



Clinical trial results:

A Phase 3, Open-label Study Evaluating the Long-term Safety and Efficacy of VX-445/TEZ/IVA Combination Therapy in Subjects With Cystic Fibrosis Who Are 6 Years of Age and Older

Summary

| | |
|--------------------------|------------------|
| EudraCT number | 2019-001827-11 |
| Trial protocol | GB IE |
| Global end of trial date | 24 February 2024 |

Results information

| | |
|--------------------------------|-------------------|
| Result version number | v1 |
| This version publication date | 07 September 2024 |
| First version publication date | 07 September 2024 |

Trial information

Trial identification

| | |
|-----------------------|--------------|
| Sponsor protocol code | VX19-445-107 |
|-----------------------|--------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT04183790 |
| 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-002324-PIP01-17 |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | Yes |

Notes:

Results analysis stage

| | |
|--|------------------|
| Analysis stage | Final |
| Date of interim/final analysis | 20 March 2024 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 24 February 2024 |
| Global end of trial reached? | Yes |
| Global end of trial date | 24 February 2024 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To evaluate the long-term safety and tolerability of elexacaftor (ELX)/tezacaftor (TEZ)/ivacaftor (IVA) in subjects with cystic fibrosis (CF) who are 6 years of age and older

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

| | |
|---|------------------|
| Actual start date of recruitment | 17 February 2020 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Safety, Efficacy |
| Long term follow-up duration | 45 Months |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-------------------|
| Country: Number of subjects enrolled | United Kingdom: 6 |
| Country: Number of subjects enrolled | Ireland: 5 |
| Country: Number of subjects enrolled | Canada: 6 |
| Country: Number of subjects enrolled | Australia: 8 |
| Country: Number of subjects enrolled | United States: 39 |
| Worldwide total number of subjects | 64 |
| EEA total number of subjects | 5 |

Notes:

Subjects enrolled per age group

| | |
|---|----|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 64 |
| Adolescents (12-17 years) | 0 |

| | |
|----------------------|---|
| Adults (18-64 years) | 0 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

The study was conducted in two parts, Part A and Part B. Subjects of both Parts A and B received the same treatment (ELX,TEZ,IVA). Therefore, results were planned to be collected and analyzed for the overall population of the study.

Pre-assignment

Screening details:

Subjects from parent study VX18-445-106 Part B (NCT03691779) were enrolled in this study. A total of 64 subjects were enrolled in this study.

Period 1

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

Arms

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

Arm description:

Subjects greater than or equal to (\geq) 6 years and less than ($<$) 12 years of age and weighing <30 kilograms (kg) received ELX (elexacaftor) 100 milligram (mg) once daily (qd) /TEZ (tezacaftor) 50 mg qd/IVA (ivacaftor) 75 mg every 12 hours (q12h) and those weighing (\geq) 30 kg received ELX 200 mg qd/TEZ 100 mg qd/IVA 150 mg in the treatment period for 192 week. Subjects \geq 12 years of age received ELX 200 mg qd/TEZ 100 mg qd/IVA 150 mg q12h in the treatment period for 192 weeks.

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

Dosage and administration details:

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

| | |
|--|-----------|
| Investigational medicinal product name | Ivacaftor |
| Investigational medicinal product code | VX-770 |
| Other name | IVA |
| 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 | ELX/TEZ/IVA |
|--------------------------------|-------------|
| Started | 64 |
| Part A completed | 60 |
| Rollover to Part B | 48 |
| Part B completed | 39 |

| | |
|--|----|
| Completed | 39 |
| Not completed | 25 |
| Subjects did not rollover to Part B | 12 |
| Adverse event | 1 |
| Withdrawal of Consent (not due to AE) | 6 |
| Commercial drug is available for subject | 6 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|----------------|
| Reporting group title | Overall Period |
|-----------------------|----------------|

Reporting group description:

Baseline data was analyzed on Full analysis set (FAS) which is defined as all subjects who received at least 1 dose of study drug.

| Reporting group values | Overall Period | Total | |
|------------------------|----------------|-------|--|
| Number of subjects | 64 | 64 | |
| Age categorical | | | |
| Units: Subjects | | | |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 9.3 | | |
| standard deviation | ± 1.8 | - | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 39 | 39 | |
| Male | 25 | 25 | |

End points

End points reporting groups

| | |
|---|-------------|
| Reporting group title | ELX/TEZ/IVA |
| Reporting group description: | |
| Subjects greater than or equal to (\geq) 6 years and less than ($<$) 12 years of age and weighing <30 kilograms (kg) received ELX (elexacaftor) 100 milligram (mg) once daily (qd) /TEZ (tezacaftor) 50 mg qd/IVA (ivacaftor) 75 mg every 12 hours (q12h) and those weighing (\geq) 30 kg received ELX 200 mg qd/TEZ 100 mg qd/IVA 150 mg in the treatment period for 192 week. Subjects \geq 12 years of age received ELX 200 mg qd/TEZ 100 mg qd/IVA 150 mg q12h in the treatment period for 192 weeks. | |

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

| | |
|--|---|
| End point title | Safety and Tolerability as Assessed by Number of Subjects With Treatment-Emergent Adverse Events (TEAEs) and Serious Adverse Events (SAEs) ^[1] |
| End point description: | |
| Safety Set is defined as all subjects who received at least 1 dose of study drug in the study. | |
| End point type | Primary |
| End point timeframe: | |
| Day 1 up to Week 196 | |

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Only descriptive statistics were planned. No statistical comparisons were planned for this endpoint.

| | | | | |
|-----------------------------|-----------------|--|--|--|
| End point values | ELX/TEZ/IVA | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 64 | | | |
| Units: Subjects | | | | |
| Subjects with TEAEs | 64 | | | |
| Subjects with SAEs | 7 | | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Day 1 up to Week 196

Adverse event reporting additional description:

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

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 26.1 |
|--------------------|------|

Reporting groups

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

Reporting group description:

Subjects ≥ 6 years and < 12 years of age and weighing < 30 kg received ELX 100 mg qd /TEZ 50 mg qd/IVA 75 mg q12h and those weighing ≥ 30 kg received ELX 200 mg qd/TEZ 100 mg qd/IVA 150 mg in the treatment period for 192 weeks. Subjects ≥ 12 years of age received ELX 200 mg qd/TEZ 100 mg qd/IVA 150 mg q12h in the treatment period for 192 weeks

| Serious adverse events | ELX/TEZ/IVA | | |
|--|-----------------|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 7 / 64 (10.94%) | | |
| number of deaths (all causes) | 0 | | |
| number of deaths resulting from adverse events | | | |
| Injury, poisoning and procedural complications | | | |
| Haematuria traumatic | | | |
| subjects affected / exposed | 1 / 64 (1.56%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nervous system disorders | | | |
| Idiopathic intracranial hypertension | | | |
| subjects affected / exposed | 1 / 64 (1.56%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| General disorders and administration site conditions | | | |
| Pyrexia | | | |
| subjects affected / exposed | 1 / 64 (1.56%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|---|----------------|--|--|
| Immune system disorders | | | |
| Anaphylactic reaction | | | |
| subjects affected / exposed | 1 / 64 (1.56%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |
| Constipation | | | |
| subjects affected / exposed | 3 / 64 (4.69%) | | |
| occurrences causally related to treatment / all | 1 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| Infective pulmonary exacerbation of cystic fibrosis | | | |
| subjects affected / exposed | 2 / 64 (3.13%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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

| Non-serious adverse events | ELX/TEZ/IVA | | |
|---|------------------|--|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 62 / 64 (96.88%) | | |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 6 / 64 (9.38%) | | |
| occurrences (all) | 9 | | |
| Bacterial test positive | | | |
| subjects affected / exposed | 7 / 64 (10.94%) | | |
| occurrences (all) | 12 | | |
| SARS-CoV-2 test positive | | | |
| subjects affected / exposed | 8 / 64 (12.50%) | | |
| occurrences (all) | 8 | | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 5 / 64 (7.81%) | | |
| occurrences (all) | 7 | | |
| Injury, poisoning and procedural complications | | | |

| | | | |
|---|---|--|--|
| Immunisation reaction subjects affected / exposed occurrences (all) | 4 / 64 (6.25%) 4 | | |
| Nervous system disorders Headache subjects affected / exposed occurrences (all) | 26 / 64 (40.63%) 39 | | |
| General disorders and administration site conditions Pyrexia subjects affected / exposed occurrences (all) Fatigue subjects affected / exposed occurrences (all) | 28 / 64 (43.75%) 52 10 / 64 (15.63%) 11 | | |
| Ear and labyrinth disorders Ear pain subjects affected / exposed occurrences (all) | 5 / 64 (7.81%) 6 | | |
| Gastrointestinal disorders Abdominal discomfort subjects affected / exposed occurrences (all) Abdominal pain subjects affected / exposed occurrences (all) Constipation subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Vomiting | 4 / 64 (6.25%) 5 14 / 64 (21.88%) 16 10 / 64 (15.63%) 15 10 / 64 (15.63%) 16 6 / 64 (9.38%) 10 | | |

| | | | |
|---|------------------|--|--|
| subjects affected / exposed | 17 / 64 (26.56%) | | |
| occurrences (all) | 33 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 40 / 64 (62.50%) | | |
| occurrences (all) | 103 | | |
| Epistaxis | | | |
| subjects affected / exposed | 4 / 64 (6.25%) | | |
| occurrences (all) | 4 | | |
| Nasal congestion | | | |
| subjects affected / exposed | 23 / 64 (35.94%) | | |
| occurrences (all) | 43 | | |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 24 / 64 (37.50%) | | |
| occurrences (all) | 43 | | |
| Productive cough | | | |
| subjects affected / exposed | 11 / 64 (17.19%) | | |
| occurrences (all) | 23 | | |
| Rhinorrhoea | | | |
| subjects affected / exposed | 21 / 64 (32.81%) | | |
| occurrences (all) | 36 | | |
| Sinus congestion | | | |
| subjects affected / exposed | 4 / 64 (6.25%) | | |
| occurrences (all) | 9 | | |
| Infections and infestations | | | |
| COVID-19 | | | |
| subjects affected / exposed | 18 / 64 (28.13%) | | |
| occurrences (all) | 21 | | |
| Ear infection | | | |
| subjects affected / exposed | 4 / 64 (6.25%) | | |
| occurrences (all) | 4 | | |
| Hordeolum | | | |
| subjects affected / exposed | 9 / 64 (14.06%) | | |
| occurrences (all) | 16 | | |
| Infective pulmonary exacerbation of cystic fibrosis | | | |

| | | | |
|---|------------------|--|--|
| subjects affected / exposed | 8 / 64 (12.50%) | | |
| occurrences (all) | 8 | | |
| Influenza | | | |
| subjects affected / exposed | 7 / 64 (10.94%) | | |
| occurrences (all) | 7 | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 10 / 64 (15.63%) | | |
| occurrences (all) | 22 | | |
| Pharyngitis streptococcal | | | |
| subjects affected / exposed | 5 / 64 (7.81%) | | |
| occurrences (all) | 6 | | |
| Sinusitis | | | |
| subjects affected / exposed | 6 / 64 (9.38%) | | |
| occurrences (all) | 9 | | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 19 / 64 (29.69%) | | |
| occurrences (all) | 61 | | |
| Viral upper respiratory tract infection | | | |
| subjects affected / exposed | 7 / 64 (10.94%) | | |
| occurrences (all) | 12 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|--------------|---|
| 10 June 2021 | Amended to extend treatment period by adding Part B (additional 96 weeks of treatment duration) and updated monitoring text to include flexibility for remote monitoring. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported