Clinical trial results:
A Phase 3 Study Evaluating the Pharmacokinetics, Safety, and Tolerability of VX-445/TEZ/IVA Triple Combination Therapy in Cystic Fibrosis Subjects 6 Through 11 Years of Age

Summary

EudraCT number	2018-001695-38
Trial protocol	GB IE
Global end of trial date	07 August 2020

Results information

Result version number	v2 (current)
This version publication date	10 November 2021
First version publication date	22 February 2021
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	VX18-445-106

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03691779
WHO universal trial number (UTN)	-

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)	EMEA-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	24 August 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	07 August 2020
Global end of trial reached?	Yes
Global end of trial date	07 August 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the pharmacokinetics (PK), safety and tolerability of elexacaftor (ELX), tezacaftor (TEZ), and ivacaftor (IVA) when dosed in triple combination (TC).

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	02 October 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: 6
Country: Number of subjects enrolled	Ireland: 5
Country: Number of subjects enrolled	United States: 46
Country: Number of subjects enrolled	Australia: 8
Country: Number of subjects enrolled	Canada: 6
Worldwide total number of subjects	71
EEA total number of subjects	5

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)	71
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. All results were planned to be analyzed and reported separately for Part A and Part B of the study.

Pre-assignment

Screening details:

This study was conducted in cystic fibrosis (CF) subjects 6 through 11 years of age who were homozygous for F508del (F/F) genotype or heterozygous for F508del and a CF transmembrane conductance regulator gene (CFTR) minimal function mutation (F/MF) genotypes.

Period 1

Period 1 title	Triple Combination Treatment Period (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 in Part A received ELX 100 milligrams (mg) once daily (qd)/TEZ 50 mg qd/IVA 75 mg every 12 hours (q12h) in the treatment period for 15 days.

Arm type	Experimental
Investigational medicinal product name	IVA
Investigational medicinal product code	VX-770
Other name	Ivacaftor
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received IVA once daily in the evening.

Investigational medicinal product name	ELX/TEZ/IVA
Investigational medicinal product code	VX-445/VX-661/VX-770
Other name	Elexacaftor/Tezacaftor/Ivacaftor
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

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

Arm title	Part B: ELX/TEZ/IVA

Arm description:

Subjects in Part B weighing less than (<) 30 kilograms (kg) at Day 1 received ELX 100 mg qd/TEZ 50 mg qd/IVA 75 mg q12h and subjects weighing greater than equals to (>=) 30 kg at Day 1 received ELX 200 mg qd/TEZ 100 mg qd/IVA 150 mg q12h in the treatment period for 24 weeks.

Arm type	Experimental
Investigational medicinal product name	IVA
Investigational medicinal product code	VX-770
Other name	Ivacaftor
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received IVA once daily in the evening.

Investigational medicinal product name	ELX/TEZ/IVA
Investigational medicinal product code	VX-445/VX-661/VX-770
Other name	Elexacaftor/Tezacaftor/Ivacaftor
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received ELX/TEZ/IVA FDC once daily in the morning.

Number of subjects in period 1	Part A: ELX/TEZ/IVA	Part B: ELX/TEZ/IVA
Started	16	66
Completed	16	64
Not completed	0	2
Adverse event	-	1
Withdrawal of consent (not due to AE)	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Part A: ELX/TEZ/IVA
Reporting group description:	
Subjects in Part A received ELX 100 milligrams (mg) once daily (qd)/TEZ 50 mg qd/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 in Part B weighing less than (<) 30 kilograms (kg) at Day 1 received ELX 100 mg qd/TEZ 50 mg qd/IVA 75 mg q12h and subjects weighing greater than equals to (>=) 30 kg at Day 1 received ELX 200 mg qd/TEZ 100 mg qd/IVA 150 mg q12h in the treatment period for 24 weeks.	

Reporting group values	Part A: ELX/TEZ/IVA	Part B: ELX/TEZ/IVA	Total
Number of subjects	16	66	82
Age categorical			
There were 71 unique subjects enrolled in the study. Out of 16 subjects from Part A, 11 subjects also participated in Part B.			
Units: Subjects			
Children (2-11 years)	16	66	71
Gender categorical			
There were 71 unique subjects enrolled in the study. Out of 16 subjects from Part A, 11 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 71 subjects was not collected separately.			
Units: Subjects			
Female	11	39	50
Male	5	27	32
Ethnicity (NIH/OMB)			
There were 71 unique subjects enrolled in the study. Out of 16 subjects from Part A, 11 subjects also participated in Part B.			
Units: Subjects			
Hispanic or Latino	0	0	0
Not Hispanic or Latino	16	58	63
Unknown or Not Reported	0	8	8
Race (NIH/OMB)			
There were 71 unique subjects enrolled in the study. Out of 16 subjects from Part A, 11 subjects also participated in Part B.			
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	16	57	62
More than one race	0	1	1
Unknown or Not Reported	0	8	8

End points

End points reporting groups

Reporting group title	Part A: ELX/TEZ/IVA
Reporting group description:	
Subjects in Part A received ELX 100 milligrams (mg) once daily (qd)/TEZ 50 mg qd/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 in Part B weighing less than (<) 30 kilograms (kg) at Day 1 received ELX 100 mg qd/TEZ 50 mg qd/IVA 75 mg q12h and subjects weighing greater than equals to (>=) 30 kg at Day 1 received ELX 200 mg qd/TEZ 100 mg qd/IVA 150 mg q12h in the treatment period for 24 weeks.	

Primary: Part A: Maximum Observed Plasma Concentration (Cmax) of ELX, TEZ, and IVA

End point title	Part A: Maximum Observed Plasma Concentration (Cmax) of ELX, TEZ, and IVA[1][2]
End point description:	
PK set for Part A included all subjects who have received at least 1 dose of study drug in Part A. Here, the "n" signifies subjects who were evaluable at the specified time point.	
End point type	Primary
End point timeframe:	
Part A: 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 endpoint was planned only for Part A arm.

End point values	Part A: ELX/TEZ/IVA			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: microgram per milliliter (mcg/mL)				
arithmetic mean (standard deviation)				
ELX (n=15)	6.13 (± 1.52)			
TEZ (n=15)	6.93 (± 1.96)			
IVA (n=15)	1.01 (± 0.281)			

Statistical analyses

No statistical analyses for this end point

Primary: Part A: Observed Pre-dose Plasma Concentration (Ctrough) of ELX, TEZ, and IVA

End point title	Part A: Observed Pre-dose Plasma Concentration (Ctrough) of ELX, TEZ, and IVA[3][4]

End point description:

PK set (Part A). Here, the "n" signifies subjects who were evaluable at the specified time point.

End point type	Primary

End point timeframe:

Part A: Day 15

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 endpoint was planned only for Part A arm.

End point values	Part A: ELX/TEZ/IVA			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: mcg/mL				
arithmetic mean (standard deviation)				
ELX (n=15) TEZ (n=15) IVA (n=15)	2.86 (± 1.37) 1.06 (± 0.366) 0.297 (± 0.173)			

Statistical analyses

No statistical analyses for this end point

Primary: Part A: Area Under the Concentration Versus Time Curve From 0 to 24 hours (AUC0-24h) of ELX, TEZ, and IVA

End point title	Part A: Area Under the Concentration Versus Time Curve From 0 to 24 hours (AUC0-24h) of ELX, TEZ, and IVA[5][6]

End point description:

PK set (Part A).

End point type	Primary

End point timeframe:

Part A: Day 15

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 endpoint was planned only for Part A arm.

End point values	Part A: ELX/TEZ/IVA			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: hour*microgram per milliliter (h*mcg/mL)				
arithmetic mean (standard deviation)				
ELX	107 (± 28.7)			
TEZ	58.4 (± 13.5)			
IVA	8.12 (± 2.93)			

Statistical analyses

No statistical analyses for this end point

Primary: Part B: Safety and Tolerability as Assessed by Number of Subjects With Treatment Emergent Adverse Events (TEAEs) and Serious Adverse Events (SAEs)

End point title	Part B: Safety and Tolerability as Assessed by Number of Subjects With Treatment Emergent Adverse Events (TEAEs) and Serious Adverse Events (SAEs)[7][8]

End point description:

Safety set for Part B included all subjects who received at least 1 dose of study drug in Part B. 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.

End point type	Primary

End point timeframe:

Part B: Day 1 Through Safety Follow-up Visit (up to Week 28)

Notes:

[7] - 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.
[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 was planned only for Part B arm.

End point values	Part B: ELX/TEZ/IVA			
Subject group type	Reporting group			
Number of subjects analysed	66			
Units: subjects				
Subjects With TEAEs	65			
Subjects With SAEs	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: Cmax of ELX Metabolite (M23-ELX), TEZ Metabolite (M1-TEZ), and IVA Metabolite (M1-IVA)

End point title	Part A: Cmax of ELX Metabolite (M23-ELX), TEZ Metabolite (M1-TEZ), and IVA Metabolite (M1-IVA)[9]

End point description:

PK set (Part A). Here, the "n" signifies subjects who were evaluable at the specified time point.

End point type	Secondary

End point timeframe:

Part A: Day 15

Notes:

[9] - 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 was planned only for Part A arm.

End point values	Part A: ELX/TEZ/IVA			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: mcg/mL				
arithmetic mean (standard deviation)				
M23-ELX (n=15)	1.60 (± 0.657)			
M1-TEZ (n=15)	6.26 (± 1.54)			
M1-IVA (n=15)	2.36 (± 0.694)			

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: Ctrough of ELX Metabolite (M23-ELX), TEZ Metabolite (M1-TEZ), and IVA Metabolite (M1-IVA)

End point title	Part A: Ctrough of ELX Metabolite (M23-ELX), TEZ Metabolite (M1-TEZ), and IVA Metabolite (M1-IVA)[10]

End point description:

PK set (Part A). Here, the "n" signifies subjects who were evaluable at the specified time point.

End point type	Secondary

End point timeframe:

Part A: Day 15

Notes:

[10] - 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 was planned only for Part A arm.

End point values	Part A: ELX/TEZ/IVA			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: mcg/mL				
arithmetic mean (standard deviation)				
M23-ELX (n=15)	1.30 (± 0.585)			
M1-TEZ (n=15)	4.64 (± 1.36)			
M1-IVA (n=15)	0.890 (± 0.460)			

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: AUC0-24h of ELX Metabolite (M23-ELX) and TEZ Metabolite (M1-TEZ)

End point title	Part A: AUC0-24h of ELX Metabolite (M23-ELX) and TEZ Metabolite (M1-TEZ)[11]

End point description:

PK set (Part A).

End point type	Secondary

End point timeframe:

Part A: Day 15

Notes:

[11] - 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 was planned only for Part A arm.

End point values	Part A: ELX/TEZ/IVA			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: h*mcg/mL				
arithmetic mean (standard deviation)				
M23-ELX	35.6 (± 13.2)			
M1-TEZ	133 (± 30.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: Area Under the Concentration Versus Time Curve From 0 to 6 Hours (AUC0-6h) of IVA Metabolite (M1-IVA)

End point title	Part A: Area Under the Concentration Versus Time Curve From 0 to 6 Hours (AUC0-6h) of IVA Metabolite (M1-IVA)[12]

End point description:

PK set (Part A). The AUC data was analysed for up to 6 hours for IVA metabolite (M1-IVA). Therefore, AUC0-6h is reported for M1-IVA metabolite. Here "number of subjects analysed" signifies subjects who were evaluable at the specified time point.

End point type	Secondary

End point timeframe:

Part A: Day 15

Notes:

[12] - 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 was planned only for Part A arm.

End point values	Part A: ELX/TEZ/IVA			
Subject group type	Reporting group			
Number of subjects analysed	15			
Units: h*mcg/mL				
arithmetic mean (standard deviation)	9.41 (± 3.06)			

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: Safety and Tolerability as Assessed by Number of Subjects With TEAEs and SAEs

End point title	Part A: Safety and Tolerability as Assessed by Number of Subjects With TEAEs and SAEs[13]

End point description:

Safety set for Part A included all subjects who received at least 1 dose of study drug in Part A.

End point type	Secondary

End point timeframe:

Part A: Day 1 Through Safety Follow-up Visit (up to Day 43)

Notes:

[13] - 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 was planned only for Part A arm.

End point values	Part A: ELX/TEZ/IVA			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: subjects				
Subjects With TEAEs	12			
Subjects With SAEs	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Part B: Absolute Change in Percent Predicted Forced Expiratory Volume in 1 Second (ppFEV1)

End point title	Part B: Absolute Change in Percent Predicted Forced Expiratory Volume in 1 Second (ppFEV1)[14]

End point description:

FEV1 is the volume of air that can forcibly be blown out in one second, after full inspiration. Full analysis

set (FAS) for Part B included all enrolled subjects who carry the intended CFTR allele mutation and received at least 1 dose of study drug in 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

End point timeframe:

Part B: From Baseline Through Week 24

Notes:

[14] - 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 was planned only for Part B arm.

End point values	Part B: ELX/TEZ/IVA			
Subject group type	Reporting group			
Number of subjects analysed	66			
Units: percentage points				
least squares mean (confidence interval 95%)	10.2 (7.9 to 12.6)			

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)[15]

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

End point timeframe:

Part B: From Baseline Through Week 24

Notes:

[15] - 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 was planned only for Part B arm.

End point values	Part B: ELX/TEZ/IVA			
Subject group type	Reporting group			
Number of subjects analysed	66			
Units: millimole per liter (mmol/L)				
least squares mean (confidence interval 95%)	-60.9 (-63.7 to -58.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Part B: Absolute Change in Cystic Fibrosis Questionnaire Revised (CFQ-R) Respiratory Domain Score

End point title	Part B: Absolute Change in Cystic Fibrosis Questionnaire Revised (CFQ-R) Respiratory Domain Score[16]

End point description:

The CFQ-R is a validated subject-reported outcome measuring health-related quality of life for subjects with
cystic fibrosis. Respiratory domain assessed respiratory symptoms, score range: 0-100; higher scores indicating fewer
symptoms and better health-related quality of life. 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

End point timeframe:

Part B: From Baseline Through Week 24

Notes:

[16] - 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 was planned only for Part B arm.

End point values	Part B: ELX/TEZ/IVA			
Subject group type	Reporting group			
Number of subjects analysed	66			
Units: units on a scale				
least squares mean (confidence interval 95%)	7.0 (4.7 to 9.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Part B: Absolute Change in Body Mass Index (BMI)

End point title	Part B: Absolute Change in Body Mass Index (BMI)[17]

End point description:

BMI was defined as weight in kg divided by squared height in meters (m^2). 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

End point timeframe:

Part B: From Baseline at Week 24

Notes:

[17] - 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 was planned only for Part B arm.

End point values	Part B: ELX/TEZ/IVA			
Subject group type	Reporting group			
Number of subjects analysed	66			
Units: kg/m^2				
least squares mean (confidence interval 95%)	1.02 (0.76 to 1.28)			

Statistical analyses

No statistical analyses for this end point

Secondary: Part B: Absolute Change in BMI For-Age Z-Score

End point title	Part B: Absolute Change in BMI For-Age Z-Score[18]

End point description:

BMI was defined as weight in kg divided by squared height in meters (m^2). The z-score is a statistical measure to describe whether a value was above or below the standard. A z-score of 0 is equal to the standard. Lower numbers indicate values lower than the standard and higher numbers indicate values higher than the standard. 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

End point timeframe:

Part B: From Baseline at Week 24

Notes:

[18] - 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 was planned only for Part B arm.

End point values	Part B: ELX/TEZ/IVA			
Subject group type	Reporting group			
Number of subjects analysed	66			
Units: z-score				
least squares mean (confidence interval 95%)	0.37 (0.26 to 0.48)			

Statistical analyses

No statistical analyses for this end point

Secondary: Part B: Absolute Change in Weight

End point title	Part B: Absolute Change in Weight[19]

End point description:

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

End point timeframe:

Part B: From Baseline at Week 24

Notes:

[19] - 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 was planned only for Part B arm.

End point values	Part B: ELX/TEZ/IVA			
Subject group type	Reporting group			
Number of subjects analysed	66			
Units: kg				
least squares mean (confidence interval 95%)	3.0 (2.5 to 3.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Part B: Absolute Change in Weight-for-age Z-Score

End point title	Part B: Absolute Change in Weight-for-age Z-Score[20]

End point description:

The z-score is a statistical measure to describe whether a mean was above or below the standard. The z-score is a statistical measure to describe whether a value was above or below the standard. A z-score of 0 is equal to the standard. Lower numbers indicate values lower than the standard and higher numbers indicate values higher than the standard. 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

End point timeframe:

Part B: From Baseline at Week 24

Notes:

[20] - 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 was planned only for Part B arm.

End point values	Part B: ELX/TEZ/IVA			
Subject group type	Reporting group			
Number of subjects analysed	66			
Units: z-score				
least squares mean (confidence interval 95%)	0.25 (0.16 to 0.33)			

Statistical analyses

No statistical analyses for this end point

Secondary: Part B: Absolute Change in Height

End point title	Part B: Absolute Change in Height[21]

End point description:

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

End point timeframe:

Part B: From Baseline at Week 24

Notes:

[21] - 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 was planned only for Part B arm.

End point values	Part B: ELX/TEZ/IVA			
Subject group type	Reporting group			
Number of subjects analysed	66			
Units: centimeters (cm)				
least squares mean (confidence interval 95%)	2.3 (1.9 to 2.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Part B: Absolute Change in Height-for-Age Z-Score

End point title	Part B: Absolute Change in Height-for-Age Z-Score[22]

End point description:

The z-score is a statistical measure to describe whether a value was above or below the standard. A z-score of 0 is equal to the standard. Lower numbers indicate values lower than the standard and higher numbers indicate values higher than the standard. 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

End point timeframe:

Part B: From Baseline at Week 24

Notes:

[22] - 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 was planned only for Part B arm.

End point values	Part B: ELX/TEZ/IVA			
Subject group type	Reporting group			
Number of subjects analysed	66			
Units: z-score				
least squares mean (confidence interval 95%)	-0.05 (-0.12 to 0.01)			

Statistical analyses

No statistical analyses for this end point

Secondary: Part B: Drug Acceptability Assessment Using Modified Facial Hedonic Scale

End point title	Part B: Drug Acceptability Assessment Using Modified Facial Hedonic Scale[23]

End point description:

The study drug acceptability (subject reaction) was assessed by a visual analog scale that incorporates a 5 point
facial hedonic scale (Liked it Very Much, Liked it a Little, Not sure, Disliked it a Little, Disliked it Very Much). Number of subjects with the indicated categorical response in the drug acceptability assessment were reported. 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. Here "number analyzed" signifies those subjects who were evaluable for this outcome.

End point type	Secondary

End point timeframe:

Part B: At Week 24

Notes:

[23] - 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 was planned only for Part B arm.

End point values	Part B: ELX/TEZ/IVA			
Subject group type	Reporting group			
Number of subjects analysed	33			
Units: subjects				
Liked it Very Much	16			
Liked it a Little	6			
Not sure	10			
Disliked it a Little	1			
Disliked it Very Much	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Part B: Number of Pulmonary Exacerbations Events

End point title	Part B: Number of Pulmonary Exacerbations Events[24]

End point description:

Pulmonary exacerbation was defined as new or changed treatment with oral, inhaled, or intravenous antibiotics and
fulfillment of pre-specified protocol defined criteria. FAS (Part B). The total number of pulmonary exacerbations events across all subjects were reported. 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

End point timeframe:

Part B: From Baseline Through Week 24

Notes:

[24] - 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 was planned only for Part B arm.

End point values	Part B: ELX/TEZ/IVA			
Subject group type	Reporting group			
Number of subjects analysed	66			
Units: pulmonary exacerbations events	4			

Statistical analyses

No statistical analyses for this end point

Secondary: Part B: Number of CF Related Hospitalizations

End point title	Part B: Number of CF Related Hospitalizations[25]

End point description:

FAS (Part B). The efficacy analysis for Part B was assessed for the overall treatment arm, irrespective of weight based dose regimen. The total number of CF related hospitalization events across all subjects were reported. Therefore, the analysis is reported for the single triple combination (Part B: ELX/TEZ/IVA) arm.

End point type	Secondary

End point timeframe:

Part B: From Baseline Through Week 24

Notes:

[25] - 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 was planned only for Part B arm.

End point values	Part B: ELX/TEZ/IVA			
Subject group type	Reporting group			
Number of subjects analysed	66			
Units: hospitalizations	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Part B: Ctrough of ELX, ELX Metabolite (M23-ELX), TEZ, TEZ Metabolite (M1-TEZ), IVA and IVA Metabolite (M1-IVA)

End point title	Part B: Ctrough of ELX, ELX Metabolite (M23-ELX), TEZ, TEZ Metabolite (M1-TEZ), IVA and IVA Metabolite (M1-IVA)[26]

End point description:

The PK set for Part B included all subjects who have received at least 1 dose of study drug in Part B. Here "n" signifies those subjects who were evaluable at specified time points.

End point type	Secondary

End point timeframe:

Part B: At Week 4

Notes:

[26] - 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 was planned only for Part B arm.

End point values	Part B: ELX/TEZ/IVA			
Subject group type	Reporting group			
Number of subjects analysed	65			
Units: mcg/mL				
arithmetic mean (standard deviation)				
ELX: Week 4 (<30 kg) (n=33)	2.71 (± 1.77)			
ELX: Week 4 (>=30 kg) (n=30)	5.69 (± 3.00)			
M23-ELX: Week 4 (<30 kg) (n=33)	1.59 (± 1.24)			
M23-ELX: Week 4 (>=30 kg) (n=30)	4.41 (± 2.97)			
TEZ: Week 4 (<30 kg) (n=33)	1.43 (± 1.19)			
TEZ: Week 4 (>=30 kg) (n=30)	2.37 (± 1.07)			
M1-TEZ: Week 4 (<30 kg) (n=33)	5.57 (± 1.78)			
M1-TEZ: Week 4 (>=30 kg) (n=30)	8.12 (± 1.88)			
IVA: Week 4 (<30 kg) (n=33)	0.455 (± 0.681)			
IVA: Week 4 (>=30 kg) (n=30)	0.851 (± 0.489)			
M1-IVA: Week 4 (<30 kg) (n=33)	1.00 (± 0.630)			
M1-IVA: Week 4 (>=30 kg) (n=30)	2.18 (± 1.04)			

Statistical analyses

No statistical analyses for this end point

Secondary: Part B: Absolute Change in Lung Clearance Index 2.5 (LCI2.5)

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

End point description:

LCI 2.5 represents the number of lung turnovers required to reduce the end tidal inert gas concentration to 1/40th of its
starting value. 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

End point timeframe:

Part B: From Baseline Through Week 24

Notes:

[27] - 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 was planned only for Part B arm.

End point values	Part B: ELX/TEZ/IVA			
Subject group type	Reporting group			
Number of subjects analysed	66			
Units: lung clearance index				
least squares mean (confidence interval 95%)	-1.71 (-2.11 to -1.30)			

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 21.1 applied for Part A, MedDRA version 23.0 applied for Part B.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.1, 23.0

Reporting groups

Reporting group title	Part A: ELX/TEZ/IVA

Reporting group description:

Subjects in Part A 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

Reporting group description:

Subjects in Part B weighing <30 kg at Day 1 received ELX 100 mg qd/TEZ 50 mg qd/IVA 75 mg q12h and
subjects weighing >=30 kg at Day 1 received ELX 200 mg qd/TEZ 100 mg qd/IVA 150 mg q12h 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 / 16 (0.00%)	1 / 66 (1.52%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Infections and infestations			
Metapneumovirus infection			
subjects affected / exposed	0 / 16 (0.00%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 16 (0.00%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhinovirus infection			

subjects affected / exposed	0 / 16 (0.00%)	1 / 66 (1.52%)	
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	12 / 16 (75.00%)	62 / 66 (93.94%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 16 (0.00%)	7 / 66 (10.61%)	
occurrences (all)	0	9	
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 16 (6.25%)	0 / 66 (0.00%)	
occurrences (all)	1	0	
Human rhinovirus test positive			
subjects affected / exposed	1 / 16 (6.25%)	0 / 66 (0.00%)	
occurrences (all)	1	0	
Pulmonary function test decreased			
subjects affected / exposed	1 / 16 (6.25%)	0 / 66 (0.00%)	
occurrences (all)	1	0	
Transaminases increased			
subjects affected / exposed	1 / 16 (6.25%)	0 / 66 (0.00%)	
occurrences (all)	1	0	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	1 / 16 (6.25%)	1 / 66 (1.52%)	
occurrences (all)	1	1	
Craniocerebral injury			
subjects affected / exposed	1 / 16 (6.25%)	0 / 66 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 16 (0.00%)	16 / 66 (24.24%)	
occurrences (all)	0	19	

Lethargy			
subjects affected / exposed	1 / 16 (6.25%)	0 / 66 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 16 (6.25%)	0 / 66 (0.00%)	
occurrences (all)	1	0	
Chest pain			
subjects affected / exposed	1 / 16 (6.25%)	0 / 66 (0.00%)	
occurrences (all)	1	0	
Pyrexia			
subjects affected / exposed	1 / 16 (6.25%)	14 / 66 (21.21%)	
occurrences (all)	1	19	
Fatigue			
subjects affected / exposed	0 / 16 (0.00%)	5 / 66 (7.58%)	
occurrences (all)	0	5	
Vessel puncture site pain			
subjects affected / exposed	1 / 16 (6.25%)	0 / 66 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 16 (6.25%)	8 / 66 (12.12%)	
occurrences (all)	1	9	
Abdominal pain upper			
subjects affected / exposed	1 / 16 (6.25%)	5 / 66 (7.58%)	
occurrences (all)	1	5	
Diarrhoea			
subjects affected / exposed	0 / 16 (0.00%)	7 / 66 (10.61%)	
occurrences (all)	0	8	
Constipation			
subjects affected / exposed	0 / 16 (0.00%)	4 / 66 (6.06%)	
occurrences (all)	0	4	
Nausea			
subjects affected / exposed	1 / 16 (6.25%)	2 / 66 (3.03%)	
occurrences (all)	1	2	
Vomiting			

subjects affected / exposed	1 / 16 (6.25%)	7 / 66 (10.61%)	
occurrences (all)	1	10	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	5 / 16 (31.25%)	28 / 66 (42.42%)	
occurrences (all)	5	42	
Nasal congestion			
subjects affected / exposed	2 / 16 (12.50%)	10 / 66 (15.15%)	
occurrences (all)	3	14	
Oropharyngeal pain			
subjects affected / exposed	1 / 16 (6.25%)	12 / 66 (18.18%)	
occurrences (all)	1	14	
Productive cough			
subjects affected / exposed	2 / 16 (12.50%)	5 / 66 (7.58%)	
occurrences (all)	2	5	
Respiration abnormal			
subjects affected / exposed	1 / 16 (6.25%)	1 / 66 (1.52%)	
occurrences (all)	1	1	
Rhinorrhoea			
subjects affected / exposed	1 / 16 (6.25%)	8 / 66 (12.12%)	
occurrences (all)	1	9	
Sinus congestion			
subjects affected / exposed	1 / 16 (6.25%)	0 / 66 (0.00%)	
occurrences (all)	1	0	
Sputum increased			
subjects affected / exposed	3 / 16 (18.75%)	3 / 66 (4.55%)	
occurrences (all)	3	3	
Skin and subcutaneous tissue disorders			
Pruritus generalised			
subjects affected / exposed	1 / 16 (6.25%)	0 / 66 (0.00%)	
occurrences (all)	1	0	
Rash			
subjects affected / exposed	3 / 16 (18.75%)	8 / 66 (12.12%)	
occurrences (all)	3	10	
Rash erythematous			

subjects affected / exposed	1 / 16 (6.25%)	3 / 66 (4.55%)	
occurrences (all)	1	3	
Rash maculo-papular			
subjects affected / exposed	1 / 16 (6.25%)	2 / 66 (3.03%)	
occurrences (all)	1	3	
Rash papular			
subjects affected / exposed	1 / 16 (6.25%)	2 / 66 (3.03%)	
occurrences (all)	1	3	
Infections and infestations			
Croup infectious			
subjects affected / exposed	1 / 16 (6.25%)	0 / 66 (0.00%)	
occurrences (all)	1	0	
Ear infection			
subjects affected / exposed	0 / 16 (0.00%)	4 / 66 (6.06%)	
occurrences (all)	0	5	
Influenza			
subjects affected / exposed	0 / 16 (0.00%)	7 / 66 (10.61%)	
occurrences (all)	0	8	
Parainfluenzae virus infection			
subjects affected / exposed	1 / 16 (6.25%)	0 / 66 (0.00%)	
occurrences (all)	1	0	
Pneumonia			
subjects affected / exposed	1 / 16 (6.25%)	0 / 66 (0.00%)	
occurrences (all)	1	0	
Respiratory tract infection viral			
subjects affected / exposed	1 / 16 (6.25%)	0 / 66 (0.00%)	
occurrences (all)	1	0	
Upper respiratory tract infection			
subjects affected / exposed	0 / 16 (0.00%)	11 / 66 (16.67%)	
occurrences (all)	0	14	
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 16 (0.00%)	8 / 66 (12.12%)	
occurrences (all)	0	8	
Vulvovaginal mycotic infection			
subjects affected / exposed	1 / 16 (6.25%)	0 / 66 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 June 2019	Amended to update secondary endpoints and incorporate dose justification and weight cutoff based on data from Part A.
18 December 2019	Amended to update pre-dose assessment window.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported