



## Clinical trial results:

### A Phase 3, Open-label Study to Evaluate the Pharmacokinetics, Safety, and Tolerability of VX-661 in Combination With Ivacaftor in Subjects 6 Through 11 Years of Age With Cystic Fibrosis, Homozygous or Heterozygous for the F508del-CFTR Mutation

#### Summary

EudraCT number	2017-001164-38
Trial protocol	Outside EU/EEA
Global end of trial date	11 September 2018

#### Results information

Result version number	v1 (current)
This version publication date	12 March 2020
First version publication date	12 March 2020

#### Trial information

##### Trial identification

Sponsor protocol code	VX15-661-113
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02953314
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)	EMA-001640-PIP01-14
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	20 September 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	11 September 2018
Global end of trial reached?	Yes
Global end of trial date	11 September 2018
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

To evaluate the Pharmacokinetics (PK) of Tezacaftor (TEZ) and Ivacaftor (IVA) after administration of multiple doses of TEZ in combination with IVA in Part A and to evaluate the safety and tolerability of TEZ in combination with IVA through Week 24 in Part B.

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	11 November 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	United States: 77
Country: Number of subjects enrolled	Canada: 6
Worldwide total number of subjects	83
EEA total number of subjects	0

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: -

### Pre-assignment

Screening details:

This study consisted of 2-parts (Part A and B). The planned primary analysis was designed to assess overall treatment arm "TEZ/IVA", irrespective of weight-based dosing regimen. The aim of weight based dosing is to achieve similar exposures in children of different weights, thus analysis is presented for the single treatment arm "TEZ/IVA".

### Period 1

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

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Part A

Arm description:

Subjects weighing <25 kg received TEZ 50 mg/IVA 75 mg for 14 days.

Subjects weighing ≥25 kg received TEZ 50 mg/IVA 150 mg for 14 days.

Arm type	Experimental
Investigational medicinal product name	TEZ
Investigational medicinal product code	VX-661
Other name	Tezacaftor
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received TEZ 50 mg once daily.

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

Dosage and administration details:

Subjects received IVA 75 mg or 150 mg every 12 hours.

<b>Arm title</b>	Part B
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Arm description:

Subjects weighing <40 kg received TEZ 50 mg/IVA 75 mg as fixed dose combination in the morning and IVA 75 mg in the evening for 24 weeks.

Subjects weighing ≥40 kg received TEZ 100 mg/IVA 150 mg as fixed dose combination in the morning and IVA 150 mg in the evening for 24 weeks.

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

Dosage and administration details:

Subjects received TEZ/IVA as fixed dose combination orally once daily in the morning.

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 as mono tablet once daily in the evening.

<b>Number of subjects in period 1</b>	Part A	Part B
Started	13	70
Completed	13	67
Not completed	0	3
Adverse Event	-	1
Withdrawal of consent (not due to AE)	-	2

## Baseline characteristics

### Reporting groups

Reporting group title	Part A
Reporting group description:	
Subjects weighing <25 kg received TEZ 50 mg/IVA 75 mg for 14 days.	
Subjects weighing ≥25 kg received TEZ 50 mg/IVA 150 mg for 14 days.	
Reporting group title	Part B
Reporting group description:	
Subjects weighing <40 kg received TEZ 50 mg/IVA 75 mg as fixed dose combination in the morning and IVA 75 mg in the evening for 24 weeks.	
Subjects weighing ≥40 kg received TEZ 100 mg/IVA 150 mg as fixed dose combination in the morning and IVA 150 mg in the evening for 24 weeks.	

Reporting group values	Part A	Part B	Total
Number of subjects	13	70	83
Age categorical			
Units: Subjects			
≤18 years	13	70	83
Between 18 and 65 years	0	0	0
≥65 years	0	0	0
Gender categorical			
Units: Subjects			
Female	7	34	41
Male	6	36	42
Ethnicity			
Units: Subjects			
Hispanic or Latino	0	3	3
Not Hispanic or Latino	13	67	80
Unknown or Not Reported	0	0	0
Race			
Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	1	1
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	1	0	1
White	12	68	80
More than one race	0	1	1
Unknown or Not Reported	0	0	0

## End points

### End points reporting groups

Reporting group title	Part A
Reporting group description:	
Subjects weighing <25 kg received TEZ 50 mg/IVA 75 mg for 14 days.	
Subjects weighing ≥25 kg received TEZ 50 mg/IVA 150 mg for 14 days.	
Reporting group title	Part B
Reporting group description:	
Subjects weighing <40 kg received TEZ 50 mg/IVA 75 mg as fixed dose combination in the morning and IVA 75 mg in the evening for 24 weeks.	
Subjects weighing ≥40 kg received TEZ 100 mg/IVA 150 mg as fixed dose combination in the morning and IVA 150 mg in the evening for 24 weeks.	

### Primary: Part A: Maximum Observed Concentration (C<sub>max</sub>) of TEZ and IVA

End point title	Part A: Maximum Observed Concentration (C <sub>max</sub> ) of TEZ and IVA <sup>[1][2]</sup>
End point description:	
Pharmacokinetic (PK) set included subjects who received at least 1 dose of study drug and for whom the primary PK data were considered to be sufficient and interpretable. Here "n" signifies those subjects who were evaluable for this endpoint at specified time points and "99999" represents "Not Applicable" as data for geometric coefficient of variation could not be calculated for the category with n=1 subject.	
End point type	Primary
End point timeframe:	
Day 1 and Day 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 data was planned to be reported for this primary PK 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 is reporting data only for Part A.

End point values	Part A			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: nanogram per milliliter (ng/mL)				
geometric mean (geometric coefficient of variation)				
Day 1: TEZ (<25 Kg) (n= 2)	6630 (± 10.3)			
Day 1: TEZ (≥25 Kg) (n= 11)	4310 (± 42.6)			
Day 14: TEZ (<25 Kg) (n= 2)	6300 (± 10.3)			
Day 14: TEZ (≥25 Kg) (n= 10)	5340 (± 49.0)			
Day 1: IVA (<25 Kg) (n= 1)	656 (± 99999)			
Day 1: IVA (≥25 Kg) (n= 9)	1010 (± 64.3)			
Day 14: IVA (<25 Kg) (n= 2)	578 (± 60.4)			
Day 14: IVA (≥25 Kg) (n= 10)	1490 (± 105)			

## Statistical analyses

No statistical analyses for this end point

### Primary: Part A: Area Under the Concentration Versus Time Curve During Dosing Interval (AUC<sub>tau</sub>) of TEZ and IVA

End point title	Part A: Area Under the Concentration Versus Time Curve During Dosing Interval (AUC <sub>tau</sub> ) of TEZ and IVA <sup>[3]</sup> <sup>[4]</sup>
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End point description:

PK set was used. Here "n" signifies those subjects who were evaluable for this endpoint at specified time points and "99999" represents "Not Applicable" as data could not be calculated for the category with n=0 subject.

End point type	Primary
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End point timeframe:

Day 1 and Day 14

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 data was planned to be reported for this primary PK 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 is reporting data only for Part A.

End point values	Part A			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: hour*nanogram per milliliter (hr*ng/mL)				
geometric mean (geometric coefficient of variation)				
Day 1: TEZ (<25 Kg) (n= 2)	54300 (± 16.2)			
Day 1: TEZ (≥25 Kg) (n= 11)	41600 (± 36.2)			
Day 14: TEZ (<25 Kg) (n= 2)	66500 (± 30.5)			
Day 14: TEZ (≥25 Kg) (n= 10)	71600 (± 61.1)			
Day 1: IVA (<25 Kg) (n= 0)	99999 (± 99999)			
Day 1: IVA (≥25 Kg) (n= 0)	99999 (± 99999)			
Day 14: IVA (<25 Kg) (n= 2)	5050 (± 49.1)			
Day 14: IVA (≥25 Kg) (n= 10)	12400 (± 118)			

## Statistical analyses

No statistical analyses for this end point

### Primary: Part B: Number of Subjects With Treatment-Emergent Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point title	Part B: Number of Subjects With Treatment-Emergent Adverse Events (AEs) and Serious Adverse Events (SAEs) <sup>[5]</sup> <sup>[6]</sup>
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End point description:

Safety set included all subjects who received at least 1 dose of study drug. The planned analysis was designed to assess overall treatment arm, irrespective of weight-based dosing regimen. The aim of weight-based dosing is to achieve similar exposures in children of different weights, thus analysis is presented for the single treatment arm.

End point type	Primary			
End point timeframe: 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 data was planned to be reported for this primary safety 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 is reporting data only for Part B.				
<b>End point values</b>	Part B			
Subject group type	Reporting group			
Number of subjects analysed	70			
Units: Subjects				
Subjects with AEs	65			
Subjects with SAEs	6			

## Statistical analyses

No statistical analyses for this end point

## Secondary: Part A: Cmax of TEZ Metabolites (M1-TEZ, M2-TEZ) and IVA Metabolites (M1-IVA, M6-IVA)

End point title	Part A: Cmax of TEZ Metabolites (M1-TEZ, M2-TEZ) and IVA Metabolites (M1-IVA, M6-IVA) <sup>[7]</sup>			
End point description: PK set. Here "Number Analyzed" signifies those subjects who were evaluable for this outcome measure at specified time points and "99999" represents "Not Applicable" as data for geometric coefficient of variation could not be calculated for the category with n=1 subject.				
End point type	Secondary			
End point timeframe: Day 1 and Day 14				
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 reporting data only for Part A.				
End point values	Part A			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
Day 1: M1-TEZ (<25 kg)(n=2)	1720 (± 3.29)			
Day 1: M1-TEZ (≥25 kg)(n=11)	1530 (± 22.0)			
Day 14: M1-TEZ (<25 kg)(n=2)	8360 (± 22)			
Day 14: M1-TEZ (≥25 kg)(n=10)	5930 (± 19.9)			
Day 1: M2-TEZ (<25 kg)(n=2)	1130 (± 4.36)			
Day 1: M2-TEZ (≥25 kg)(n=11)	922 (± 25.8)			
Day 14: M2-TEZ (<25 kg)(n=2)	6180 (± 27.2)			



Day 14: M2-TEZ ( $\geq 25$ kg)(n=10)	5350 ( $\pm 27.2$ )			
Day 1: M1-IVA ( $< 25$ kg)(n=1)	2320 ( $\pm 99999$ )			
Day 1: M1-IVA ( $\geq 25$ kg)(n=9)	2430 ( $\pm 57.1$ )			
Day 14: M1-IVA ( $< 25$ kg)(n=2)	1460 ( $\pm 34.6$ )			
Day 14: M1-IVA ( $\geq 25$ kg)(n=10)	3420 ( $\pm 72.7$ )			
Day 1: M6-IVA ( $< 25$ kg)(n=1)	849 ( $\pm 99999$ )			
Day 1: M6-IVA ( $\geq 25$ kg)(n=9)	1070 ( $\pm 55.7$ )			
Day 14: M6-IVA ( $< 25$ kg)(n=2)	1090 ( $\pm 31.4$ )			
Day 14: M6-IVA ( $\geq 25$ kg)(n=10)	2720 ( $\pm 59.2$ )			

## Statistical analyses

No statistical analyses for this end point

## Secondary: Part A: AUCtau of TEZ Metabolites (M1-TEZ, M2-TEZ) and IVA Metabolites (M1-IVA, M6-IVA)

End point title	Part A: AUCtau of TEZ Metabolites (M1-TEZ, M2-TEZ) and IVA Metabolites (M1-IVA, M6-IVA) <sup>[8]</sup>
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End point description:

PK set. Here "Number Analyzed" signifies those subjects who were evaluable for this outcome measure at specified time points. "Number Analyzed=0" signified no subjects were evaluated for the specified parameter at that time point and "99999" represents "Not Applicable" as data for geometric mean and geometric coefficient of variation could not be calculated for the category with n=0 subject.

End point type	Secondary
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End point timeframe:

Day 1 and Day 14

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 reporting data only for Part A.

End point values	Part A			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: hr*ng/mL				
geometric mean (geometric coefficient of variation)				
Day 1: M1-TEZ ( $< 25$ kg)(n=2)	36500 ( $\pm 5.80$ )			
Day 1: M1-TEZ ( $\geq 25$ kg)(n=11)	27400 ( $\pm 26.3$ )			
Day 14: M1-TEZ ( $< 25$ kg)(n=2)	160000 ( $\pm 15.5$ )			
Day 14: M1-TEZ ( $\geq 25$ kg)(n=10)	121000 ( $\pm 17.1$ )			
Day 1: M2-TEZ ( $< 25$ kg)(n=2)	14200 ( $\pm 12.3$ )			
Day 1: M2-TEZ ( $\geq 25$ kg)(n=11)	11100 ( $\pm 25.9$ )			
Day 14: M2-TEZ ( $< 25$ kg)(n=2)	137000 ( $\pm 32.7$ )			
Day 14: M2-TEZ ( $\geq 25$ kg)(n=10)	119000 ( $\pm 27.7$ )			
Day 1: M1-IVA ( $< 25$ kg)(n=0)	99999 ( $\pm 99999$ )			

Day 1: M1-IVA ( $\geq 25$ kg)(n=0)	99999 ( $\pm$ 99999)			
Day 14: M1-IVA ( $< 25$ kg)(n=2)	13700 ( $\pm$ 52.1)			
Day 14: M1-IVA ( $\geq 25$ kg)(n=10)	30300 ( $\pm$ 81.1)			
Day 1: M6-IVA ( $< 25$ kg)(n=0)	99999 ( $\pm$ 99999)			
Day 1: M6-IVA ( $\geq 25$ kg)(n=0)	99999 ( $\pm$ 99999)			
Day 14: M6-IVA ( $< 25$ kg)(n=2)	10200 ( $\pm$ 58.5)			
Day 14: M6-IVA ( $\geq 25$ kg)(n=10)	26000 ( $\pm$ 70.6)			

## Statistical analyses

No statistical analyses for this end point

### Secondary: Part A: Number of Subjects With AEs and SAEs

End point title	Part A: Number of Subjects With AEs and SAEs <sup>[9]</sup>
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End point description:

Safety set. The planned analysis was designed to assess overall treatment arm, irrespective of weight-based dosing regimen. The aim of weight based dosing is to achieve similar exposures in children of different weights, thus analysis is presented for the single treatment arm.

End point type	Secondary
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End point timeframe:

Day 1 up to Day 28

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 is reporting data only for Part A.

End point values	Part A			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: subjects				
Subjects with AEs	12			
Subjects with SAEs	0			

## Statistical analyses

No statistical analyses for this end point

### Secondary: Part B: Cmax of TEZ, TEZ Metabolites (M1-TEZ, M2-TEZ), IVA, and IVA Metabolites (M1-IVA, M6-IVA)

End point title	Part B: Cmax of TEZ, TEZ Metabolites (M1-TEZ, M2-TEZ), IVA, and IVA Metabolites (M1-IVA, M6-IVA) <sup>[10]</sup>
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End point description:

PK set. Here "Overall Number of subjects Analyzed" signifies those subjects who were evaluable for this outcome measure.

End point type	Secondary
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End point timeframe:

Week 16

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 is reporting data only for Part B.

End point values	Part B			
Subject group type	Reporting group			
Number of subjects analysed	69			
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
TEZ (<40 kg)(n=62)	4800 (± 33.7)			
TEZ (≥40 kg)(n=7)	5870 (± 46.5)			
M1-TEZ (<40 kg)(n=62)	5310 (± 36.0)			
M1-TEZ (≥40 kg)(n=7)	5440 (± 61.5)			
M2-TEZ (<40 kg)(n=62)	4170 (± 47.4)			
M2-TEZ (≥40 kg)(n=7)	5210 (± 55.0)			
IVA (<40 kg)(n=62)	725 (± 56.9)			
IVA (≥40 kg)(n=7)	886 (± 58.7)			
M1-IVA (<40 kg)(n=62)	1560 (± 54.8)			
M1-IVA (≥40 kg)(n=7)	1870 (± 50.2)			
M6-IVA (<40 kg)(n=62)	870 (± 69.2)			
M6-IVA (≥40 kg)(n=7)	1120 (± 29.5)			

## Statistical analyses

No statistical analyses for this end point

## Secondary: Part B: AUCtau of TEZ, TEZ Metabolites (M1-TEZ, M2-TEZ), IVA, and IVA Metabolites (M1-IVA, M6-IVA )

End point title	Part B: AUCtau of TEZ, TEZ Metabolites (M1-TEZ, M2-TEZ), IVA, and IVA Metabolites (M1-IVA, M6-IVA ) <sup>[11]</sup>
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End point description:

PK set. Here "Number Analyzed" signifies those subjects who were evaluable for this outcome measure at specified time points.

End point type	Secondary
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End point timeframe:

Week 16

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 is reporting data only for Part B.

End point values	Part B			
Subject group type	Reporting group			
Number of subjects analysed	69			
Units: hr*ng/mL				
geometric mean (geometric coefficient of variation)				
TEZ (<40 kg)(n=61)	50300 (± 36.3)			
TEZ (≥40 kg)(n=6)	60900 (± 50.6)			
M1-TEZ (<40 kg)(n=61)	104000 (± 44.2)			
M1-TEZ (≥40 kg)(n=6)	100000 (± 87.2)			
M2-TEZ (<40 kg)(n=61)	88400 (± 57.0)			
M2-TEZ (≥40 kg)(n=6)	93600 (± 46.5)			
IVA (<40 kg)(n=59)	5330 (± 62.2)			
IVA (≥40 kg)(n=6)	7410 (± 53.8)			
M1-IVA (<40 kg)(n=59)	12700 (± 55.9)			
M1-IVA (≥40 kg)(n=6)	17200 (± 40.4)			
M6-IVA (<40 kg)(n=59)	8140 (± 70.2)			
M6-IVA (≥40 kg)(n=6)	11100 (± 39.4)			

## 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) <sup>[12]</sup>
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End point description:

FEV1 is the volume of air that can forcibly be blown out in one second, after full inspiration. FAS: subjects who carry the intended CFTR mutations and received at least 1 dose of study drug. The aim of weight based dosing is to achieve similar exposures in children of different weights, thus the planned analysis is presented for the single treatment arm irrespective of weight-based dosing regimen.

End point type	Secondary
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End point timeframe:

From Baseline through Week 24

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 is reporting data only for Part B.

End point values	Part B			
Subject group type	Reporting group			
Number of subjects analysed	70			
Units: percentage points				
least squares mean (confidence interval 95%)	0.9 (-0.6 to 2.3)			

## Statistical analyses

No statistical analyses for this end point

### Secondary: Part B: Relative Change in ppFEV1

End point title	Part B: Relative Change in ppFEV1 <sup>[13]</sup>
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End point description:

FEV1 is the volume of air that can forcibly be blown out in one second, after full inspiration. FAS was used. The aim of weight based dosing is to achieve similar exposures in children of different weights, thus the planned analysis is presented for the single treatment arm irrespective of weight-based dosing regimen.

End point type	Secondary
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End point timeframe:

From Baseline through Week 24

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 is reporting data only for Part B.

End point values	Part B			
Subject group type	Reporting group			
Number of subjects analysed	70			
Units: percent change				
least squares mean (confidence interval 95%)	1.4 (-0.4 to 3.1)			

## 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 <sup>[14]</sup>
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End point description:

FAS was used. The aim of weight based dosing is to achieve similar exposures in children of different weights, thus the planned analysis is presented for the single treatment arm irrespective of weight-based dosing regimen.

End point type	Secondary
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End point timeframe:

From Baseline at 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 is reporting data only for Part B.

End point values	Part B			
Subject group type	Reporting group			
Number of subjects analysed	70			
Units: kg				
least squares mean (confidence interval 95%)	1.7 (1.3 to 2.0)			

## 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 <sup>[15]</sup>
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End point description:

z-score is a statistical measure to describe whether a mean was above or below the standard. Weight, adjusted for age and sex, was analyzed as weight-for-age z-score. A z-score of 0 is equal to the mean and is considered normal. Lower numbers indicate values lower than the mean and higher numbers indicate values higher than the mean. Higher values are indicative of higher weight. FAS was used. The aim of weight based dosing is to achieve similar exposures in children of different weights, thus the planned analysis is presented for the single treatment arm irrespective of weight-based dosing regimen.

End point type	Secondary
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End point timeframe:

From Baseline at 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 is reporting data only for Part B.

End point values	Part B			
Subject group type	Reporting group			
Number of subjects analysed	70			
Units: z-score				
least squares mean (confidence interval 95%)	0.00 (-0.05 to 0.05)			

## 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 <sup>[16]</sup>
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End point description:

FAS was used. The aim of weight based dosing is to achieve similar exposures in children of different weights, thus the planned analysis is presented for the single treatment arm irrespective of weight-based dosing regimen.

End point type	Secondary
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End point timeframe:

From Baseline at 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 is reporting data only for Part B.

End point values	Part B			
Subject group type	Reporting group			
Number of subjects analysed	70			
Units: centimeter (cm)				
least squares mean (confidence interval 95%)	2.7 (2.4 to 2.9)			

## 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 <sup>[17]</sup>
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End point description:

z-score is a statistical measure to describe whether a mean was above or below the standard. Height, adjusted for age and sex, was analyzed as height-for-age z-score. A z-score of 0 is equal to the mean and is considered normal. Lower numbers indicate values lower than the mean and higher numbers indicate values higher than the mean. Higher values are indicative of higher height. FAS was used. The aim of weight based dosing is to achieve similar exposures in children of different weights, thus the planned analysis is presented for the single treatment arm irrespective of weight-based dosing regimen.

End point type	Secondary
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End point timeframe:

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 is reporting data only for Part B.

End point values	Part B			
Subject group type	Reporting group			
Number of subjects analysed	70			
Units: z-score				
least squares mean (confidence interval 95%)	0.00 (-0.05 to 0.05)			

## 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) <sup>[18]</sup>
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End point description:

BMI was defined as weight in kg divided by height in square meter ( $m^2$ ). FAS was used. The aim of weight based dosing is to achieve similar exposures in children of different weights, thus the planned analysis is presented for the single treatment arm irrespective of weight-based dosing regimen.

End point type	Secondary
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End point timeframe:

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 is reporting data only for Part B.

End point values	Part B			
Subject group type	Reporting group			
Number of subjects analysed	70			
Units: $kg/m^2$				
least squares mean (confidence interval 95%)	0.23 (0.06 to 0.40)			

## 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 <sup>[19]</sup>
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End point description:

BMI was defined as weight in kg divided by height in  $m^2$ . z-score is a statistical measure to describe whether a mean was above or below the standard. BMI, adjusted for age and sex, was analyzed as BMI-for-age z-score. A z-score of 0 is equal to the mean and is considered normal. Lower numbers indicate values lower than the mean and higher numbers indicate values higher than the mean. Higher values are indicative of higher BMI. FAS was used. The aim of weight based dosing is to achieve similar exposures in children of different weights, thus the planned analysis is presented for the single treatment arm irrespective of weight-based dosing regimen.

End point type	Secondary
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End point timeframe:

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 is reporting data only for Part B.

End point values	Part B			
Subject group type	Reporting group			
Number of subjects analysed	70			
Units: z-score				
least squares mean (confidence interval 95%)	-0.03 (-0.10 to 0.04)			



## Statistical analyses

No statistical analyses for this end point

### Secondary: Part B: Absolute Change in Sweat Chloride

End point title	Part B: Absolute Change in Sweat Chloride <sup>[20]</sup>
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End point description:

Sweat samples were collected using an approved collection device. FAS was used. The aim of weight based dosing is to achieve similar exposures in children of different weights, thus the planned analysis is presented for the single treatment arm irrespective of weight-based dosing regimen.

End point type	Secondary
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End point timeframe:

From Baseline through Week 4

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 is reporting data only for Part B.

End point values	Part B			
Subject group type	Reporting group			
Number of subjects analysed	70			
Units: millimole per liter (mmol/L)				
least squares mean (confidence interval 95%)	-13.0 (-16.2 to -9.9)			

## Statistical analyses

No statistical analyses for this end point

### Secondary: Part B: Absolute Change in Sweat Chloride

End point title	Part B: Absolute Change in Sweat Chloride <sup>[21]</sup>
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End point description:

Sweat samples were collected using an approved collection device. FAS was used. The aim of weight based dosing is to achieve similar exposures in children of different weights, thus the planned analysis is presented for the single treatment arm irrespective of weight-based dosing regimen.

End point type	Secondary
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End point timeframe:

From Baseline through 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 is reporting data only for Part B.

End point values	Part B			
Subject group type	Reporting group			
Number of subjects analysed	70			
Units: mmol/L				
least squares mean (confidence interval 95%)	-14.5 (-17.4 to -11.6)			

## 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 <sup>[22]</sup>
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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 was used. The aim of weight based dosing is to achieve similar exposures in children of different weights, thus the planned analysis is presented for the single treatment arm irrespective of weight-based dosing regimen.

End point type	Secondary
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End point timeframe:

From Baseline through 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 is reporting data only for Part B.

End point values	Part B			
Subject group type	Reporting group			
Number of subjects analysed	70			
Units: units on a scale				
least squares mean (confidence interval 95%)	3.4 (1.4 to 5.5)			

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Part A: Day 1 up to Day 28; Part B: Day 1 up to Week 28

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	21.0
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### Reporting groups

Reporting group title	Part A
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Reporting group description:

Subjects weighing <25 kg received TEZ 50 mg/IVA 75 mg for 14 days. Subjects weighing ≥25 kg received TEZ 50 mg/IVA 150 mg for 14 days.

Reporting group title	Part B
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Reporting group description:

Subjects weighing <40 kg received TEZ 50 mg/IVA 75 mg as fixed dose combination in the morning and IVA 75 mg orally in the evening for 24 weeks.

Subjects weighing ≥40 kg received TEZ 100 mg/IVA 150 mg as fixed dose combination in the morning and IVA 150 mg in the evening for 24 weeks.

Serious adverse events	Part A	Part B	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 13 (0.00%)	6 / 70 (8.57%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Gastrointestinal disorders			
Breath odour			
subjects affected / exposed	0 / 13 (0.00%)	1 / 70 (1.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	0 / 13 (0.00%)	1 / 70 (1.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Snoring			
subjects affected / exposed	0 / 13 (0.00%)	1 / 70 (1.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Infections and infestations Infective pulmonary exacerbation of cystic fibrosis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	 0 / 13 (0.00%) 0 / 0 0 / 0	 2 / 70 (2.86%) 0 / 2 0 / 0	
Sinusitis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	 0 / 13 (0.00%) 0 / 0 0 / 0	 1 / 70 (1.43%) 0 / 1 0 / 0	
Metabolism and nutrition disorders Failure to thrive subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	 0 / 13 (0.00%) 0 / 0 0 / 0	 1 / 70 (1.43%) 0 / 1 0 / 0	

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

<b>Non-serious adverse events</b>	Part A	Part B	
Total subjects affected by non-serious adverse events subjects affected / exposed	12 / 13 (92.31%)	62 / 70 (88.57%)	
Investigations Activated partial thromboplastin time prolonged subjects affected / exposed occurrences (all)  Alanine aminotransferase increased subjects affected / exposed occurrences (all)  International normalised ratio increased subjects affected / exposed occurrences (all)  Prothrombin time prolonged subjects affected / exposed occurrences (all)	 1 / 13 (7.69%) 1  0 / 13 (0.00%) 0  1 / 13 (7.69%) 1  1 / 13 (7.69%) 1	 0 / 70 (0.00%) 0  6 / 70 (8.57%) 6  0 / 70 (0.00%) 0  0 / 70 (0.00%) 0	
Vascular disorders			

Pallor subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1	0 / 70 (0.00%) 0	
Nervous system disorders Headache subjects affected / exposed occurrences (all)	3 / 13 (23.08%) 3	6 / 70 (8.57%) 10	
General disorders and administration site conditions Pyrexia subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1	13 / 70 (18.57%) 14	
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all)  Abdominal pain upper subjects affected / exposed occurrences (all)  Constipation subjects affected / exposed occurrences (all)  Vomiting subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0  0 / 13 (0.00%) 0  1 / 13 (7.69%) 1  0 / 13 (0.00%) 0	10 / 70 (14.29%) 11  5 / 70 (7.14%) 5  2 / 70 (2.86%) 2  7 / 70 (10.00%) 8	
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)  Nasal congestion subjects affected / exposed occurrences (all)  Oropharyngeal pain subjects affected / exposed occurrences (all)  Productive cough	3 / 13 (23.08%) 4  2 / 13 (15.38%) 2  1 / 13 (7.69%) 1	25 / 70 (35.71%) 37  10 / 70 (14.29%) 12  6 / 70 (8.57%) 6	

subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0	6 / 70 (8.57%) 7	
Rhinorrhoea subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0	7 / 70 (10.00%) 7	
Sputum increased subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1	3 / 70 (4.29%) 3	
Skin and subcutaneous tissue disorders Rash erythematous subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1	0 / 70 (0.00%) 0	
Psychiatric disorders Abnormal behaviour subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1	0 / 70 (0.00%) 0	
Musculoskeletal and connective tissue disorders Neck pain subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1	1 / 70 (1.43%) 1	
Pain in extremity subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1	2 / 70 (2.86%) 2	
Infections and infestations Acute sinusitis subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1	0 / 70 (0.00%) 0	
Ear infection subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1	5 / 70 (7.14%) 5	
Infective pulmonary exacerbation of cystic fibrosis subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0	15 / 70 (21.43%) 20	
Influenza subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0	5 / 70 (7.14%) 5	

Nasopharyngitis subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1	6 / 70 (8.57%) 7	
Upper respiratory tract infection subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0	6 / 70 (8.57%) 9	
Urinary tract infection subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1	1 / 70 (1.43%) 1	
Viral upper respiratory tract infection subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0	4 / 70 (5.71%) 5	
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1	2 / 70 (2.86%) 2	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 April 2017	- Revised target enrollment, revised inclusion criteria
19 July 2017	- Defined dose for Part B

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported