



Clinical trial results:

A Phase 2, Randomized, Placebo-Controlled, Double-blind Study to Evaluate the Effect of VX-661 in Combination With Ivacaftor on Chest Imaging Endpoints in Subjects Aged 12 Years and Older With Cystic Fibrosis, Homozygous for the F508del-CFTR Mutation

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2019-002189-11 |
| Trial protocol | Outside EU/EEA |
| Global end of trial date | 24 July 2018 |

Results information

| | |
|--------------------------------|------------------|
| Result version number | v1 (current) |
| This version publication date | 07 November 2019 |
| First version publication date | 07 November 2019 |

Trial information

Trial identification

| | |
|-----------------------|--------------|
| Sponsor protocol code | VX15-661-112 |
|-----------------------|--------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02730208 |
| 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) | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | Yes |

Notes:

Results analysis stage

| | |
|--|----------------|
| Analysis stage | Final |
| Date of interim/final analysis | 23 August 2018 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 24 July 2018 |
| Global end of trial reached? | Yes |
| Global end of trial date | 24 July 2018 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To evaluate the treatment effect of tezacaftor in combination with ivacaftor (TEZ/IVA) on chest imaging endpoints using low-dose computed tomography (LDCT) at Week 72, and to evaluate the safety of TEZ/IVA through Week 72.

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 | 13 September 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 | Australia: 41 |
| Worldwide total number of subjects | 41 |
| 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) | 19 |
| Adults (18-64 years) | 22 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 41 subjects were randomized and treated in the study.

Period 1

| | |
|------------------------------|--------------------------------|
| Period 1 title | Overall Trial (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Carer |

Arms

| | |
|------------------------------|---------|
| Are arms mutually exclusive? | Yes |
| Arm title | TEZ/IVA |

Arm description:

Subjects received TEZ/IVA fixed dose combination in the morning and IVA in the evening for 72 weeks.

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

Dosage and administration details:

Subjects received TEZ 100 milligram (mg)/IVA 150 mg once daily.

| | |
|--|-----------|
| 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 150 mg once daily.

| | |
|------------------|---------|
| Arm title | Placebo |
|------------------|---------|

Arm description:

Subjects received placebo matched to TEZ/IVA fixed dose combination in the morning and placebo matched to IVA in the evening for 72 weeks.

| | |
|--|------------------------------|
| Arm type | Placebo |
| Investigational medicinal product name | Placebo (matched to TEZ/IVA) |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Subjects received placebo matched to TEZ/IVA once daily.

| | |
|--|--------------------------|
| Investigational medicinal product name | Placebo (matched to IVA) |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |

| | |
|--------------------------|----------|
| Routes of administration | Oral use |
|--------------------------|----------|

Dosage and administration details:

Subjects received placebo matched to IVA once daily.

| Number of subjects in period 1 | TEZ/IVA | Placebo |
|---------------------------------------|---------|---------|
| Started | 20 | 21 |
| Completed | 20 | 20 |
| Not completed | 0 | 1 |
| Withdrawal of consent (not due to AE) | - | 1 |

Baseline characteristics

Reporting groups

| | |
|--|---------|
| Reporting group title | TEZ/IVA |
| Reporting group description: | |
| Subjects received TEZ/IVA fixed dose combination in the morning and IVA in the evening for 72 weeks. | |
| Reporting group title | Placebo |
| Reporting group description: | |
| Subjects received placebo matched to TEZ/IVA fixed dose combination in the morning and placebo matched to IVA in the evening for 72 weeks. | |

| Reporting group values | TEZ/IVA | Placebo | Total |
|--|---------|---------|-------|
| Number of subjects | 20 | 21 | 41 |
| Age categorical Units: Subjects | | | |
| Age continuous Units: years | | | |
| arithmetic mean | 20.4 | 20.1 | |
| standard deviation | ± 7.5 | ± 9.3 | - |
| Gender categorical Units: Subjects | | | |
| Female | 11 | 10 | 21 |
| Male | 9 | 11 | 20 |
| Ethnicity (NIH/ OMB) Units: Subjects | | | |
| Hispanic or Latino | 0 | 0 | 0 |
| Not Hispanic or Latino | 20 | 21 | 41 |
| Unknown or Not Reported | 0 | 0 | 0 |
| Race (NIH/OMB) 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 | 20 | 21 | 41 |
| More than one race | 0 | 0 | 0 |
| Unknown or Not Reported | 0 | 0 | 0 |
| Total Brody/ Cystic Fibrosis - Computed Tomography (CFCT) Score | | | |
| The exploratory Brody/CF-CT score semi-quantitatively scores the degree of structural lung disease as shown on CT in subjects with CF. The score ranges from a minimum of 0 to a maximum of 219 with higher scores indicating more severe structural lung disease. | | | |
| Units: scores on a scale | | | |
| arithmetic mean | 38.29 | 43.68 | |
| standard deviation | ± 22.91 | ± 33.96 | - |

End points

End points reporting groups

| | |
|--|---------|
| Reporting group title | TEZ/IVA |
| Reporting group description: | |
| Subjects received TEZ/IVA fixed dose combination in the morning and IVA in the evening for 72 weeks. | |
| Reporting group title | Placebo |
| Reporting group description: | |
| Subjects received placebo matched to TEZ/IVA fixed dose combination in the morning and placebo matched to IVA in the evening for 72 weeks. | |

Primary: Absolute Change in Total Brody/CF-CT Score

| | |
|--|--|
| End point title | Absolute Change in Total Brody/CF-CT Score |
| End point description: | |
| The exploratory Brody/CF-CT score semi-quantitatively scores the degree of structural lung disease as shown on CT in subjects with CF. The score ranges from a minimum of 0 to a maximum of 219 with higher scores indicating more severe structural lung disease. The full analysis set (FAS) included all subjects who were randomized and received at least 1 dose of study drug. | |
| End point type | Primary |
| End point timeframe: | |
| From Baseline at Week 72 | |

| End point values | TEZ/IVA | Placebo | | |
|-------------------------------------|--------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 20 | 21 | | |
| Units: scores on a scale | | | | |
| least squares mean (standard error) | 0.90 (\pm 2.09) | 2.38 (\pm 2.07) | | |

Statistical analyses

| | |
|---|------------------------------------|
| Statistical analysis title | Statistical Analysis |
| Comparison groups | TEZ/IVA v Placebo |
| Number of subjects included in analysis | 41 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[1] |
| Parameter estimate | Least Squares (LS) Mean Difference |
| Point estimate | -1.48 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -7.47 |
| upper limit | 4.52 |

Notes:

[1] - Treatment effect outcomes are estimates.

Secondary: Number of Subjects With Treatment-Emergent Adverse Events (AEs) and Serious Adverse Events (SAEs)

| | |
|-----------------|---|
| End point title | Number of Subjects With Treatment-Emergent Adverse Events (AEs) and Serious Adverse Events (SAEs) |
|-----------------|---|

End point description:

The safety set included all subjects who received at least 1 dose of study drug.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Day 1 up to Week 76

| End point values | TEZ/IVA | Placebo | | |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 20 | 21 | | |
| Units: Subjects | | | | |
| Subjects with AEs | 20 | 21 | | |
| Subjects with SAEs | 8 | 13 | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Day 1 up to Week 76

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 21.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|---------|
| Reporting group title | TEZ/IVA |
|-----------------------|---------|

Reporting group description:

Subjects received TEZ/IVA fixed dose combination in the morning and IVA in the evening for 72 weeks.

| | |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

Subjects received placebo matched to TEZ/IVA fixed dose combination in the morning and placebo matched to IVA in the evening for 72 weeks.

| Serious adverse events | TEZ/IVA | Placebo | |
|---|-----------------|------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 8 / 20 (40.00%) | 13 / 21 (61.90%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | | | |
| Investigations | | | |
| Bacterial test positive | | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 1 / 21 (4.76%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Weight decreased | | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 1 / 21 (4.76%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Atrioventricular block first degree | | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 0 / 21 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Immune system disorders | | | |
| Type I hypersensitivity | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 0 / 20 (0.00%) | 1 / 21 (4.76%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 1 / 21 (4.76%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abdominal pain upper | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 0 / 21 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vomiting | | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 1 / 21 (4.76%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Reproductive system and breast disorders | | | |
| Testicular torsion | | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 0 / 21 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Hepatic cirrhosis | | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 1 / 21 (4.76%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Atelectasis | | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 1 / 21 (4.76%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemoptysis | | | |

| | | | |
|--|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 20 (0.00%) | 1 / 21 (4.76%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Atypical mycobacterial lower respiratory tract infection | | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 1 / 21 (4.76%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastroenteritis | | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 1 / 21 (4.76%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infective pulmonary exacerbation of cystic fibrosis | | | |
| subjects affected / exposed | 5 / 20 (25.00%) | 6 / 21 (28.57%) | |
| occurrences causally related to treatment / all | 0 / 7 | 1 / 18 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lung infection pseudomonal | | | |
| subjects affected / exposed | 2 / 20 (10.00%) | 0 / 21 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 1 / 21 (4.76%) | |
| 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 | TEZ/IVA | Placebo | |
|---|------------------|------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 19 / 20 (95.00%) | 20 / 21 (95.24%) | |
| Investigations | | | |

| | | | |
|--|----------------------|----------------------|--|
| Bacterial test positive subjects affected / exposed occurrences (all) | 0 / 20 (0.00%) 0 | 5 / 21 (23.81%) 8 | |
| Blood alkaline phosphatase increased subjects affected / exposed occurrences (all) | 0 / 20 (0.00%) 0 | 2 / 21 (9.52%) 2 | |
| Fungal test positive subjects affected / exposed occurrences (all) | 1 / 20 (5.00%) 1 | 2 / 21 (9.52%) 3 | |
| Injury, poisoning and procedural complications | | | |
| Arthropod bite subjects affected / exposed occurrences (all) | 0 / 20 (0.00%) 0 | 2 / 21 (9.52%) 2 | |
| Sunburn subjects affected / exposed occurrences (all) | 1 / 20 (5.00%) 1 | 3 / 21 (14.29%) 3 | |
| Nervous system disorders | | | |
| Headache subjects affected / exposed occurrences (all) | 1 / 20 (5.00%) 1 | 4 / 21 (19.05%) 9 | |
| Migraine subjects affected / exposed occurrences (all) | 2 / 20 (10.00%) 5 | 0 / 21 (0.00%) 0 | |
| General disorders and administration site conditions | | | |
| Chest pain subjects affected / exposed occurrences (all) | 0 / 20 (0.00%) 0 | 2 / 21 (9.52%) 6 | |
| Fatigue subjects affected / exposed occurrences (all) | 1 / 20 (5.00%) 1 | 2 / 21 (9.52%) 2 | |
| Pyrexia subjects affected / exposed occurrences (all) | 3 / 20 (15.00%) 4 | 2 / 21 (9.52%) 2 | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 20 (5.00%) | 2 / 21 (9.52%) | |
| occurrences (all) | 2 | 3 | |
| Constipation | | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 2 / 21 (9.52%) | |
| occurrences (all) | 0 | 2 | |
| Nausea | | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 4 / 21 (19.05%) | |
| occurrences (all) | 0 | 8 | |
| Vomiting | | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 3 / 21 (14.29%) | |
| occurrences (all) | 0 | 4 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 8 / 20 (40.00%) | 9 / 21 (42.86%) | |
| occurrences (all) | 9 | 12 | |
| Epistaxis | | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 2 / 21 (9.52%) | |
| occurrences (all) | 0 | 4 | |
| Haemoptysis | | | |
| subjects affected / exposed | 4 / 20 (20.00%) | 2 / 21 (9.52%) | |
| occurrences (all) | 4 | 2 | |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 2 / 20 (10.00%) | 2 / 21 (9.52%) | |
| occurrences (all) | 2 | 2 | |
| Productive cough | | | |
| subjects affected / exposed | 4 / 20 (20.00%) | 4 / 21 (19.05%) | |
| occurrences (all) | 5 | 7 | |
| Rhinorrhoea | | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 2 / 21 (9.52%) | |
| occurrences (all) | 1 | 2 | |
| Sputum increased | | | |
| subjects affected / exposed | 2 / 20 (10.00%) | 1 / 21 (4.76%) | |
| occurrences (all) | 2 | 1 | |
| Upper respiratory tract congestion | | | |

| | | | |
|--|---------------------|---------------------|--|
| subjects affected / exposed occurrences (all) | 1 / 20 (5.00%) 1 | 2 / 21 (9.52%) 2 | |
| Infections and infestations | | | |
| Gastroenteritis | | | |
| subjects affected / exposed | 2 / 20 (10.00%) | 0 / 21 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Infective pulmonary exacerbation of cystic fibrosis | | | |
| subjects affected / exposed | 5 / 20 (25.00%) | 9 / 21 (42.86%) | |
| occurrences (all) | 12 | 16 | |
| Influenza | | | |
| subjects affected / exposed | 2 / 20 (10.00%) | 1 / 21 (4.76%) | |
| occurrences (all) | 2 | 1 | |
| Lower respiratory tract infection bacterial | | | |
| subjects affected / exposed | 3 / 20 (15.00%) | 2 / 21 (9.52%) | |
| occurrences (all) | 5 | 3 | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 3 / 20 (15.00%) | 1 / 21 (4.76%) | |
| occurrences (all) | 6 | 1 | |
| Pharyngitis | | | |
| subjects affected / exposed | 2 / 20 (10.00%) | 0 / 21 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Rhinitis | | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 2 / 21 (9.52%) | |
| occurrences (all) | 0 | 2 | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 4 / 20 (20.00%) | 2 / 21 (9.52%) | |
| occurrences (all) | 5 | 3 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|---|
| 06 January 2016 | Clarified assessment requirements and analysis timing |
| 15 December 2016 | Removed interim analysis, revised assessments, clarified eligibility requirements |
| 24 October 2017 | Clarified visit requirements |
| 26 February 2018 | Clarified visit requirements, added endpoint |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported