Clinical trial results:
A Phase 1, Open-label, Randomized, Crossover Study to Evaluate the Relative Bioavailability of a Granule Formulation of Tezacaftor and Ivacaftor Compared to a Fixed-dose Combination Tablet in Healthy Adult Subjects

Summary

EudraCT number	2020-000689-40
Trial protocol	Outside EU/EEA
Global end of trial date	08 November 2020

Results information

Result version number	v1 (current)
This version publication date	19 November 2021
First version publication date	19 November 2021

Trial information

Trial identification

Sponsor protocol code	VX19-661-012

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
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-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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	07 December 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	08 November 2020
Global end of trial reached?	Yes
Global end of trial date	08 November 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the relative bioavailability (BA) of a granule formulation of tezacaftor (TEZ)/ivacaftor (IVA) compared to a reference fixed-dose combination (FDC) tablet of TEZ/IVA.

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	05 October 2020
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 16
Worldwide total number of subjects	16
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)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	16
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

This study was conducted in healthy subjects 19 to 55 years of age.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	TEZ/IVA Sequence 1: First Granules Then Tablet

Arm description:

Subjects received TEZ 50 milligrams (mg)/IVA 75 mg granules on Day 1 in dosing period 1 followed by TEZ 50 mg/IVA 75 mg fixed-dose combination (FDC) tablet on Day 15 in dosing period 2.

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

Dosage and administration details:

Subjects received a single dose of TEZ/IVA granule and tablet formulation in the fed state in dosing period 1 and 2 as per the sequence.

Arm title	TEZ/IVA Sequence 2: First Tablet Then Granules

Arm description:

Subjects received TEZ 50 mg/IVA 75 mg FDC tablet on Day 1 in dosing period 1 followed by TEZ 50 mg/IVA 75 mg granules on Day 15 in dosing period 2.

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

Dosage and administration details:

Subjects received a single dose of TEZ/IVA granule and tablet formulation in the fed state in dosing period 1 and 2 as per the sequence.

Number of subjects in period 1	TEZ/IVA Sequence 1: First Granules Then Tablet	TEZ/IVA Sequence 2: First Tablet Then Granules
Started	8	8
Completed	8	8

Baseline characteristics

Reporting groups	
Reporting group title	TEZ/IVA Sequence 1: First Granules Then Tablet
Reporting group description:	
Subjects received TEZ 50 milligrams (mg)/IVA 75 mg granules on Day 1 in dosing period 1 followed by TEZ 50 mg/IVA 75 mg fixed-dose combination (FDC) tablet on Day 15 in dosing period 2.	
Reporting group title	TEZ/IVA Sequence 2: First Tablet Then Granules
Reporting group description:	
Subjects received TEZ 50 mg/IVA 75 mg FDC tablet on Day 1 in dosing period 1 followed by TEZ 50 mg/IVA 75 mg granules on Day 15 in dosing period 2.	

Reporting group values	TEZ/IVA Sequence 1: First Granules Then Tablet	TEZ/IVA Sequence 2: First Tablet Then Granules	Total
Number of subjects	8	8	16
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	39.5	41.8	
standard deviation	± 5.5	± 6.4	-
Gender categorical			
Units: Subjects			
Female	4	5	9
Male	4	3	7

End points

End points reporting groups

Reporting group title	TEZ/IVA Sequence 1: First Granules Then Tablet
Reporting group description:	
Subjects received TEZ 50 milligrams (mg)/IVA 75 mg granules on Day 1 in dosing period 1 followed by TEZ 50 mg/IVA 75 mg fixed-dose combination (FDC) tablet on Day 15 in dosing period 2.	
Reporting group title	TEZ/IVA Sequence 2: First Tablet Then Granules
Reporting group description:	
Subjects received TEZ 50 mg/IVA 75 mg FDC tablet on Day 1 in dosing period 1 followed by TEZ 50 mg/IVA 75 mg granules on Day 15 in dosing period 2.	
Subject analysis set title	TEZ/IVA Granules
Subject analysis set type	Full analysis
Subject analysis set description:	
All subjects who received TEZ 50 mg/IVA 75 mg granules formulation in sequence 1 or 2.	
Subject analysis set title	TEZ/IVA FDC Tablet
Subject analysis set type	Full analysis
Subject analysis set description:	
All subjects who received TEZ 50 mg/IVA 75 mg tablet formulation in sequence 1 or 2.	

Primary: Maximum Observed Plasma Concentration (Cmax) of TEZ and IVA

End point title	Maximum Observed Plasma Concentration (Cmax) of TEZ and IVA
End point description:	
End point type	Primary
End point timeframe:	
Day 1 up to 144 hours post-dose	

End point values	TEZ/IVA Granules	TEZ/IVA FDC Tablet		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	16	16		
Units: microgram per milliliter (mcg/mL)				
geometric mean (geometric coefficient of variation)				
TEZ	2.63 (± 24.6)	3.23 (± 34.4)		
IVA	0.333 (± 50.0)	0.339 (± 58.7)		

Statistical analyses

Statistical analysis title	TEZ: Granules vs TEZ: Tablet
Statistical analysis description:	
As this is a cross-over study, actual number of subjects analysed for the statistical comparison was "16" for TEZ/IVA Granules arm and TEZ/IVA FDC Tablet arm. "Number of subjects included in analysis = 32" is reflected due to EudraCT database limitation of summing up the comparison arm numbers.	
Comparison groups	TEZ/IVA Granules v TEZ/IVA FDC Tablet

Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	Geometric Least Squares Mean Ratio
Point estimate	81.5
Confidence interval	
level	90 %
sides	2-sided
lower limit	71.4
upper limit	93.1

Statistical analysis title	IVA: Granules vs IVA: Tablet

Statistical analysis description:

As this is a cross-over study, actual number of subjects analysed for the statistical comparison was "16" for TEZ/IVA Granules arm and TEZ/IVA FDC Tablet arm. "Number of subjects included in analysis = 32" is reflected due to EudraCT database limitation of summing up the comparison arm numbers.

Comparison groups	TEZ/IVA FDC Tablet v TEZ/IVA Granules
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	Geometric Least Squares Mean Ratio
Point estimate	98.2
Confidence interval	
level	90 %
sides	2-sided
lower limit	85.5
upper limit	113

Primary: Area Under the Concentration Versus Time Curve From the Time of Dosing Extrapolated to Infinity [AUC(0 - inf)] of TEZ and IVA

End point title	Area Under the Concentration Versus Time Curve From the Time of Dosing Extrapolated to Infinity [AUC(0 - inf)] of TEZ and IVA

End point description:

End point type	Primary

End point timeframe:

Day 1 up to 144 hours post-dose

End point values	TEZ/IVA Granules	TEZ/IVA FDC Tablet		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	16	16		
Units: hours*microgram per milliliter(h*mcg/mL)				
geometric mean (geometric coefficient of variation)				
TEZ	48.4 (± 27.3)	51.8 (± 27.8)		
IVA	4.31 (± 67.0)	4.10 (± 61.3)		

Statistical analyses

Statistical analysis title	TEZ: Granules vs TEZ: Tablet

Statistical analysis description:

As this is a cross-over study, actual number of subjects analysed for the statistical comparison was "16" for TEZ/IVA Granules arm and TEZ/IVA FDC Tablet arm. "Number of subjects included in analysis = 32" is reflected due to EudraCT database limitation of summing up the comparison arm numbers.

Comparison groups	TEZ/IVA Granules v TEZ/IVA FDC Tablet
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	Geometric Least Squares Mean Ratio
Point estimate	93.4
Confidence interval	
level	90 %
sides	2-sided
lower limit	88.4
upper limit	98.7

Statistical analysis title	IVA: Granules vs IVA: Tablet

Statistical analysis description:

As this is a cross-over study, actual number of subjects analysed for the statistical comparison was "16" for TEZ/IVA Granules arm and TEZ/IVA FDC Tablet arm. "Number of subjects included in analysis = 32" is reflected due to EudraCT database limitation of summing up the comparison arm numbers.

Comparison groups	TEZ/IVA Granules v TEZ/IVA FDC Tablet
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	Geometric Least Squares Mean Ratio
Point estimate	105
Confidence interval	
level	90 %
sides	2-sided
lower limit	90.7
upper limit	122

Primary: Area Under the Concentration Versus Time Curve From the Time of Dosing to the Last Measurable Concentration [AUC(0-tlast)] of TEZ and IVA

End point title	Area Under the Concentration Versus Time Curve From the Time of Dosing to the Last Measurable Concentration [AUC(0-tlast)] of TEZ and IVA

End point description:

End point type	Primary

End point timeframe:

Day 1 up to 144 hours post-dose

End point values	TEZ/IVA Granules	TEZ/IVA FDC Tablet		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	16	16		
Units: h*mcg/mL				
geometric mean (geometric coefficient of variation)				
TEZ	42.9 (± 27.8)	45.7 (± 27.7)		
IVA	4.22 (± 68.2)	4.01 (± 62.5)		

Statistical analyses

Statistical analysis title	TEZ: Granules vs TEZ: Tablet

Statistical analysis description:

As this is a cross-over study, actual number of subjects analysed for the statistical comparison was "16" for TEZ/IVA Granules arm and TEZ/IVA FDC Tablet arm. "Number of subjects included in analysis = 32" is reflected due to EudraCT database limitation of summing up the comparison arm numbers.

Comparison groups	TEZ/IVA Granules v TEZ/IVA FDC Tablet
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	Geometric Least Squares Mean Ratio
Point estimate	93.9
Confidence interval	
level	90 %
sides	2-sided
lower limit	88.6
upper limit	99.5

Statistical analysis title	IVA: Granules vs IVA: Tablet

Statistical analysis description:

As this is a cross-over study, actual number of subjects analysed for the statistical comparison was "16" for TEZ/IVA Granules arm and TEZ/IVA FDC Tablet arm. "Number of subjects included in analysis = 32" is reflected due to EudraCT database limitation of summing up the comparison arm numbers.

Comparison groups	TEZ/IVA Granules v TEZ/IVA FDC Tablet

Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	Geometric Least Squares Mean Ratio
Point estimate	105
Confidence interval	
level	90 %
sides	2-sided
lower limit	90.6
upper limit	123

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Day 1 up to Day 21	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	23.1
Reporting groups	
Reporting group title	TEZ/IVA Granules
Reporting group description:	
All subjects who received TEZ 50 mg/IVA 75 mg granules formulation in sequence 1 or 2.	
Reporting group title	TEZ/IVA FDC Tablet
Reporting group description:	
All subjects who received TEZ 50 mg/IVA 75 mg tablet formulation in sequence 1 or 2.	

Serious adverse events	TEZ/IVA Granules	TEZ/IVA FDC Tablet	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			

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

Non-serious adverse events	TEZ/IVA Granules	TEZ/IVA FDC Tablet	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 16 (50.00%)	6 / 16 (37.50%)	
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Chest discomfort			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Eye disorders			

Dry eye			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Abdominal pain			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Constipation			
subjects affected / exposed	6 / 16 (37.50%)	3 / 16 (18.75%)	
occurrences (all)	6	3	
Dyspepsia			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Lip dry			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Nausea			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Epistaxis			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	2 / 16 (12.50%)	1 / 16 (6.25%)	
occurrences (all)	2	1	
Pruritus			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported