



Clinical trial results:

A Phase 3b, Randomized, Double blind, Controlled Study Evaluating the Efficacy and Safety of VX-445/Tezacaftor/Ivacaftor in Cystic Fibrosis Subjects, Homozygous for F508del

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2019-001735-31 |
| Trial protocol | GB BE |
| Global end of trial date | 24 July 2020 |

Results information

| | |
|--------------------------------|------------------|
| Result version number | v1 |
| This version publication date | 06 February 2021 |
| First version publication date | 06 February 2021 |

Trial information

Trial identification

| | |
|-----------------------|--------------|
| Sponsor protocol code | VX18-445-109 |
|-----------------------|--------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT04105972 |
| 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 | 11 August 2020 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 24 July 2020 |
| Global end of trial reached? | Yes |
| Global end of trial date | 24 July 2020 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of VX-445/TEZ/IVA in CF subjects, homozygous for F508del (F/F).

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 | 03 October 2019 |
| 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 Kingdom: 88 |
| Country: Number of subjects enrolled | Belgium: 20 |
| Country: Number of subjects enrolled | Germany: 38 |
| Country: Number of subjects enrolled | Australia: 30 |
| Worldwide total number of subjects | 176 |
| EEA total number of subjects | 146 |

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) | 53 |
| Adults (18-64 years) | 123 |
| 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 cystic fibrosis (CF) subjects aged 12 years or older.

Period 1

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

Arms

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

Arm description:

Following TEZ/IVA run-in period of 4 weeks, subjects received TEZ/IVA in the treatment period for 24 weeks.

| | |
|----------------------------------------|----------------------|
| Arm type | Active comparator |
| 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 fixed-dose combination (FDC) 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 once daily in the evening.

| | |
|------------------|-------------|
| Arm title | ELX/TEZ/IVA |
|------------------|-------------|

Arm description:

Following TEZ/IVA run-in period of 4 weeks, subjects received ELX/TEZ/IVA in the treatment period for 24 weeks.

| | |
|----------------------------------------|----------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | ELX/TEZ/IVA |
| Investigational medicinal product code | VX-445/VX-661/VX-770 |
| Other name | 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.

| | |
|----------------------------------------|-----------|
| 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.

| Number of subjects in period 1^[1] | TEZ/IVA | ELX/TEZ/IVA |
|-----------------------------------------------------|---------|-------------|
| Started | 88 | 87 |
| Completed | 86 | 86 |
| Not completed | 2 | 1 |
| Adverse Event | 2 | 1 |

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: A total of 176 subjects enrolled in the study. Out of those 176 subjects, 1 subject was randomized but not dosed in the treatment period. Therefore, only 175 subjects are included in the subject disposition and baseline section.

Baseline characteristics

Reporting groups

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

Reporting group description:

Following TEZ/IVA run-in period of 4 weeks, subjects received TEZ/IVA in the treatment period for 24 weeks.

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

Reporting group description:

Following TEZ/IVA run-in period of 4 weeks, subjects received ELX/TEZ/IVA in the treatment period for 24 weeks.

| Reporting group values | TEZ/IVA | ELX/TEZ/IVA | Total |
|-------------------------------------------------------------------------|----------------|----------------|-------|
| Number of subjects | 88 | 87 | 175 |
| Age categorical Units: Subjects | | | |
| Age continuous Units: years arithmetic mean standard deviation | 27.8 ± 11.0 | 27.9 ± 11.8 | - |
| Gender categorical Units: Subjects | | | |
| Female | 45 | 43 | 88 |
| Male | 43 | 44 | 87 |

End points

End points reporting groups

| | |
|-------------------------------------------------------------------------------------------------------------------------------------------------|-------------|
| Reporting group title | TEZ/IVA |
| Reporting group description: Following TEZ/IVA run-in period of 4 weeks, subjects received TEZ/IVA in the treatment period for 24 weeks. | |
| Reporting group title | ELX/TEZ/IVA |
| Reporting group description: Following TEZ/IVA run-in period of 4 weeks, subjects received ELX/TEZ/IVA in the treatment period for 24 weeks. | |

Primary: Absolute Change in CF Questionnaire-Revised (CFQ-R) Respiratory Domain Score

| | |
|-------------------------------------------------------|------------------------------------------------------------------------------|
| End point title | Absolute Change in CF Questionnaire-Revised (CFQ-R) Respiratory Domain Score |
| End point description: | |
| End point type | Primary |
| End point timeframe: From Baseline Through Week 24 | |

| End point values | TEZ/IVA | ELX/TEZ/IVA | | |
|----------------------------------------------|-------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 88 | 87 | | |
| Units: units on scale | | | | |
| least squares mean (confidence interval 95%) | 1.2 (-1.7 to 4.2) | 17.1 (14.1 to 20.1) | | |

Statistical analyses

| | |
|-----------------------------------------|------------------------------------------|
| Statistical analysis title | Statistical Analysis |
| Comparison groups | ELX/TEZ/IVA v TEZ/IVA |
| Number of subjects included in analysis | 175 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | Mixed-effects Model for Repeated Measure |
| Parameter estimate | Least Squares (LS) Mean Difference |
| Point estimate | 15.9 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 11.7 |
| upper limit | 20.1 |

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From Day 1 in the treatment period up to 28 days after last dose of study drug or to the completion of study participation date, whichever occurs first (up to Week 28)

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 23.0 |
|--------------------|------|

Reporting groups

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

Reporting group description:

Following TEZ/IVA run-in period of 4 weeks, subjects received TEZ/IVA in the treatment period for 24 weeks.

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

Reporting group description:

Following TEZ/IVA run-in period of 4 weeks, subjects received ELX/TEZ/IVA in the treatment period for 24 weeks.

| Serious adverse events | TEZ/IVA | ELX/TEZ/IVA | |
|---------------------------------------------------|------------------|----------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 14 / 88 (15.91%) | 5 / 87 (5.75%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | | | |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 0 / 88 (0.00%) | 1 / 87 (1.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Extrasystoles | | | |
| subjects affected / exposed | 1 / 88 (1.14%) | 0 / 87 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 0 / 88 (0.00%) | 1 / 87 (1.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|-------------------------------------------------|----------------|----------------|--|
| Gastrointestinal disorders | | | |
| Distal intestinal obstruction syndrome | | | |
| subjects affected / exposed | 1 / 88 (1.14%) | 0 / 87 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Haemoptysis | | | |
| subjects affected / exposed | 1 / 88 (1.14%) | 0 / 87 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Psychiatric disorders | | | |
| Anxiety | | | |
| subjects affected / exposed | 1 / 88 (1.14%) | 1 / 87 (1.15%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Depression | | | |
| subjects affected / exposed | 0 / 88 (0.00%) | 1 / 87 (1.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Insomnia | | | |
| subjects affected / exposed | 1 / 88 (1.14%) | 0 / 87 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Obsessive-compulsive disorder | | | |
| subjects affected / exposed | 1 / 88 (1.14%) | 0 / 87 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Psychotic disorder | | | |
| subjects affected / exposed | 1 / 88 (1.14%) | 0 / 87 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Nephrolithiasis | | | |

| | | | |
|-----------------------------------------------------|-----------------|----------------|--|
| subjects affected / exposed | 0 / 88 (0.00%) | 1 / 87 (1.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Infective pulmonary exacerbation of cystic fibrosis | | | |
| subjects affected / exposed | 9 / 88 (10.23%) | 1 / 87 (1.15%) | |
| occurrences causally related to treatment / all | 0 / 12 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 1 / 88 (1.14%) | 0 / 87 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Type 3 diabetes mellitus | | | |
| subjects affected / exposed | 0 / 88 (0.00%) | 1 / 87 (1.15%) | |
| 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 | ELX/TEZ/IVA | |
|--------------------------------------------------------------|------------------|------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 72 / 88 (81.82%) | 59 / 87 (67.82%) | |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 1 / 88 (1.14%) | 6 / 87 (6.90%) | |
| occurrences (all) | 2 | 7 | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 0 / 88 (0.00%) | 5 / 87 (5.75%) | |
| occurrences (all) | 0 | 6 | |
| Bacterial test positive | | | |
| subjects affected / exposed | 5 / 88 (5.68%) | 1 / 87 (1.15%) | |
| occurrences (all) | 8 | 1 | |
| Nervous system disorders | | | |

| | | | |
|--------------------------------------------------------------------------------------------------------------|------------------------|------------------------|--|
| Headache subjects affected / exposed occurrences (all) | 18 / 88 (20.45%) 26 | 25 / 87 (28.74%) 38 | |
| Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all) | 7 / 88 (7.95%) 10 | 4 / 87 (4.60%) 6 | |
| Diarrhoea subjects affected / exposed occurrences (all) | 7 / 88 (7.95%) 8 | 8 / 87 (9.20%) 10 | |
| Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) | 23 / 88 (26.14%) 32 | 11 / 87 (12.64%) 17 | |
| Haemoptysis subjects affected / exposed occurrences (all) | 6 / 88 (6.82%) 8 | 3 / 87 (3.45%) 3 | |
| Nasal congestion subjects affected / exposed occurrences (all) | 0 / 88 (0.00%) 0 | 6 / 87 (6.90%) 6 | |
| Oropharyngeal pain subjects affected / exposed occurrences (all) | 7 / 88 (7.95%) 8 | 11 / 87 (12.64%) 12 | |
| Productive cough subjects affected / exposed occurrences (all) | 3 / 88 (3.41%) 4 | 8 / 87 (9.20%) 10 | |
| Sputum increased subjects affected / exposed occurrences (all) | 16 / 88 (18.18%) 18 | 10 / 87 (11.49%) 10 | |
| Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all) | 0 / 88 (0.00%) 0 | 7 / 87 (8.05%) 8 | |
| Infections and infestations Infective pulmonary exacerbation of cystic fibrosis | | | |

| | | | |
|-----------------------------------|------------------|------------------|--|
| subjects affected / exposed | 32 / 88 (36.36%) | 10 / 87 (11.49%) | |
| occurrences (all) | 38 | 12 | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 13 / 88 (14.77%) | 17 / 87 (19.54%) | |
| occurrences (all) | 18 | 19 | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 5 / 88 (5.68%) | 9 / 87 (10.34%) | |
| occurrences (all) | 6 | 11 | |

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