# Clinical trial results:
# A Phase 2, Randomized, Double-Blind, Placebo-Controlled, Crossover Study to Evaluate the Efficacy of Lumacaftor/Ivacaftor Combination Therapy in Subjects With Cystic Fibrosis Who Have an A455E-CFTR Mutation

## Summary

| | |
|---|---|
| EudraCT number | 2016-001585-29 |
| Trial protocol | NL |
| Global end of trial date | 04 October 2017 |

**Results information**

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 17 May 2018 |
| First version publication date | 17 May 2018 |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | VX15-809-111 |

**Additional study identifiers**

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT03061331 |
| WHO universal trial number (UTN) | - |

Notes:

**Sponsors**

| | |
|---|---|
| Sponsor organisation name | Vertex Pharmaceuticals Incorporated |
| Sponsor organisation address | 50 Northern Avenue, Boston, Massachusetts, United States, 022101862 |
| 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 | 23 October 2017 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 06 September 2017 |
| Global end of trial reached? | Yes |
| Global end of trial date | 04 October 2017 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

To evaluate the efficacy of LUM/IVA in subjects with Cystic Fibrosis (CF) 12 years of age and older who have at least one A455E 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 | 31 January 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 | Netherlands: 20 |
| Worldwide total number of subjects | 20 |
| EEA total number of subjects | 20 |

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) | 2 |
| Adults (18-64 years) | 18 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

A total of 20 subjects were enrolled in this cross-over study.

### Period 1

| | |
|---|---|
| Period 1 title | Overall Trial (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 LUM/IVA, Then Placebo |

Arm description:

Subjects received LUM/IVA fixed dose combination in treatment period 1 followed by placebo matched to LUM/IVA fixed dose combination in treatment period 2. Treatment periods were separated by a wash-out period.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | LUM/IVA fixed-dose combination |
| Investigational medicinal product code | VX-809/VX-770 |
| Other name | |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Administered every 12 hours for 8 weeks.

| | |
|---|---|
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Administered every 12 hours for 8 weeks.

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

Arm description:

Subjects received placebo matched to LUM/IVA fixed dose combination in treatment period 1 followed by LUM/IVA fixed dose combination in treatment period 2. Treatment periods were separated by a wash-out period.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | LUM/IVA fixed-dose combination |
| Investigational medicinal product code | VX-809/VX-770 |
| Other name | |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Administered every 12 hours for 8 weeks.

| | |
|---|---|
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Administered every 12 hours for 8 weeks.

| **Number of subjects in period 1** | Sequence 1: First LUM/IVA, Then Placebo | Sequence 2: First Placebo, Then LUM/IVA |
|---|---|---|
| Started | 10 | 10 |
| Completed | 8 | 9 |
| Not completed | 2 | 1 |
| Adverse event | 2 | 1 |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Sequence 1: First LUM/IVA, Then Placebo |
| Reporting group description: | |
| Subjects received LUM/IVA fixed dose combination in treatment period 1 followed by placebo matched to LUM/IVA fixed dose combination in treatment period 2. Treatment periods were separated by a wash-out period. | |
| Reporting group title | Sequence 2: First Placebo, Then LUM/IVA |
| Reporting group description: | |
| Subjects received placebo matched to LUM/IVA fixed dose combination in treatment period 1 followed by LUM/IVA fixed dose combination in treatment period 2. Treatment periods were separated by a wash-out period. | |

| Reporting group values | Sequence 1: First LUM/IVA, Then Placebo | Sequence 2: First Placebo, Then LUM/IVA | Total |
|---|---|---|---|
| Number of subjects | 10 | 10 | 20 |
| Age categorical | | | |
| Units: Subjects | | | |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 41.2 | 34.7 | |
| standard deviation | ± 15.1 | ± 11.8 | - |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 7 | 5 | 12 |
| Male | 3 | 5 | 8 |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | Sequence 1: First LUM/IVA, Then Placebo |
| Reporting group description: | |
| Subjects received LUM/IVA fixed dose combination in treatment period 1 followed by placebo matched to LUM/IVA fixed dose combination in treatment period 2. Treatment periods were separated by a wash-out period. | |
| Reporting group title | Sequence 2: First Placebo, Then LUM/IVA |
| Reporting group description: | |
| Subjects received placebo matched to LUM/IVA fixed dose combination in treatment period 1 followed by LUM/IVA fixed dose combination in treatment period 2. Treatment periods were separated by a wash-out period. | |
| Subject analysis set title | Placebo |
| Subject analysis set type | Full analysis |
| Subject analysis set description: | |
| Placebo matched to LUM/IVA every 12 hours for 8 weeks in Treatment Period 1 or 2. | |
| Subject analysis set title | LUM/IVA |
| Subject analysis set type | Full analysis |
| Subject analysis set description: | |
| LUM/IVA fixed-dose combination every 12 hours for 8 weeks in Treatment Period 1 or 2. | |

### Primary: Absolute Change From Study Baseline in Percent Predicted Forced Expiratory Volume in 1 Second (ppFEV1) Through Week 8

| | |
|---|---|
| End point title | Absolute Change From Study Baseline in Percent Predicted Forced Expiratory Volume in 1 Second (ppFEV1) Through Week 8 |
| End point description: | |
| FEV1 is the volume of air that can forcibly be blown out in one second, after full inspiration. | |
| End point type | Primary |
| End point timeframe: | |
| Study Baseline, Through Week 8 | |

| End point values | Placebo | LUM/IVA | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 18 | 18 | | |
| Units: percentage points | | | | |
| least squares mean (confidence interval 95%) | 2.6 (0.2 to 4.9) | 2.7 (0.3 to 5.0) | | |

### Statistical analyses

| Statistical analysis title | Absolute Change From Study Baseline in ppFEV1 |
|---|---|
| Statistical analysis description: | |
| As this is a cross-over study, actual number of subjects analysed for the statistical comparison were 20 (16 of them being counted twice in two treatment periods). "Number of subjects included in analysis = 36 " is incorrect and is reflected due to EudraCT database limitation. | |
| Comparison groups | LUM/IVA v Placebo |

| | |
|---|---|
| Number of subjects included in analysis | 36 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.9277 |
| Method | Mixed Model Repeated Measure (MMRM) |
| Parameter estimate | Least Squares Mean difference |
| Point estimate | 0.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.5 |
| upper limit | 2.7 |

## Adverse events

| Adverse events information | |
|---|---|
| Timeframe for reporting adverse events: Up to Week 28 | |
| Assessment type | Systematic |
| **Dictionary used** | |
| Dictionary name | MedDRA |
| Dictionary version | 19.0 |
| **Reporting groups** | |
| Reporting group title | Placebo |
| Reporting group description: - | |
| Reporting group title | LUM/IVA |
| Reporting group description: - | |

| Serious adverse events | Placebo | LUM/IVA | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | 0 / 19 (0.00%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | | | |

Frequency threshold for reporting non-serious adverse events: 0 %

| Non-serious adverse events | Placebo | LUM/IVA | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 13 / 18 (72.22%) | 15 / 19 (78.95%) | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | 1 / 19 (5.26%) | |
| occurrences (all) | 0 | 1 | |
| General disorders and administration site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 2 / 18 (11.11%) | 3 / 19 (15.79%) | |
| occurrences (all) | 2 | 3 | |
| Exercise tolerance decreased | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | 1 / 19 (5.26%) | |
| occurrences (all) | 0 | 1 | |

| | | | |
|---|---|---|---|
| Influenza like illness | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | 1 / 19 (5.26%) | |
| occurrences (all) | 0 | 1 | |
| Reproductive system and breast disorders | | | |
| Menopausal symptoms | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | 1 / 19 (5.26%) | |
| occurrences (all) | 0 | 1 | |
| Menstruation irregular | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | 1 / 19 (5.26%) | |
| occurrences (all) | 0 | 1 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Sputum increased | | | |
| subjects affected / exposed | 3 / 18 (16.67%) | 3 / 19 (15.79%) | |
| occurrences (all) | 3 | 3 | |
| Asthma | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | 2 / 19 (10.53%) | |
| occurrences (all) | 0 | 2 | |
| Cough | | | |
| subjects affected / exposed | 3 / 18 (16.67%) | 2 / 19 (10.53%) | |
| occurrences (all) | 3 | 2 | |
| Dyspnoea | | | |
| subjects affected / exposed | 3 / 18 (16.67%) | 2 / 19 (10.53%) | |
| occurrences (all) | 3 | 3 | |
| Dysphonia | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | 1 / 19 (5.26%) | |
| occurrences (all) | 0 | 1 | |
| Paranasal sinus discomfort | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | 1 / 19 (5.26%) | |
| occurrences (all) | 0 | 1 | |
| Rhinorrhoea | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | 1 / 19 (5.26%) | |
| occurrences (all) | 1 | 1 | |
| Dyspnoea exertional | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | 0 / 19 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Haemoptysis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 18 (5.56%) | 0 / 19 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Respiration abnormal | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | 0 / 19 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Sputum discoloured | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | 0 / 19 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Wheezing | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | 0 / 19 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Psychiatric disorders | | | |
| Libido decreased | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | 1 / 19 (5.26%) | |
| occurrences (all) | 0 | 1 | |
| Investigations | | | |
| Blood pressure increased | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | 1 / 19 (5.26%) | |
| occurrences (all) | 0 | 1 | |
| Injury, poisoning and procedural complications | | | |
| Contusion | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | 1 / 19 (5.26%) | |
| occurrences (all) | 0 | 1 | |
| Muscle strain | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | 0 / 19 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | 4 / 19 (21.05%) | |
| occurrences (all) | 0 | 4 | |
| Dizziness | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | 2 / 19 (10.53%) | |
| occurrences (all) | 0 | 3 | |
| Dysgeusia | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | 1 / 19 (5.26%) | |
| occurrences (all) | 0 | 2 | |

| | | | |
|---|---|---|---|
| Paraesthesia | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | 0 / 19 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Ear and labyrinth disorders | | | |
| Tinnitus | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | 0 / 19 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | 8 / 19 (42.11%) | |
| occurrences (all) | 0 | 8 | |
| Flatulence | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | 4 / 19 (21.05%) | |
| occurrences (all) | 0 | 4 | |
| Nausea | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | 4 / 19 (21.05%) | |
| occurrences (all) | 0 | 4 | |
| Abdominal pain | | | |
| subjects affected / exposed | 3 / 18 (16.67%) | 2 / 19 (10.53%) | |
| occurrences (all) | 3 | 2 | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | 2 / 19 (10.53%) | |
| occurrences (all) | 0 | 2 | |
| Abdominal discomfort | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | 1 / 19 (5.26%) | |
| occurrences (all) | 1 | 1 | |
| Eructation | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | 1 / 19 (5.26%) | |
| occurrences (all) | 0 | 1 | |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | 0 / 19 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Skin and subcutaneous tissue disorders | | | |
| Pruritus | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | 1 / 19 (5.26%) | |
| occurrences (all) | 0 | 1 | |
| Rash pruritic | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 18 (0.00%) | 1 / 19 (5.26%) | |
| occurrences (all) | 0 | 1 | |
| Skin exfoliation | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | 1 / 19 (5.26%) | |
| occurrences (all) | 0 | 1 | |
| Acne | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | 0 / 19 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Photosensitivity reaction | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | 0 / 19 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Musculoskeletal chest pain | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | 2 / 19 (10.53%) | |
| occurrences (all) | 0 | 2 | |
| Back pain | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | 1 / 19 (5.26%) | |
| occurrences (all) | 0 | 1 | |
| Muscle spasms | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | 1 / 19 (5.26%) | |
| occurrences (all) | 0 | 1 | |
| Pain in extremity | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | 1 / 19 (5.26%) | |
| occurrences (all) | 0 | 1 | |
| Arthralgia | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | 0 / 19 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Infections and infestations | | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 2 / 18 (11.11%) | 3 / 19 (15.79%) | |
| occurrences (all) | 2 | 3 | |
| Vulvovaginal mycotic infection | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | 3 / 19 (15.79%) | |
| occurrences (all) | 0 | 3 | |
| Infective pulmonary exacerbation of cystic fibrosis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 2 / 18 (11.11%) | 2 / 19 (10.53%) | |
| occurrences (all) | 2 | 2 | |
| Herpes zoster | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | 1 / 19 (5.26%) | |
| occurrences (all) | 0 | 1 | |
| Laryngitis | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | 1 / 19 (5.26%) | |
| occurrences (all) | 0 | 1 | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | 1 / 19 (5.26%) | |
| occurrences (all) | 0 | 1 | |
| Eye infection | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | 0 / 19 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Impetigo | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | 0 / 19 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Sinusitis | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | 0 / 19 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Tooth infection | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | 0 / 19 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Wound infection | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | 0 / 19 (0.00%) | |
| occurrences (all) | 1 | 0 | |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 17 February 2017 | - Removed restriction on number of subjects with F508del mutation |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported