# Clinical trial results:
# A Phase 3b Open-label Study to Assess the Effect of Elexacaftor/Tezacaftor/Ivacaftor on Glucose Tolerance in Cystic Fibrosis Subjects with Abnormal Glucose Metabolism

## Summary

| | |
|---|---|
| EudraCT number | 2020-003170-44 |
| Trial protocol | BE CZ FR NL IT |
| Global end of trial date | 14 July 2022 |

### Results information

| | |
|---|---|
| Result version number | v1 |
| This version publication date | 29 January 2023 |
| First version publication date | 29 January 2023 |

## Trial information

### Trial identification

| | |
|---|---|
| Sponsor protocol code | VX19-445-117 |

### Additional study identifiers

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT04599465 |
| 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 | 19 August 2022 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 14 July 2022 |
| Global end of trial reached? | Yes |
| Global end of trial date | 14 July 2022 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

To evaluate the effect of elexacaftor (ELX)/tezacaftor (TEZ)/ivacaftor (IVA) on glucose tolerance in Cystic Fibrosis (CF) subjects with impaired glucose tolerance (IGT) or CF-related diabetes (CFRD)

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 | 15 January 2021 |
| 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 | Australia: 11 |
| Country: Number of subjects enrolled | Netherlands: 9 |
| Country: Number of subjects enrolled | Spain: 14 |
| Country: Number of subjects enrolled | Belgium: 7 |
| Country: Number of subjects enrolled | Czechia: 3 |
| Country: Number of subjects enrolled | France: 13 |
| Country: Number of subjects enrolled | Italy: 12 |
| Worldwide total number of subjects | 69 |
| EEA total number of subjects | 58 |

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) | 50 |
| 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 subjects with CF aged 12 years and older who are heterozygous for the F508del mutation and a minimal function mutation (F/MF genotypes), with abnormal glucose metabolism.

### 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 received ELX/TEZ/IVA fixed dose combination (FDC) in the morning and ivacaftor (IVA) in the evening.

| | |
|---|---|
| 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 combination 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 dose once daily in the evening.

| **Number of subjects in period 1** | ELX/TEZ/IVA |
|---|---|
| Started | 69 |
| Completed | 66 |
| Not completed | 3 |
| Physician decision | 1 |
| Withdrawal of consent (not due to AE) | 2 |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Overall Period |
| Reporting group description: | |
| Subjects received ELX/TEZ/IVA fixed dose combination (FDC) in the morning and ivacaftor (IVA) in the evening. | |

| Reporting group values | Overall Period | Total | |
|---|---|---|---|
| Number of subjects | 69 | 69 | |
| Age categorical<br>Units: Subjects | | | |
| Less than (<)18 years | 19 | 19 | |
| More than or equal to (≥)18 years | 50 | 50 | |
| Age continuous<br>Units: years | | | |
| arithmetic mean | 25.1 | | |
| standard deviation | ± 9.5 | - | |
| Gender categorical<br>Units: Subjects | | | |
| Female | 31 | 31 | |
| Male | 38 | 38 | |

## End points

### End points reporting groups

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

Reporting group description:

Subjects received ELX/TEZ/IVA fixed dose combination (FDC) in the morning and ivacaftor (IVA) in the evening.

### Primary: Change From Baseline in 2-hour Blood Glucose Levels Following an Oral Glucose Tolerance Test (OGTT) to the Average of Week 36 and Week 48

| | |
|---|---|
| End point title | Change From Baseline in 2-hour Blood Glucose Levels Following an Oral Glucose Tolerance Test (OGTT) to the Average of Week 36 and Week 48[1] |

End point description:

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

End point timeframe:

Baseline, Week 36 and 48

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: This is a single arm study, and thus no between-group comparisons were planned. However, participants' post-baseline values were compared to their pre-treatment baseline values with a mixed model for repeated measures (MMRM) with change from baseline in 2-hour post-OGTT blood glucose levels at each post-baseline visit as the dependent variable. The primary result obtained from the model was the estimated mean change from baseline to the average of Week 36 and Week 48.

| End point values | ELX/TEZ/IVA | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 66 | | | |
| Units: milligrams per deciliter (mg/dl) | | | | |
| least squares mean (confidence interval 95%) | -35.0 (-49.2 to -20.7) | | | |

### Statistical analyses

No statistical analyses for this end point

## Adverse events

| Adverse events information | |
|---|---|
| Timeframe for reporting adverse events: | |
| Day 1 up to Week 52 | |
| Assessment type | Systematic |

| Dictionary used | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 25.0 |

| Reporting groups | |
|---|---|
| Reporting group title | ELX/TEZ/IVA |
| Reporting group description: | |
| Subjects received ELX/TEZ/IVA fixed dose combination (FDC) in the morning and ivacaftor (IVA) in the evening. | |

| Serious adverse events | ELX/TEZ/IVA | | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 6 / 69 (8.70%) | | |
| number of deaths (all causes) | 0 | | |
| number of deaths resulting from adverse events | | | |
| Injury, poisoning and procedural complications | | | |
| Clavicle fracture | | | |
| subjects affected / exposed | 1 / 69 (1.45%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 1 / 69 (1.45%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |
| Gastritis | | | |
| subjects affected / exposed | 1 / 69 (1.45%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Reproductive system and breast disorders | | | |
| Heavy menstrual bleeding | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 69 (1.45%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Pulmonary haemorrhage | | | |
| subjects affected / exposed | 1 / 69 (1.45%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| Infective pulmonary exacerbation of cystic fibrosis | | | |
| subjects affected / exposed | 1 / 69 (1.45%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Influenza | | | |
| subjects affected / exposed | 1 / 69 (1.45%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Sinusitis | | | |
| subjects affected / exposed | 1 / 69 (1.45%) | | |
| 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 | 62 / 69 (89.86%) | | |
| Investigations | | | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 5 / 69 (7.25%) | | |
| occurrences (all) | 5 | | |
| Alanine aminotransferase increased | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 6 / 69 (8.70%) | | |
| occurrences (all) | 6 | | |
| Blood bilirubin increased | | | |
| subjects affected / exposed | 7 / 69 (10.14%) | | |
| occurrences (all) | 7 | | |
| Blood creatine phosphokinase increased | | | |
| subjects affected / exposed | 5 / 69 (7.25%) | | |
| occurrences (all) | 6 | | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 16 / 69 (23.19%) | | |
| occurrences (all) | 22 | | |
| General disorders and administration site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 5 / 69 (7.25%) | | |
| occurrences (all) | 5 | | |
| Pyrexia | | | |
| subjects affected / exposed | 16 / 69 (23.19%) | | |
| occurrences (all) | 22 | | |
| Immune system disorders | | | |
| Immunisation reaction | | | |
| subjects affected / exposed | 6 / 69 (8.70%) | | |
| occurrences (all) | 9 | | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 9 / 69 (13.04%) | | |
| occurrences (all) | 13 | | |
| Diarrhoea | | | |
| subjects affected / exposed | 13 / 69 (18.84%) | | |
| occurrences (all) | 16 | | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 8 / 69 (11.59%) | | |
| occurrences (all) | 9 | | |
| Nausea | | | |
| subjects affected / exposed | 6 / 69 (8.70%) | | |
| occurrences (all) | 6 | | |

| | | | |
|---|---|---|---|
| Vomiting | | | |
| subjects affected / exposed | 7 / 69 (10.14%) | | |
| occurrences (all) | 9 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 11 / 69 (15.94%) | | |
| occurrences (all) | 12 | | |
| Dyspnoea | | | |
| subjects affected / exposed | 4 / 69 (5.80%) | | |
| occurrences (all) | 4 | | |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 8 / 69 (11.59%) | | |
| occurrences (all) | 9 | | |
| Productive cough | | | |
| subjects affected / exposed | 5 / 69 (7.25%) | | |
| occurrences (all) | 7 | | |
| Sputum increased | | | |
| subjects affected / exposed | 12 / 69 (17.39%) | | |
| occurrences (all) | 13 | | |
| Skin and subcutaneous tissue disorders | | | |
| Acne | | | |
| subjects affected / exposed | 4 / 69 (5.80%) | | |
| occurrences (all) | 4 | | |
| Rash | | | |
| subjects affected / exposed | 7 / 69 (10.14%) | | |
| occurrences (all) | 10 | | |
| Infections and infestations | | | |
| COVID-19 | | | |
| subjects affected / exposed | 22 / 69 (31.88%) | | |
| occurrences (all) | 22 | | |
| Infective pulmonary exacerbation of cystic fibrosis | | | |
| subjects affected / exposed | 10 / 69 (14.49%) | | |
| occurrences (all) | 14 | | |
| Influenza | | | |
| subjects affected / exposed | 6 / 69 (8.70%) | | |
| occurrences (all) | 6 | | |

| | | | |
|---|---|---|---|
| Nasopharyngitis<br>subjects affected / exposed<br>occurrences (all)<br><br>Rhinitis<br>subjects affected / exposed<br>occurrences (all)<br><br>Tonsillitis<br>subjects affected / exposed<br>occurrences (all)<br><br>Upper respiratory tract infection<br>subjects affected / exposed<br>occurrences (all) | <br>15 / 69 (21.74%)<br>17<br><br><br>7 / 69 (10.14%)<br>11<br><br><br>4 / 69 (5.80%)<br>4<br><br><br>4 / 69 (5.80%)<br>5 | | |
| Metabolism and nutrition disorders<br>Hypoglycaemia<br>subjects affected / exposed<br>occurrences (all) | <br><br>4 / 69 (5.80%)<br>8 | | |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 22 September 2020 | Removed option for use of remote measures at certain study visits such that those visits are to be performed in the clinic; clarified different glomerular filtration rates for subjects ≥18 years of age and subjects <18 years of age; clarified that during in-clinic visits, spirometry assessments may be performed on more than 1 spirometer, as applicable; removed sweat chloride assessment at Week 4. |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported