**Trial identification**

Sponsor protocol code	VX20-445-111
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04537793
WHO universal trial number (UTN)	-
Other trial identifiers	IND Number: 132547

Notes:

Sponsors

Sponsor organisation name	Vertex Pharmaceuticals Incorporated
Sponsor organisation address	50 Northern Avenue, Boston, Massachusetts, United States,
Public contact	Medical Monitor, Vertex Pharmaceuticals Incorporated, +1 617-341-6777, medicalinfo@vrtx.com
Scientific contact	Medical Monitor, Vertex Pharmaceuticals Incorporated, +1 617-341-6777, medicalinfo@vrtx.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMA-002324-PIP01-17
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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	21 June 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	03 June 2022
Global end of trial reached?	Yes
Global end of trial date	03 June 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate safety, tolerability, pharmacokinetics, pharmacodynamics and efficacy of elexacaftor (ELX)/tezacaftor (TEZ)/ivacaftor (IVA) triple combination therapy in cystic fibrosis (CF) subjects 2 through 5 years of age.

Protection of trial subjects:

The study was conducted in accordance with the ethical principles stated in the Declaration of Helsinki and the International Conference on Harmonization (ICH) Guideline for Good Clinical Practice (GCP).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	19 November 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	Australia: 11
Country: Number of subjects enrolled	Canada: 11
Country: Number of subjects enrolled	United States: 49
Country: Number of subjects enrolled	Germany: 7
Country: Number of subjects enrolled	United Kingdom: 5
Worldwide total number of subjects	83
EEA total number of subjects	7

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)	83
Adolescents (12-17 years)	0
Adults (18-64 years)	0

From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted in 2 parts, Part A and Part B. The Participant flow was planned to be presented for the overall treatment arms (i.e. Part A and Part B), irrespective of weight-based dose regimen.

Pre-assignment

Screening details:

This study was conducted in subjects with CF aged 2 through 5 years of age (inclusive).

Period 1

Period 1 title	Overall Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	No
Arm title	Part A: ELX/TEZ/IVA

Arm description:

Subjects weighing greater than or equals to ($\geq$)14 kilograms (kg) at screening received elexacaftor (ELX) 100 milligrams (mg) once daily (qd)/tezacaftor (TEZ) 50 mg qd/ivacaftor (IVA) 75 mg every 12 hours (q12h) in the treatment period for 15 days.

Arm type	Experimental
Investigational medicinal product name	ELX/TEZ/IVA
Investigational medicinal product code	VX-445/VX-661/VX-770
Other name	Elxacaftor/Tezacaftor/Ivacaftor
Pharmaceutical forms	Granules
Routes of administration	Oral use

Dosage and administration details:

Subjects received ELX/TEZ/IVA fixed-dose combination once daily in the morning.

Investigational medicinal product name	IVA
Investigational medicinal product code	VX-770
Other name	Ivacaftor
Pharmaceutical forms	Granules
Routes of administration	Oral use

Dosage and administration details:

Subjects received IVA once daily in the evening.

Arm title	Part B: ELX/TEZ/IVA
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Arm description:

Subjects weighing ≥ 14 kg at screening received ELX 100 mg qd/TEZ 50 mg qd/IVA 75 mg q12h and subjects weighing ≥ 10 kg to less than ($<$)14 kg received ELX 80 mg qd/TEZ 40 mg qd/IVA 60 mg once every morning (qAM) and IVA 59.5 mg once every evening (qPM) in the treatment period for 24 weeks.

Arm type	Experimental
Investigational medicinal product name	ELX/TEZ/IVA
Investigational medicinal product code	VX-445/VX-661/VX-770
Other name	Elxacaftor/Tezacaftor/Ivacaftor
Pharmaceutical forms	Granules
Routes of administration	Oral use

Dosage and administration details:

Subjects received ELX/TEZ/IVA fixed-dose combination once daily in the morning.

Investigational medicinal product name	IVA
Investigational medicinal product code	VX-770
Other name	Ivacaftor
Pharmaceutical forms	Granules
Routes of administration	Oral use

Dosage and administration details:

Subjects received IVA once daily in the evening.

Number of subjects in period 1	Part A: ELX/TEZ/IVA	Part B: ELX/TEZ/IVA
Started	18	75
Completed	18	74
Not completed	0	1
Adverse event	-	1

Baseline characteristics

Reporting groups

Reporting group title	Part A: ELX/TEZ/IVA
Reporting group description:	
Subjects weighing greater than or equals to ($\geq$)14 kilograms (kg) at screening received elexacaftor (ELX) 100 milligrams (mg) once daily (qd)/tezacaftor (TEZ) 50 mg qd/ivacaftor (IVA) 75 mg every 12 hours (q12h) in the treatment period for 15 days.	
Reporting group title	Part B: ELX/TEZ/IVA
Reporting group description:	
Subjects weighing $\geq$ 14 kg at screening received ELX 100 mg qd/TEZ 50 mg qd/IVA 75 mg q12h and subjects weighing $\geq$ 10 kg to less than ($<$)14 kg received ELX 80 mg qd/TEZ 40 mg qd/IVA 60 mg once every morning (qAM) and IVA 59.5 mg once every evening (qPM) in the treatment period for 24 weeks.	

Reporting group values	Part A: ELX/TEZ/IVA	Part B: ELX/TEZ/IVA	Total
Number of subjects	18	75	93
Age categorical			
There were 83 unique subjects enrolled in the study. Out of 18 subjects from Part A, 10 subjects also participated in Part B.			
Units: Subjects			
Children (2-11 years)	18	75	83
Gender categorical			
There were 83 unique subjects enrolled in the study. Out of 18 subjects from Part A, 10 subjects also participated in Part B. The total column for gender represents the sum of Part A and Part B numbers as the data for unique 83 subjects was not collected separately.			
Units: Subjects			
Female	11	41	52
Male	7	34	41
Ethnicity			
There were 83 unique subjects enrolled in the study. Out of 18 subjects from Part A, 10 subjects also participated in Part B.			
Units: Subjects			
Hispanic or Latino	0	6	6
Not Hispanic or Latino	18	63	71
Not collected per local regulations	0	6	6
Race			
There were 83 unique subjects enrolled in the study. Out of 18 subjects from Part A, 10 subjects also participated in Part B.			
Units: Subjects			
White	18	68	76
Black or African American	0	1	1
Asian	0	0	0
American Indian or Alaska Native	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Not collected per local Regulations	0	6	6

End points

End points reporting groups

Reporting group title	Part A: ELX/TEZ/IVA
Reporting group description: Subjects weighing greater than or equals to ($\geq$)14 kilograms (kg) at screening received elexacaftor (ELX) 100 milligrams (mg) once daily (qd)/tezacaftor (TEZ) 50 mg qd/ivacaftor (IVA) 75 mg every 12 hours (q12h) in the treatment period for 15 days.	
Reporting group title	Part B: ELX/TEZ/IVA
Reporting group description: Subjects weighing $\geq$ 14 kg at screening received ELX 100 mg qd/TEZ 50 mg qd/IVA 75 mg q12h and subjects weighing $\geq$ 10 kg to less than ($<$)14 kg received ELX 80 mg qd/TEZ 40 mg qd/IVA 60 mg once every morning (qAM) and IVA 59.5 mg once every evening (qPM) in the treatment period for 24 weeks.	
Subject analysis set title	Part B: ELX/TEZ/IVA ($\geq$ 10 kg to $<$ 14 kg)
Subject analysis set type	Full analysis
Subject analysis set description: Subjects weighing $\geq$ 10 kg to $<$ 14 kg received ELX 80 mg qd/TEZ 40 mg qd/IVA 60 mg qAM and IVA 59.5 mg qPM in the treatment period for 24 weeks.	
Subject analysis set title	Part B: ELX/TEZ/IVA ($\geq$ 14 kg)
Subject analysis set type	Full analysis
Subject analysis set description: Subjects weighing $\geq$ 14 kg at screening received ELX 100 mg qd/TEZ 50 mg qd/IVA 75 mg q12h in the treatment period for 24 weeks.	

Primary: Part A: Observed Pre-dose Concentration (C_{trough}) of ELX, TEZ, IVA, and Relevant Metabolites

End point title	Part A: Observed Pre-dose Concentration (C _{trough}) of ELX, TEZ, IVA, and Relevant Metabolites ^{[1][2]}
End point description: Pharmacokinetic (PK) set included subjects who received at least 1 dose of study drug. Here "n" signifies those subjects who were evaluable at specified time points for each reporting group respectively.	
End point type	Primary
End point timeframe: From Day 1 through Day 15	

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. No statistical comparisons were planned for this endpoint.

[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 primary endpoint is only applicable for Part A.

End point values	Part A: ELX/TEZ/IVA			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: micrograms per milliliter (mcg/ml)				
arithmetic mean (standard deviation)				
Day 1: ELX (n= 18)	0.00 ($\pm$ 0.00)			
Day 8: ELX (n= 18)	3.44 ($\pm$ 2.09)			
Day 15: ELX (n= 17)	3.69 ($\pm$ 2.11)			
Day 1: ELX-M23 (n= 18)	0.00 ($\pm$ 0.00)			
Day 8: ELX-M23 (n= 18)	2.39 ($\pm$ 1.65)			

Day 15: ELX-M23 (n= 17)	2.47 (± 1.65)			
Day 1: IVA (n= 18)	0.00 (± 0.00)			
Day 8: IVA (n= 18)	0.702 (± 0.503)			
Day 15: IVA (n= 17)	0.746 (± 0.526)			
Day 1: IVA-M1 (n= 18)	0.00 (± 0.00)			
Day 8: IVA-M1 (n= 18)	1.78 (± 0.990)			
Day 15: IVA-M1 (n= 17)	1.91 (± 0.990)			
Day 1: TEZ (n= 18)	0.00 (± 0.00)			
Day 8: TEZ (n= 18)	1.86 (± 1.07)			
Day 15: TEZ (n= 17)	1.85 (± 1.10)			
Day 1: TEZ-M1 (n= 18)	0.00 (± 0.00)			
Day 8: TEZ-M1 (n= 18)	6.42 (± 1.42)			
Day 15: TEZ-M1 (n= 17)	7.68 (± 1.52)			

Statistical analyses

No statistical analyses for this end point

Primary: Part A : Safety and Tolerability as Assessed by Number of Subjects With Treatment-Emergent Adverse

End point title	Part A : Safety and Tolerability as Assessed by Number of Subjects With Treatment-Emergent Adverse ^{[3][4]}
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End point description:

Safety set included all subjects who received at least 1 dose of study drug in the treatment period.

End point type	Primary
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End point timeframe:

From Day 1 up to Day 43

Notes:

[3] - 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. No statistical comparisons were planned for this endpoint.

[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 primary endpoint is only applicable for Part A.

End point values	Part A: ELX/TEZ/IVA			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: Subjects				
Subjects with TEAEs	15			
Subjects with SAEs	0			

Statistical analyses

No statistical analyses for this end point

Primary: Part B : Safety and Tolerability as Assessed by Number of Subjects With Treatment-Emergent

End point title	Part B : Safety and Tolerability as Assessed by Number of Subjects With Treatment-Emergent ^{[5][6]}
End point description: Safety set included all subjects who received at least 1 dose of study drug in the treatment period.	
End point type	Primary
End point timeframe: From Day 1 up to Week 28	

Notes:

[5] - 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. No statistical comparisons were planned for this endpoint.

[6] - 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 primary endpoint is only applicable for Part B.

End point values	Part B: ELX/TEZ/IVA			
Subject group type	Reporting group			
Number of subjects analysed	75			
Units: Subjects				
Subjects with TEAEs	74			
Subjects with SAEs	2			

Statistical analyses

No statistical analyses for this end point

Secondary: Part B: Observed Pre-dose Plasma Concentration (Ctough) of ELX, TEZ, IVA, and Relevant Metabolites

End point title	Part B: Observed Pre-dose Plasma Concentration (Ctrough) of ELX, TEZ, IVA, and Relevant Metabolites
End point description: PK set included subjects who received at least 1 dose of study drug. Here “n” signifies those subjects who were evaluable at specified time points for each reporting group respectively.	
End point type	Secondary
End point timeframe: From Day 1 through Week 16	

End point values	Part B: ELX/TEZ/IVA (≥10 kg to <14 kg)	Part B: ELX/TEZ/IVA (≥14 kg)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	16	59		
Units: micrograms per milliliter (mcg/ml)				
arithmetic mean (standard deviation)				

Day 15: ELX (n=14,54)	2.91 (± 1.38)	3.87 (± 2.75)		
Week 4: ELX (n=16,59)	3.13 (± 1.90)	3.56 (± 2.19)		
Week 12: ELX (n=16, 56)	2.48 (± 1.65)	3.49 (± 2.22)		
Week 16: ELX (n=15,58)	3.01 (± 1.11)	3.18 (± 2.19)		
Day 15: ELX-M23 (n=14,54)	1.85 (± 1.12)	2.33 (± 1.87)		
Week 4: ELX-M23 (n=16,59)	2.32 (± 2.01)	2.22 (± 1.66)		
Week 12: ELX-M23 (n=16,56)	1.48 (± 1.27)	2.17 (± 1.69)		
Week 16: ELX-M23 (n=15,58)	1.73 (± 0.828)	1.94 (± 1.58)		
Day 15: IVA (n=14,52)	0.549 (± 0.373)	0.661 (± 0.552)		
Week 4: IVA (n=16,59)	0.535 (± 0.402)	0.594 (± 0.405)		
Week 12: IVA (n=16,56)	0.383 (± 0.203)	0.530 (± 0.474)		
Week 16: IVA (n=15,58)	0.483 (± 0.347)	0.580 (± 0.511)		
Day15: IVA-M1 (n=14,52)	1.47 (± 0.969)	1.67 (± 0.961)		
Week 4: IVA-M1 (n=16,59)	1.64 (± 1.29)	1.52 (± 0.737)		
Week 12: IVA-M1 (n=16,56)	1.19 (± 0.602)	1.45 (± 0.907)		
Week 16: IVA-M1 (n=15,58)	1.24 (± 0.673)	1.51 (± 0.911)		
Day 15: TEZ (n=14,52)	1.73 (± 0.666)	2.14 (± 1.72)		
Week 4: TEZ (n=16,59)	1.62 (± 0.716)	1.79 (± 0.947)		
Week 12: TEZ (n=16,56)	1.60 (± 0.951)	1.76 (± 1.10)		
Week 16: TEZ (n=15,58)	1.52 (± 0.701)	1.80 (± 1.42)		
Day 15: TEZ-M1 (n=14,52)	7.07 (± 1.08)	7.07 (± 2.11)		
Week 4: TEZ-M1 (n=16,59)	6.80 (± 1.64)	7.09 (± 2.18)		
Week 12: TEZ-M1 (n=16,56)	7.06 (± 2.37)	7.18 (± 2.38)		
Week 16: TEZ-M1 (n=15,58)	6.88 (± 1.94)	6.95 (± 2.77)		

Statistical analyses

No statistical analyses for this end point

Secondary: Part B: Absolute Change in Sweat Chloride (SwCl)

End point title	Part B: Absolute Change in Sweat Chloride (SwCl) ^[7]
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End point description:

Sweat samples were collected using an approved collection device. FAS (Part B). The efficacy analysis for Part B was assessed for the overall treatment arm, irrespective of weight based dose regimen. Therefore, the analysis is reported for the single triple combination (Part B: ELX/TEZ/IVA) arm.

End point type	Secondary
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End point timeframe:

From Baseline through Week 24

Notes:

[7] - 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 endpoint is only applicable for Part B.

End point values	Part B: ELX/TEZ/IVA			
Subject group type	Reporting group			
Number of subjects analysed	75			
Units: millimole per liter (mmol/L)				
least squares mean (confidence interval 95%)	-57.9 (-61.3 to -54.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Part B: Absolute Change in Lung Clearance Index 2.5 (LCI 2.5)

End point title	Part B: Absolute Change in Lung Clearance Index 2.5 (LCI
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End point description:

The LCI2.5 index is the number of lung turnovers required to reduce the end tidal inert gas concentration to 1/40th of its starting values and is calculated by dividing the sum of exhaled tidal breaths (cumulative exhaled volume (CEV)) by simultaneously measured functional residual capacity (FRC). An LCI of 7.5 and below is normal; values greater than 7.5 are abnormal. LCI is able to detect abnormalities in lung function earlier than more traditional modalities such as spirometry.

FAS (Part B). The efficacy analysis for Part B was assessed for the overall treatment arm, irrespective of weight- based dose regimen. Therefore, the analysis is reported for the single triple combination (Part B: ELX/TEZ/IVA) arm.

End point type	Secondary
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End point timeframe:

From Baseline through Week 24

Notes:

[8] - 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 endpoint is only applicable for Part B.

End point values	Part B: ELX/TEZ/IVA			
Subject group type	Reporting group			
Number of subjects analysed	63			
Units: index				
least squares mean (confidence interval 95%)	-0.83 (-1.01 to -0.66)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Day 1 Through Safety Follow-up Visit (up to Day 43 for Part A, up to Week 28 for Part B)

Adverse event reporting additional description:

The safety analysis for Part B was assessed for the overall treatment arm, irrespective of weight- based dose regimen. Therefore, the analysis is reported for the single triple combination (Part B: ELX/TEZ/IVA) arm. MedDRA version 23.1 applied for Part A, MedDRA version 25.0 applied for Part B.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	23.1,25.0
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Reporting groups

Reporting group title	Part A: ELX/TEZ/IVA
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Reporting group description:

Subjects weighing ≥ 14 kg at screening received ELX 100 mg qd/TEZ 50 mg qd/IVA 75 mg q12h in the treatment period for 15 days.

Reporting group title	Part B: ELX/TEZ/IVA
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Reporting group description:

Subjects weighing ≥ 14 kg at Day 1 received ELX 100 mg qd/TEZ 50 mg qd/IVA 75 mg q12h and subjects weighing ≥ 10 kg to < 14 kg received ELX 80 mg qd/TEZ 400 mg qd/IVA 60 mg qAM and IVA 59.5 mg qPM in the treatment period for 24 weeks.

Serious adverse events	Part A: ELX/TEZ/IVA	Part B: ELX/TEZ/IVA	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 18 (0.00%)	2 / 75 (2.67%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Gastrointestinal disorders			
Anal incontinence			
subjects affected / exposed	0 / 18 (0.00%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Abnormal behaviour			
subjects affected / exposed	0 / 18 (0.00%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Urinary incontinence			

subjects affected / exposed	0 / 18 (0.00%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Infective pulmonary exacerbation of cystic fibrosis			
subjects affected / exposed	0 / 18 (0.00%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Part A: ELX/TEZ/IVA	Part B: ELX/TEZ/IVA	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	15 / 18 (83.33%)	71 / 75 (94.67%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	3 / 18 (16.67%)	8 / 75 (10.67%)	
occurrences (all)	3	9	
Aspartate aminotransferase increased			
subjects affected / exposed	2 / 18 (11.11%)	4 / 75 (5.33%)	
occurrences (all)	2	7	
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 18 (5.56%)	4 / 75 (5.33%)	
occurrences (all)	1	4	
SARS-CoV-2 test positive			
subjects affected / exposed	0 / 18 (0.00%)	7 / 75 (9.33%)	
occurrences (all)	0	7	
Injury, poisoning and procedural complications			
Scratch			
subjects affected / exposed	1 / 18 (5.56%)	0 / 75 (0.00%)	
occurrences (all)	1	0	
Skin abrasion			
subjects affected / exposed	1 / 18 (5.56%)	0 / 75 (0.00%)	
occurrences (all)	1	0	

Nervous system disorders			
Headache			
subjects affected / exposed	0 / 18 (0.00%)	7 / 75 (9.33%)	
occurrences (all)	0	7	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 18 (5.56%)	26 / 75 (34.67%)	
occurrences (all)	1	33	
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	0 / 18 (0.00%)	5 / 75 (6.67%)	
occurrences (all)	0	6	
Abdominal pain			
subjects affected / exposed	1 / 18 (5.56%)	4 / 75 (5.33%)	
occurrences (all)	1	4	
Constipation			
subjects affected / exposed	1 / 18 (5.56%)	6 / 75 (8.00%)	
occurrences (all)	1	6	
Vomiting			
subjects affected / exposed	0 / 18 (0.00%)	21 / 75 (28.00%)	
occurrences (all)	0	25	
Diarrhoea			
subjects affected / exposed	0 / 18 (0.00%)	5 / 75 (6.67%)	
occurrences (all)	0	5	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	4 / 18 (22.22%)	46 / 75 (61.33%)	
occurrences (all)	4	84	
Nasal congestion			
subjects affected / exposed	0 / 18 (0.00%)	13 / 75 (17.33%)	
occurrences (all)	0	18	
Productive cough			
subjects affected / exposed	1 / 18 (5.56%)	3 / 75 (4.00%)	
occurrences (all)	1	3	
Rhinorrhoea			

subjects affected / exposed occurrences (all)	3 / 18 (16.67%) 4	25 / 75 (33.33%) 34	
Sputum increased subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1	0 / 75 (0.00%) 0	
Skin and subcutaneous tissue disorders			
Papule subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1	0 / 75 (0.00%) 0	
Pruritus subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1	1 / 75 (1.33%) 1	
Rash subjects affected / exposed occurrences (all)	2 / 18 (11.11%) 4	12 / 75 (16.00%) 14	
Rash erythematous subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1	1 / 75 (1.33%) 1	
Urticaria subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1	1 / 75 (1.33%) 1	
Psychiatric disorders			
Irritability subjects affected / exposed occurrences (all)	0 / 18 (0.00%) 0	4 / 75 (5.33%) 4	
Infections and infestations			
COVID-19 subjects affected / exposed occurrences (all)	0 / 18 (0.00%) 0	14 / 75 (18.67%) 14	
Infective pulmonary exacerbation of cystic fibrosis subjects affected / exposed occurrences (all)	0 / 18 (0.00%) 0	8 / 75 (10.67%) 8	
Nasopharyngitis subjects affected / exposed occurrences (all)	0 / 18 (0.00%) 0	6 / 75 (8.00%) 13	
Upper respiratory tract infection			

subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1	11 / 75 (14.67%) 13	
Product issues Product taste abnormal subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1	0 / 75 (0.00%) 0	
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	0 / 18 (0.00%) 0	9 / 75 (12.00%) 9	
Hyperamylasaemia subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1	0 / 75 (0.00%) 0	
Hyperlipasaemia subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1	0 / 75 (0.00%) 0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 June 2021	Updated the dose in Part B; Updated the sample size for subjects between 2 and 3 years of age (inclusive) in Part B; Added guidance for blood draws; Updated exclusion criterion to avoid enrolling subjects with liver function test (LFT) abnormalities in the previous year in the study.
21 October 2021	Amended to expand the study population to include subjects who have at least 1 F508del mutation in the CFTR gene or an ELX/TEZ/IVA-responsive CFTR mutation in part B.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported