



Clinical trial results:

A Phase 3, Rollover Study to Evaluate the Safety of Long-term Treatment With Lumacaftor/Ivacaftor Combination Therapy in Subjects Aged 2 Years and Older With Cystic Fibrosis, Homozygous for the F508del-CFTR Mutation

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2019-003112-31 |
| Trial protocol | Outside EU/EEA |
| Global end of trial date | 17 July 2019 |

Results information

| | |
|--------------------------------|------------------|
| Result version number | v1 |
| This version publication date | 01 February 2020 |
| First version publication date | 01 February 2020 |

Trial information

Trial identification

| | |
|-----------------------|--------------|
| Sponsor protocol code | VX16-809-116 |
|-----------------------|--------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT03125395 |
| 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-001582-PIP01-13 |
| 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 August 2019 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 17 July 2019 |
| Global end of trial reached? | Yes |
| Global end of trial date | 17 July 2019 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To evaluate the long-term safety of lumacaftor (LUM)/ivacaftor (IVA) combination therapy in subjects aged 2 years and older with cystic fibrosis (CF), homozygous for F508del.

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 | 12 May 2017 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-------------------|
| Country: Number of subjects enrolled | Canada: 7 |
| Country: Number of subjects enrolled | United States: 50 |
| Worldwide total number of subjects | 57 |
| 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) | 57 |
| 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:

This study was conducted in subjects with cystic fibrosis (CF) aged 2 years and older.

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 | LUM/IVA |
|-----------|---------|

Arm description:

Subjects <6 years of age and weighing <14 kilograms (kg) at enrollment received LUM 100 milligram (mg)/IVA 125 mg for 96 weeks.

Subjects <6 years of age and weighing ≥14 kg at enrollment received LUM 150 mg/IVA 188 mg for 96 weeks.

| | |
|--|----------------------|
| Arm type | Experimental |
| Investigational medicinal product name | LUM/IVA |
| Investigational medicinal product code | VX-809/VX-770 |
| Other name | Lumacaftor/Ivacaftor |
| Pharmaceutical forms | Granules |
| Routes of administration | Oral use |

Dosage and administration details:

Subjects who received LUM/IVA every 12 hours.

| Number of subjects in period 1 | LUM/IVA |
|--|---------|
| Started | 57 |
| Completed | 47 |
| Not completed | 10 |
| Commercial Drug is Available for Subject | 5 |
| Adverse Event | 2 |
| Physician Decision | 2 |
| Withdrawal of Consent (Not Due to AE) | 1 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|---------|
| Reporting group title | LUM/IVA |
|-----------------------|---------|

Reporting group description:

Subjects <6 years of age and weighing <14 kilograms (kg) at enrollment received LUM 100 milligram (mg)/IVA 125 mg for 96 weeks.

Subjects <6 years of age and weighing ≥14 kg at enrollment received LUM 150 mg/IVA 188 mg for 96 weeks.

| Reporting group values | LUM/IVA | Total | |
|------------------------------------|---------|-------|--|
| Number of subjects | 57 | 57 | |
| Age categorical Units: Subjects | | | |

| | | | |
|--|-----------------|----|--|
| Age continuous Units: months arithmetic mean standard deviation | 43.2 ± 12.17 | - | |
| Gender categorical Units: Subjects | | | |
| Female | 28 | 28 | |
| Male | 29 | 29 | |

End points

End points reporting groups

| | |
|--|---------|
| Reporting group title | LUM/IVA |
| Reporting group description: Subjects <6 years of age and weighing <14 kilograms (kg) at enrollment received LUM 100 milligram (mg)/IVA 125 mg for 96 weeks. Subjects <6 years of age and weighing ≥14 kg at enrollment received LUM 150 mg/IVA 188 mg for 96 weeks. | |

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

| | |
|-----------------|--|
| End point title | Safety as Assessed by Number of Subjects With Treatment-Emergent Adverse Events (AEs) and Serious Adverse Events (SAEs) ^[1] |
|-----------------|--|

End point description:

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

End point timeframe:

Up to 98 weeks

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 primary safety endpoint.

| End point values | LUM/IVA | | | |
|-----------------------------|-----------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 57 | | | |
| Units: subjects | | | | |
| AEs | 56 | | | |
| SAEs | 15 | | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 98 weeks

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 22.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|---------|
| Reporting group title | LUM/IVA |
|-----------------------|---------|

Reporting group description:

Subjects <6 years of age and weighing <14 kg at enrollment received LUM 100 mg/IVA 125 mg for 96 weeks. Subjects <6 years of age and weighing ≥14 kg at enrollment received LUM 150 mg/IVA 188 mg for 96 weeks.

| Serious adverse events | LUM/IVA | | |
|---|------------------|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 15 / 57 (26.32%) | | |
| number of deaths (all causes) | 0 | | |
| number of deaths resulting from adverse events | | | |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 1 / 57 (1.75%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 1 / 57 (1.75%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |
| Constipation | | | |
| subjects affected / exposed | 1 / 57 (1.75%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Haematemesis | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 1 / 57 (1.75%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pancreatitis | | | |
| subjects affected / exposed | 1 / 57 (1.75%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Sleep apnoea syndrome | | | |
| subjects affected / exposed | 1 / 57 (1.75%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| Appendicitis | | | |
| subjects affected / exposed | 1 / 57 (1.75%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Chronic sinusitis | | | |
| subjects affected / exposed | 1 / 57 (1.75%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastritis viral | | | |
| subjects affected / exposed | 1 / 57 (1.75%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastroenteritis adenovirus | | | |
| subjects affected / exposed | 1 / 57 (1.75%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastroenteritis viral | | | |
| subjects affected / exposed | 1 / 57 (1.75%) | | |
| 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 | 6 / 57 (10.53%) | | |
| occurrences causally related to treatment / all | 3 / 9 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pneumonia | | | |
| subjects affected / exposed | 2 / 57 (3.51%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory tract infection viral | | | |
| subjects affected / exposed | 1 / 57 (1.75%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Metabolism and nutrition disorders | | | |
| Weight gain poor | | | |
| subjects affected / exposed | 1 / 57 (1.75%) | | |
| 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 | LUM/IVA | | |
|---|------------------|--|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 55 / 57 (96.49%) | | |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 10 / 57 (17.54%) | | |
| occurrences (all) | 19 | | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 5 / 57 (8.77%) | | |
| occurrences (all) | 8 | | |
| Forced expiratory volume decreased | | | |
| subjects affected / exposed | 3 / 57 (5.26%) | | |
| occurrences (all) | 4 | | |
| Gamma-glutamyltransferase increased | | | |

| | | | |
|--|--|--|--|
| <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Pseudomonas test positive</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Staphylococcus test positive</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>4 / 57 (7.02%)</p> <p>4</p> <p>9 / 57 (15.79%)</p> <p>9</p> <p>12 / 57 (21.05%)</p> <p>14</p> | | |
| <p>General disorders and administration site conditions</p> <p>Fatigue</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Pyrexia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Vessel puncture site pain</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>5 / 57 (8.77%)</p> <p>6</p> <p>23 / 57 (40.35%)</p> <p>42</p> <p>4 / 57 (7.02%)</p> <p>14</p> | | |
| <p>Ear and labyrinth disorders</p> <p>Ear pain</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>3 / 57 (5.26%)</p> <p>3</p> | | |
| <p>Gastrointestinal disorders</p> <p>Abdominal pain</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Abdominal pain upper</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Constipation</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Diarrhoea</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Vomiting</p> | <p>7 / 57 (12.28%)</p> <p>8</p> <p>4 / 57 (7.02%)</p> <p>5</p> <p>7 / 57 (12.28%)</p> <p>9</p> <p>6 / 57 (10.53%)</p> <p>6</p> | | |

| | | | |
|---|------------------|--|--|
| subjects affected / exposed | 17 / 57 (29.82%) | | |
| occurrences (all) | 22 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 47 / 57 (82.46%) | | |
| occurrences (all) | 159 | | |
| Dyspnoea | | | |
| subjects affected / exposed | 3 / 57 (5.26%) | | |
| occurrences (all) | 3 | | |
| Lower respiratory tract congestion | | | |
| subjects affected / exposed | 4 / 57 (7.02%) | | |
| occurrences (all) | 4 | | |
| Nasal congestion | | | |
| subjects affected / exposed | 25 / 57 (43.86%) | | |
| occurrences (all) | 37 | | |
| Nasal discharge discolouration | | | |
| subjects affected / exposed | 3 / 57 (5.26%) | | |
| occurrences (all) | 3 | | |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 10 / 57 (17.54%) | | |
| occurrences (all) | 12 | | |
| Productive cough | | | |
| subjects affected / exposed | 5 / 57 (8.77%) | | |
| occurrences (all) | 8 | | |
| Rhinorrhoea | | | |
| subjects affected / exposed | 18 / 57 (31.58%) | | |
| occurrences (all) | 26 | | |
| Sinus congestion | | | |
| subjects affected / exposed | 3 / 57 (5.26%) | | |
| occurrences (all) | 3 | | |
| Sputum increased | | | |
| subjects affected / exposed | 5 / 57 (8.77%) | | |
| occurrences (all) | 8 | | |
| Upper respiratory tract congestion | | | |

| | | | |
|---|------------------|--|--|
| subjects affected / exposed | 3 / 57 (5.26%) | | |
| occurrences (all) | 5 | | |
| Wheezing | | | |
| subjects affected / exposed | 3 / 57 (5.26%) | | |
| occurrences (all) | 4 | | |
| Skin and subcutaneous tissue disorders | | | |
| Rash | | | |
| subjects affected / exposed | 3 / 57 (5.26%) | | |
| occurrences (all) | 3 | | |
| Infections and infestations | | | |
| Conjunctivitis | | | |
| subjects affected / exposed | 4 / 57 (7.02%) | | |
| occurrences (all) | 5 | | |
| Ear infection | | | |
| subjects affected / exposed | 12 / 57 (21.05%) | | |
| occurrences (all) | 21 | | |
| Hand-foot-and-mouth disease | | | |
| subjects affected / exposed | 3 / 57 (5.26%) | | |
| occurrences (all) | 3 | | |
| Infective pulmonary exacerbation of cystic fibrosis | | | |
| subjects affected / exposed | 10 / 57 (17.54%) | | |
| occurrences (all) | 17 | | |
| Influenza | | | |
| subjects affected / exposed | 4 / 57 (7.02%) | | |
| occurrences (all) | 4 | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 8 / 57 (14.04%) | | |
| occurrences (all) | 20 | | |
| Otitis media | | | |
| subjects affected / exposed | 7 / 57 (12.28%) | | |
| occurrences (all) | 9 | | |
| Pharyngitis streptococcal | | | |
| subjects affected / exposed | 6 / 57 (10.53%) | | |
| occurrences (all) | 11 | | |
| Pneumonia | | | |

| | | | |
|---|------------------|--|--|
| subjects affected / exposed | 3 / 57 (5.26%) | | |
| occurrences (all) | 4 | | |
| Sinusitis | | | |
| subjects affected / exposed | 12 / 57 (21.05%) | | |
| occurrences (all) | 17 | | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 13 / 57 (22.81%) | | |
| occurrences (all) | 16 | | |
| Viral upper respiratory tract infection | | | |
| subjects affected / exposed | 4 / 57 (7.02%) | | |
| occurrences (all) | 4 | | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 6 / 57 (10.53%) | | |
| occurrences (all) | 6 | | |

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