# Clinical trial results:
# A Phase 3b Open label Study Evaluating the Long term Safety and Efficacy of Elexacaftor/Tezacaftor/Ivacaftor Combination Therapy in Cystic Fibrosis Subjects Ages 6 Years and Older Who Are Heterozygous for the F508del Mutation and a Minimal Function Mutation (F/MF)

## Summary

| | |
|---|---|
| EudraCT number | 2020-001404-42 |
| Trial protocol | GB DE DK NL FR |
| Global end of trial date | 24 March 2023 |

### Results information

| | |
|---|---|
| Result version number | v2 (current) |
| This version publication date | 25 May 2024 |
| First version publication date | 08 October 2023 |
| Version creation reason | • New data added to full data set<br>Final result is updated in draft |

## Trial information

### Trial identification

| | |
|---|---|
| Sponsor protocol code | VX20-445-119 |

### Additional study identifiers

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT04545515 |
| 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, medicalinfo@vrtx.com |
| Scientific contact | Medical Monitor, Vertex Pharmaceuticals Incorporated, 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 | 20 April 2023 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 24 March 2023 |
| Global end of trial reached? | Yes |
| Global end of trial date | 24 March 2023 |
| 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)

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 | 11 January 2021 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Efficacy, Safety |
| Long term follow-up duration | 23 Months |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | United Kingdom: 17 |
| Country: Number of subjects enrolled | Switzerland: 12 |
| Country: Number of subjects enrolled | Australia: 11 |
| Country: Number of subjects enrolled | Canada: 13 |
| Country: Number of subjects enrolled | Denmark: 3 |
| Country: Number of subjects enrolled | France: 13 |
| Country: Number of subjects enrolled | Germany: 31 |
| Country: Number of subjects enrolled | Israel: 5 |
| Country: Number of subjects enrolled | Netherlands: 7 |
| Country: Number of subjects enrolled | Spain: 8 |
| Worldwide total number of subjects | 120 |
| EEA total number of subjects | 62 |

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) | 120 |
| 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:

A total of 120 subjects from the parent study VX19-445-116 (NCT04353817) 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 6 to less than <12 year of age and weighing <30 kilogram (kg) at Day 1 received ELX 100 milligram (mg)/TEZ 50 mg /IVA 75 mg as fixed dose combination (FDC) tablets in the morning and IVA as mono tablet in the evening and those weighing more than or equal to (≥) 30 kg at Day 1 received ELX 200 mg/TEZ 100 mg /IVA 150 mg as FDC tablets in the morning and IVA as mono tablet in the evening for 96 weeks. Doses were adjusted upward with subsequent changes in weight. Subjects ≥12 years age at Day 1 received ELX 200 mg/TEZ 100 mg/IVA 150 mg as FDC tablets in the morning and IVA as mono tablet in the evening for 96 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 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.

| **Number of subjects in period 1** | ELX/TEZ/IVA |
|---|---|
| Started | 120 |
| Placebo-ELX/TEZ/IVA | 61 [1] |
| ELX/TEZ/IVA-ELX/TEZ/IVA | 59 [2] |
| Completed | 110 |
| Not completed | 10 |

| | |
|---|---|
| Adverse event | 1 |
| Withdrawal of consent (not due to AE) | 2 |
| Commercial drug is available for subject | 7 |

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Subjects from the Placebo group of the parent study VX19-445-116, who received ELX/TEZ/IVA during the current study VX20-445-119.
[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Subjects from the ELX/TEZ/IVA group of the parent study VX19-445-116, who continued to receive ELX/TEZ/IVA during the current study VX20-445-119.

## Baseline characteristics

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

Reporting group description:

Baseline data for the long-term safety analysis is based on the parent study baseline, which is defined as the most recent non-missing measurement collected before the first dose of study drug in the treatment period of parent study.

| Reporting group values | Overall Period | Total | |
|---|---|---|---|
| Number of subjects | 120 | 120 | |
| Age categorical<br>Units: Subjects | | | |
| Age continuous<br>Units: years | | | |
| arithmetic mean | 9.1 | | |
| standard deviation | ± 1.7 | - | |
| Gender categorical<br>Units: Subjects | | | |
| Female | 69 | 69 | |
| Male | 51 | 51 | |
| Ethnicity<br>Units: Subjects | | | |
| Hispanic or Latino | 1 | 1 | |
| Not Hispanic or Latino | 90 | 90 | |
| Not collected per local regulations | 29 | 29 | |
| Race<br>Units: Subjects | | | |
| White | 87 | 87 | |
| Black or African American | 1 | 1 | |
| Asian | 1 | 1 | |
| American Indian or Alaska Native | 1 | 1 | |
| Other | 1 | 1 | |
| Not collected per local Regulations | 28 | 28 | |
| Multiracial | 1 | 1 | |

## End points

### End points reporting groups

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

Reporting group description:

Subjects 6 to less than <12 year of age and weighing <30 kilogram (kg) at Day 1 received ELX 100 milligram (mg)/TEZ 50 mg /IVA 75 mg as fixed dose combination (FDC) tablets in the morning and IVA as mono tablet in the evening and those weighing more than or equal to (≥) 30 kg at Day 1 received ELX 200 mg/TEZ 100 mg /IVA 150 mg as FDC tablets in the morning and IVA as mono tablet in the evening for 96 weeks. Doses were adjusted upward with subsequent changes in weight. Subjects ≥12 years age at Day 1 received ELX 200 mg/TEZ 100 mg/IVA 150 mg as FDC tablets in the morning and IVA as mono tablet in the evening for 96 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:

The Open-Label Safety Set (OL-SS) included all subjects who had received at least 1 dose of study drug in the Open label extension (OLE) study.

| End point type | Primary |
|---|---|

End point timeframe:

From Baseline up to Week 100

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 the primary safety endpoint.

| End point values | ELX/TEZ/IVA | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 120 | | | |
| Units: Subjects | | | | |
| Subjects With TEAEs | 118 | | | |
| Subjects With SAEs | 13 | | | |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Absolute Change From Parent Study Baseline in Sweat Chloride (SwCl)

| End point title | Absolute Change From Parent Study Baseline in Sweat Chloride (SwCl) |
|---|---|

End point description:

Sweat samples were collected using an approved collection device. The OL Full Analysis Set (OL-FAS) is defined as all enrolled subjects who have received at least 1 dose of study drug in the open-label extension study. Data were planned to be presented as per parent study reporting groups (i.e., Placebo-ELX/TEZ/IVA and ELX/TEZ/IVA-ELX/TEZ/IVA). Here, "n" signifies subjects who were evaluable in the

specified parent study reporting group at OL Week 96.

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

End point timeframe:

From Parent Study Baseline to Week 96

| **End point values** | ELX/TEZ/IVA | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 98 | | | |
| Units: millimole per liter (mmol/L) | | | | |
| least squares mean (standard error) | | | | |
| Placebo-ELX/TEZ/IVA (n=52) | -57.3 (± 2.2) | | | |
| ELX/TEZ/IVA-ELX/TEZ/IVA (n=46) | -57.5 (± 2.3) | | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Absolute Change From Parent Study Baseline in Lung Clearance Index 2.5 (LCI2.5)

| End point title | Absolute Change From Parent Study Baseline in Lung Clearance Index 2.5 (LCI2.5) |
|---|---|

End point description:

The LCI2.5 index is the number of lung turnovers required to reduce the end tidal inert gas concentration to 1/40th of its starting values and is calculated by dividing the sum of exhaled tidal breaths (cumulative exhaled volume (CEV)) by simultaneously measured functional residual capacity (FRC). An LCI of 7.5 and below is normal; values greater than 7.5 are abnormal. LCI is able to detect abnormalities in lung function earlier than more traditional modalities such as spirometry. OL-FAS. Data were planned to be presented as per parent study reporting groups (i.e., Placebo-ELX/TEZ/IVA and ELX/TEZ/IVA-ELX/TEZ/IVA). Here, "n" signifies subjects who were evaluable in the specified parent study reporting group at OL Week 96.

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

End point timeframe:

From Parent Study Baseline to Week 96

| **End point values** | ELX/TEZ/IVA | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 104 | | | |
| Units: Index | | | | |
| least squares mean (standard error) | | | | |
| Placebo-ELX/TEZ/IVA (n=56) | -1.74 (± 0.18) | | | |
| ELX/TEZ/IVA-ELX/TEZ/IVA (n=48) | -2.35 (± 0.19) | | | |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Day 1 up to Week 100

Adverse event reporting additional description:

The OL-SS included all subjects who had received at least 1 dose of study drug in the OLE study.

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

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 25.1 |

### Reporting groups

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

Reporting group description:

Subjects 6 to <12 year of age and weighing <30 kg at Day 1 received ELX 100 mg/TEZ 50 mg /IVA 75 mg as FDC tablets in the morning and IVA as mono tablet in the evening and those weighing ≥30 kg at Day 1 received ELX 200 mg/TEZ 100 mg /IVA 150 mg as FDC tablets in the morning and IVA as mono tablet in the evening for 96 weeks. Doses were adjusted upward with subsequent changes in weight. Subjects ≥12 years age at Day 1 received ELX 200 mg/TEZ 100 mg/IVA 150 mg as FDC tablets in the morning and IVA as mono tablet in the evening for 96 weeks.

| **Serious adverse events** | ELX/TEZ/IVA | | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 13 / 120 (10.83%) | | |
| number of deaths (all causes) | 0 | | |
| number of deaths resulting from adverse events | | | |
| Investigations | | | |
| Blood glucose increased | | | |
| subjects affected / exposed | 1 / 120 (0.83%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Injury, poisoning and procedural complications | | | |
| Head injury | | | |
| subjects affected / exposed | 1 / 120 (0.83%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| General disorders and administration site conditions | | | |
| General physical health deterioration | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 120 (0.83%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |
| Constipation | | | |
| subjects affected / exposed | 1 / 120 (0.83%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ileus paralytic | | | |
| subjects affected / exposed | 1 / 120 (0.83%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Enteritis | | | |
| subjects affected / exposed | 1 / 120 (0.83%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Steatorrhoea | | | |
| subjects affected / exposed | 1 / 120 (0.83%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Intestinal obstruction | | | |
| subjects affected / exposed | 1 / 120 (0.83%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal and urinary disorders | | | |
| Haematuria | | | |
| subjects affected / exposed | 1 / 120 (0.83%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| Pneumonia staphylococcal | | | |
| subjects affected / exposed | 1 / 120 (0.83%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|---|---|---|---|
| Pneumonia pseudomonal | | | |
| subjects affected / exposed | 1 / 120 (0.83%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infective pulmonary exacerbation of cystic fibrosis | | | |
| subjects affected / exposed | 2 / 120 (1.67%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Bacterial disease carrier | | | |
| subjects affected / exposed | 1 / 120 (0.83%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Metabolism and nutrition disorders | | | |
| Diabetes mellitus inadequate control | | | |
| subjects affected / exposed | 1 / 120 (0.83%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Weight gain poor | | | |
| subjects affected / exposed | 1 / 120 (0.83%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| 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 | 118 / 120 (98.33%) | | |
| Investigations | | | |
| Staphylococcus test positive | | | |
| subjects affected / exposed | 9 / 120 (7.50%) | | |
| occurrences (all) | 12 | | |
| SARS-CoV-2 test positive | | | |
| subjects affected / exposed | 12 / 120 (10.00%) | | |
| occurrences (all) | 13 | | |
| Bacterial test positive | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 7 / 120 (5.83%) | | |
| occurrences (all) | 10 | | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 6 / 120 (5.00%) | | |
| occurrences (all) | 8 | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 11 / 120 (9.17%) | | |
| occurrences (all) | 15 | | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 45 / 120 (37.50%) | | |
| occurrences (all) | 106 | | |
| General disorders and administration site conditions | | | |
| Pyrexia | | | |
| subjects affected / exposed | 48 / 120 (40.00%) | | |
| occurrences (all) | 85 | | |
| Fatigue | | | |
| subjects affected / exposed | 6 / 120 (5.00%) | | |
| occurrences (all) | 8 | | |
| Ear and labyrinth disorders | | | |
| Ear pain | | | |
| subjects affected / exposed | 8 / 120 (6.67%) | | |
| occurrences (all) | 13 | | |
| Immune system disorders | | | |
| Immunisation reaction | | | |
| subjects affected / exposed | 8 / 120 (6.67%) | | |
| occurrences (all) | 12 | | |
| Eye disorders | | | |
| Conjunctivitis allergic | | | |
| subjects affected / exposed | 7 / 120 (5.83%) | | |
| occurrences (all) | 12 | | |
| Gastrointestinal disorders | | | |
| Nausea | | | |
| subjects affected / exposed | 9 / 120 (7.50%) | | |
| occurrences (all) | 13 | | |
| Vomiting | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed<br>occurrences (all) | 24 / 120 (20.00%)<br>42 | | |
| Abdominal pain<br>subjects affected / exposed<br>occurrences (all) | 27 / 120 (22.50%)<br>44 | | |
| Abdominal pain upper<br>subjects affected / exposed<br>occurrences (all) | 11 / 120 (9.17%)<br>13 | | |
| Constipation<br>subjects affected / exposed<br>occurrences (all) | 8 / 120 (6.67%)<br>8 | | |
| Diarrhoea<br>subjects affected / exposed<br>occurrences (all) | 15 / 120 (12.50%)<br>22 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough<br>subjects affected / exposed<br>occurrences (all) | 62 / 120 (51.67%)<br>163 | | |
| Nasal congestion<br>subjects affected / exposed<br>occurrences (all) | 13 / 120 (10.83%)<br>15 | | |
| Oropharyngeal pain<br>subjects affected / exposed<br>occurrences (all) | 32 / 120 (26.67%)<br>51 | | |
| Productive cough<br>subjects affected / exposed<br>occurrences (all) | 17 / 120 (14.17%)<br>30 | | |
| Rhinorrhoea<br>subjects affected / exposed<br>occurrences (all) | 22 / 120 (18.33%)<br>50 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Pain in extremity<br>subjects affected / exposed<br>occurrences (all) | 9 / 120 (7.50%)<br>12 | | |
| Infections and infestations | | | |

| | | | |
|---|---|---|---|
| Bacterial disease carrier<br>subjects affected / exposed<br>occurrences (all) | 8 / 120 (6.67%)<br>11 | | |
| COVID-19<br>subjects affected / exposed<br>occurrences (all) | 70 / 120 (58.33%)<br>78 | | |
| Hordeolum<br>subjects affected / exposed<br>occurrences (all) | 10 / 120 (8.33%)<br>12 | | |
| Infective pulmonary exacerbation of cystic fibrosis<br>subjects affected / exposed<br>occurrences (all) | 19 / 120 (15.83%)<br>27 | | |
| Influenza<br>subjects affected / exposed<br>occurrences (all) | 11 / 120 (9.17%)<br>12 | | |
| Nasopharyngitis<br>subjects affected / exposed<br>occurrences (all) | 54 / 120 (45.00%)<br>115 | | |
| Viral upper respiratory tract infection<br>subjects affected / exposed<br>occurrences (all) | 13 / 120 (10.83%)<br>17 | | |
| Upper respiratory tract infection<br>subjects affected / exposed<br>occurrences (all) | 37 / 120 (30.83%)<br>65 | | |
| Rhinitis<br>subjects affected / exposed<br>occurrences (all) | 29 / 120 (24.17%)<br>50 | | |
| Metabolism and nutrition disorders<br>Decreased appetite<br>subjects affected / exposed<br>occurrences (all) | 6 / 120 (5.00%)<br>9 | | |

## 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