# Clinical trial results:
# A Randomized, Double-blind, Placebo-controlled, Crossover Study to Evaluate the Efficacy of Ivacaftor in Subjects with Cystic Fibrosis Who are 6 Years of Age and Older and Have Either a 3849 + 10KB CT or D1152H-CFTR Mutation

## Summary

| | |
|---|---|
| EudraCT number | 2017-000457-39 |
| Trial protocol | Outside EU/EEA |
| Global end of trial date | 18 December 2018 |

**Results information**

| | |
|---|---|
| Result version number | v2 (current) |
| This version publication date | 29 February 2020 |
| First version publication date | 04 July 2019 |
| Version creation reason | • New data added to full data set<br>Updated for Consistency with CT.gov Results |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | VX16-770-127 |

**Additional study identifiers**

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT03068312 |
| 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 | 22 January 2019 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 18 December 2018 |
| Global end of trial reached? | Yes |
| Global end of trial date | 18 December 2018 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

To evaluate the efficacy of ivacaftor (IVA) treatment in subjects with cystic fibrosis (CF) 6 years of age and older who have a 3849 + 10KB CT or D1152H CF transmembrane conductance regulator gene (CFTR) mutation.

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 | 18 July 2017 |
| 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 | Israel: 38 |
| Worldwide total number of subjects | 38 |
| 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) | 4 |
| Adolescents (12-17 years) | 4 |
| Adults (18-64 years) | 30 |
| 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.

### Period 1

| | |
|---|---|
| Period 1 title | Overall 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** | Sequence 1: First IVA Then Placebo |

Arm description:

Subjects received IVA for 8 weeks in treatment period 1 followed by placebo matched to IVA for 8 weeks in treatment period 2. A washout period of 8 weeks was maintained between the 2 treatment periods.

| | |
|---|---|
| Arm type | Experimental |
| 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 milligram (mg) every 12 hours.

| | |
|---|---|
| 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 every 12 hours.

| | |
|---|---|
| **Arm title** | Sequence 2: First Placebo Then IVA |

Arm description:

Subjects received placebo matched to IVA for 8 weeks in treatment period 1 followed by IVA for 8 weeks in treatment period 2. A washout period of 8 weeks was maintained between the 2 treatment periods.

| | |
|---|---|
| Arm type | Experimental |
| 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 every 12 hours.

| | |
|---|---|
| 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 every 12 hours.

| **Number of subjects in period 1** | Sequence 1: First IVA Then Placebo | Sequence 2: First Placebo Then IVA |
|---|---|---|
| Started | 19 | 19 |
| Completed | 19 | 19 |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Sequence 1: First IVA Then Placebo |
| Reporting group description: | |
| Subjects received IVA for 8 weeks in treatment period 1 followed by placebo matched to IVA for 8 weeks in treatment period 2. A washout period of 8 weeks was maintained between the 2 treatment periods. | |
| Reporting group title | Sequence 2: First Placebo Then IVA |
| Reporting group description: | |
| Subjects received placebo matched to IVA for 8 weeks in treatment period 1 followed by IVA for 8 weeks in treatment period 2. A washout period of 8 weeks was maintained between the 2 treatment periods. | |

| Reporting group values | Sequence 1: First IVA Then Placebo | Sequence 2: First Placebo Then IVA | Total |
|---|---|---|---|
| Number of subjects | 19 | 19 | 38 |
| Age categorical | | | |
| Units: Subjects | | | |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 32.6 | 32.1 | |
| standard deviation | ± 15.3 | ± 15.6 | - |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 10 | 10 | 20 |
| Male | 9 | 9 | 18 |
| Ethnicity | | | |
| Units: Subjects | | | |
| Hispanic or Latino | 0 | 0 | 0 |
| Not Hispanic or Latino | 19 | 19 | 38 |
| Unknown or Not Reported | 0 | 0 | 0 |
| Race | | | |
| 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 | 19 | 19 | 38 |
| More than one race | 0 | 0 | 0 |
| Unknown or Not Reported | 0 | 0 | 0 |
| Lung Clearance Index 2.5 (LCI2.5) | | | |
| Measure Description: LCI2.5 represents the number of lung turnovers required to reduce the end tidal inert gas concentration to 1/40th of its starting value. | | | |
| Units: Lung clearance index | | | |
| arithmetic mean | 12.74 | 13.19 | |
| standard deviation | ± 4.04 | ± 5.45 | - |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | Sequence 1: First IVA Then Placebo |
| Reporting group description: | |
| Subjects received IVA for 8 weeks in treatment period 1 followed by placebo matched to IVA for 8 weeks in treatment period 2. A washout period of 8 weeks was maintained between the 2 treatment periods. | |
| Reporting group title | Sequence 2: First Placebo Then IVA |
| Reporting group description: | |
| Subjects received placebo matched to IVA for 8 weeks in treatment period 1 followed by IVA for 8 weeks in treatment period 2. A washout period of 8 weeks was maintained between the 2 treatment periods. | |
| Subject analysis set title | Placebo |
| Subject analysis set type | Full analysis |
| Subject analysis set description: | |
| All subjects who received placebo matched to IVA for 8 weeks in treatment period 1 or 2. | |
| Subject analysis set title | IVA |
| Subject analysis set type | Full analysis |
| Subject analysis set description: | |
| All subjects who received IVA for 8 weeks in treatment period 1 or 2. | |

### Primary: Change in Lung Clearance Index 2.5

| | |
|---|---|
| End point title | Change in Lung Clearance Index 2.5 |
| End point description: | |
| LCI2.5 represents the number of lung turnovers required to reduce the end tidal inert gas concentration to 1/40th of its starting value. The Full Analysis Set (FAS) included all randomized subjects who carried the intended CFTR allele mutation and received at least 1 dose of study drug. | |
| End point type | Primary |
| End point timeframe: | |
| From baseline through 8 weeks | |

| End point values | Placebo | IVA | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 37 | 37 | | |
| Units: Lung clearance index | | | | |
| least squares mean (standard error) | 0.20 (± 0.19) | -0.46 (± 0.19) | | |

### Statistical analyses

| | |
|---|---|
| **Statistical analysis title** | Placebo vs IVA |
| Statistical analysis description: | |
| The "number of subjects included in analysis" was 37 instead of 74 because this study has a cross-over design and same subjects received both the interventions. The number "74" is auto-calculated as the sum of numbers presented in 2 comparison groups and is appearing due to EudraCT database format constraints. | |
| Comparison groups | Placebo v IVA |

| | |
|---|---|
| Number of subjects included in analysis | 74 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| Parameter estimate | Least squares mean difference |
| Point estimate | -0.66 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.1 |
| upper limit | -0.21 |

## Adverse events

| Adverse events information | |
|---|---|
| Timeframe for reporting adverse events: | |
| From first dose of study drug up to safety follow-up visit (up to Week 28) | |
| Assessment type | Systematic |

| Dictionary used | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 20.0 |

| Reporting groups | |
|---|---|
| Reporting group title | Placebo |
| Reporting group description: | |
| All subjects who received placebo matched to IVA for 8 weeks in treatment period 1 or 2. | |
| Reporting group title | Ivafactor |
| Reporting group description: | |
| All subjects who received IVA for 8 weeks in treatment period 1 or 2. | |

| Serious adverse events | Placebo | Ivafactor | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 2 / 38 (5.26%) | 1 / 38 (2.63%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | | | |
| Pregnancy, puerperium and perinatal conditions | | | |
| Abortion spontaneous | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 1 / 38 (2.63%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Pancreatitis | | | |
| subjects affected / exposed | 1 / 38 (2.63%) | 0 / 38 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Infective pulmonary exacerbation of cystic fibrosis | | | |
| subjects affected / exposed | 1 / 38 (2.63%) | 0 / 38 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| **Non-serious adverse events** | Placebo | Ivafactor | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 19 / 38 (50.00%) | 12 / 38 (31.58%) | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 2 / 38 (5.26%) | 1 / 38 (2.63%) | |
| occurrences (all) | 2 | 1 | |
| General disorders and administration site conditions | | | |
| Pyrexia | | | |
| subjects affected / exposed | 1 / 38 (2.63%) | 2 / 38 (5.26%) | |
| occurrences (all) | 1 | 2 | |
| Malaise | | | |
| subjects affected / exposed | 2 / 38 (5.26%) | 0 / 38 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| Gastrointestinal disorders | | | |
| Aphthous ulcer | | | |
| subjects affected / exposed | 2 / 38 (5.26%) | 0 / 38 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Haemoptysis | | | |
| subjects affected / exposed | 2 / 38 (5.26%) | 3 / 38 (7.89%) | |
| occurrences (all) | 6 | 4 | |
| Infections and infestations | | | |
| Infective pulmonary exacerbation of cystic fibrosis | | | |
| subjects affected / exposed | 2 / 38 (5.26%) | 5 / 38 (13.16%) | |
| occurrences (all) | 2 | 5 | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 6 / 38 (15.79%) | 3 / 38 (7.89%) | |
| occurrences (all) | 6 | 3 | |
| Viral upper respiratory tract infection | | | |
| subjects affected / exposed | 9 / 38 (23.68%) | 1 / 38 (2.63%) | |
| occurrences (all) | 9 | 1 | |

## 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