



## Clinical trial results:

### A Phase 3, 2-part, Open-label Study to Evaluate the Safety and Pharmacokinetics of Lumacaftor/Ivacaftor in Subjects 1 to Less Than 2 Years of Age With Cystic Fibrosis, Homozygous for F508del

#### Summary

|                          |                 |
|--------------------------|-----------------|
| EudraCT number           | 2017-004794-13  |
| Trial protocol           | Outside EU/EEA  |
| Global end of trial date | 29 October 2021 |

#### Results information

|                                |             |
|--------------------------------|-------------|
| Result version number          | v1          |
| This version publication date  | 14 May 2022 |
| First version publication date | 14 May 2022 |

#### Trial information

##### Trial identification

|                       |              |
|-----------------------|--------------|
| Sponsor protocol code | VX16-809-122 |
|-----------------------|--------------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT03601637 |
| 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                       | 19 November 2021 |
| Is this the analysis of the primary completion data? | Yes              |
| Primary completion date                              | 29 October 2021  |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 29 October 2021  |
| Was the trial ended prematurely?                     | No               |

Notes:

## General information about the trial

Main objective of the trial:

To evaluate the safety and pharmacokinetics (PK) of lumacaftor (LUM) and ivacaftor (IVA) in subjects 1 to less than (<) 2 years of age with cystic fibrosis (CF), homozygous for F508del (F/F).

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                          | 23 August 2018 |
| 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 | United States: 49 |
| Country: Number of subjects enrolled | Canada: 12        |
| Worldwide total number of subjects   | 61                |
| 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)  | 61 |
| Children (2-11 years)                     | 0  |
| 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 CF aged 1 through less than 2 years of age who are homozygous for F508del.

### Period 1

|                              |                                |
|------------------------------|--------------------------------|
| Period 1 title               | Overall Trial (overall period) |
| Is this the baseline period? | Yes                            |
| Allocation method            | Non-randomised - controlled    |
| Blinding used                | Not blinded                    |

### Arms

|                              |                 |
|------------------------------|-----------------|
| Are arms mutually exclusive? | Yes             |
| <b>Arm title</b>             | Part A: LUM/IVA |

Arm description:

Subjects received LUM/IVA based on their weight at screening for 15 days.

|  |                      |
|--|----------------------|
| 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 received LUM/IVA fixed-dose combination (FDC) every 12 hours.

|                  |                 |
|------------------|-----------------|
| <b>Arm title</b> | Part B: LUM/IVA |
|------------------|-----------------|

Arm description:

Subjects received LUM/IVA based on their weight at screening for 24 weeks. Doses were adjusted upwards for changes in weight.

|  |                      |
|--|----------------------|
| 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 received LUM/IVA FDC every 12 hours.

| <b>Number of subjects in period 1<sup>[1]</sup></b> | Part A: LUM/IVA | Part B: LUM/IVA |
|---|-----------------|-----------------|
| Started   | 14              | 46              |
| Completed   | 13              | 43              |
| Not completed                                       | 1               | 3               |
| Adverse Event                                       | 1               | 1               |

|                                       |   |   |
|---------------------------------------|---|---|
| Other                                 | - | 1 |
| Withdrawal of Consent (not due to AE) | - | 1 |

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Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: A total of 61 subjects were enrolled in Parts A and B of the study. One subject in Part B was enrolled but not dosed in this study. Therefore data for 60 subjects are reported in the subject disposition and baseline characteristics sections.

## Baseline characteristics

### Reporting groups

|                       |                 |
|-----------------------|-----------------|
| Reporting group title | Part A: LUM/IVA |
|-----------------------|-----------------|

Reporting group description:

Subjects received LUM/IVA based on their weight at screening for 15 days.

|                       |                 |
|-----------------------|-----------------|
| Reporting group title | Part B: LUM/IVA |
|-----------------------|-----------------|

Reporting group description:

Subjects received LUM/IVA based on their weight at screening for 24 weeks. Doses were adjusted upwards for changes in weight.

| Reporting group values   | Part A: LUM/IVA | Part B: LUM/IVA | Total |
|--|-----------------|-----------------|-------|
| Number of subjects   | 14              | 46              | 60    |
| Age categorical<br>Units: Subjects                                       |                 |                 |       |
| Age continuous<br>Units: months<br>arithmetic mean<br>standard deviation | 17.2<br>± 3.6   | 18.1<br>± 3.5   | -     |
| Gender categorical<br>Units: Subjects                                    |                 |                 |       |
| Female   | 7               | 24              | 31    |
| Male   | 7               | 22              | 29    |

## End points

### End points reporting groups

|   |                          |
|---|--------------------------|
| Reporting group title   | Part A: LUM/IVA          |
| Reporting group description:<br>Subjects received LUM/IVA based on their weight at screening for 15 days.   |                          |
| Reporting group title   | Part B: LUM/IVA          |
| Reporting group description:<br>Subjects received LUM/IVA based on their weight at screening for 24 weeks. Doses were adjusted upwards for changes in weight. |                          |
| Subject analysis set title  | Part A: LUM/IVA - Dose 1 |
| Subject analysis set type   | Full analysis            |
| Subject analysis set description:<br>Subjects received LUM/IVA Dose 1 every 12 hours for 15 days.   |                          |
| Subject analysis set title  | Part A: LUM/IVA - Dose 2 |
| Subject analysis set type   | Full analysis            |
| Subject analysis set description:<br>Subjects received LUM/IVA Dose 2 every 12 hours for 15 days.   |                          |

### Primary: Part A: Observed Plasma Concentrations From 3-4 hours (C3-4hr) of LUM and IVA

|   |  |
|---|--|
| End point title   | Part A: Observed Plasma Concentrations From 3-4 hours (C3-4hr) of LUM and IVA <sup>[1]</sup> |
| End point description:<br>PK set included subjects who received at least 1 dose of study drug. Here "n" signifies those subjects who were evaluable at specified time points for each reporting group respectively. |  |
| End point type  | Primary  |
| End point timeframe:<br>Day 1 and Day 15  |  |

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 this endpoint.

| End point values                        | Part A:<br>LUM/IVA -<br>Dose 1 | Part A:<br>LUM/IVA -<br>Dose 2 |  |  |
|---|--------------------------------|--------------------------------|--|--|
| Subject group type                      | Subject analysis set           | Subject analysis set           |  |  |
| Number of subjects analysed             | 7                              | 7                              |  |  |
| Units: nanograms per milliliter (ng/mL) |                                |                                |  |  |
| arithmetic mean (standard deviation)    |                                |                                |  |  |
| Day 1: LUM (n=7,7)                      | 14600 (± 5560)                 | 12600 (± 7190)                 |  |  |
| Day 15: LUM (n=7,5)                     | 16600 (± 9590)                 | 13900 (± 5800)                 |  |  |
| Day 1: IVA (n=7,7)                      | 1620 (± 648)                   | 1320 (± 804)                   |  |  |
| Day 15: IVA (n=7,5)                     | 718 (± 352)                    | 496 (± 268)                    |  |  |

## Statistical analyses

No statistical analyses for this end point

### Primary: Part A: Observed Pre-dose Plasma Concentration (Ctough) of LUM and IVA

|                 |   |
|-----------------|---|
| End point title | Part A: Observed Pre-dose Plasma Concentration (Ctough) of LUM and IVA <sup>[2]</sup> |
|-----------------|---|

End point description:

PK set included subjects who received at least 1 dose of study drug. Here "n" signifies those subjects who were evaluable at specified time points for each reporting group respectively.

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

End point timeframe:

Pre-dose at Day 8 and Day 15.

Notes:

[2] - 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 this endpoint.

| End point values                        | Part A:<br>LUM/IVA -<br>Dose 1 | Part A:<br>LUM/IVA -<br>Dose 2 |  |  |
|---|--------------------------------|--------------------------------|--|--|
| Subject group type                      | Subject analysis set           | Subject analysis set           |  |  |
| Number of subjects analysed             | 7                              | 7                              |  |  |
| Units: nanograms per milliliter (ng/mL) |                                |                                |  |  |
| arithmetic mean (standard deviation)    |                                |                                |  |  |
| Day 8: LUM (n=7,6)                      | 12000 (± 8880)                 | 12800 (± 3900)                 |  |  |
| Day 15: LUM (n=5,6)                     | 8380 (± 7790)                  | 10500 (± 3070)                 |  |  |
| Day 8: IVA (n=7,6)                      | 169 (± 75.5)                   | 185 (± 101)                    |  |  |
| Day 15: IVA (n=5,6)                     | 78.9 (± 19.1)                  | 120 (± 60.5)                   |  |  |

### Statistical analyses

No statistical analyses for this end point

### Primary: Part B : Safety and Tolerability as Assessed by Number of Subjects With Treatment-Emergent Adverse Events (TEAEs) and Serious Adverse Events (SAEs)

|                 |   |
|-----------------|---|
| End point title | Part B : Safety and Tolerability as Assessed by Number of Subjects With Treatment-Emergent Adverse Events (TEAEs) and Serious Adverse Events (SAEs) <sup>[3][4]</sup> |
|-----------------|---|

End point description:

Safety set included all subjects who received at least 1 dose of study drug in the treatment period.

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

End point timeframe:

From Day 1 up to Week 26

Notes:

[3] - 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 this endpoint.

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This primary endpoint is only applicable for Part B.

|                             |                    |  |  |  |
|-----------------------------|--------------------|--|--|--|
| <b>End point values</b>     | Part B:<br>LUM/IVA |  |  |  |
| Subject group type          | Reporting group    |  |  |  |
| Number of subjects analysed | 46                 |  |  |  |
| Units: subjects             |                    |  |  |  |
| Subjects with TEAEs         | 44                 |  |  |  |
| Subjects with SAEs          | 5                  |  |  |  |

## Statistical analyses

No statistical analyses for this end point



## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From Day 1 Through Safety Follow-up Period (up to Day 25 for Part A and up to Week 26 for Part B)

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 24.1 |
|--------------------|------|

### Reporting groups

|                       |                  |
|-----------------------|------------------|
| Reporting group title | Part A : LUM/IVA |
|-----------------------|------------------|

Reporting group description:

Subjects received LUM/IVA based on their weight at screening for 15 days.

|                       |                 |
|-----------------------|-----------------|
| Reporting group title | Part B: LUM/IVA |
|-----------------------|-----------------|

Reporting group description:

Subjects received LUM/IVA based on their weight at screening for 24 weeks. Doses were adjusted upwards for changes in weight.

| Serious adverse events                              | Part A : LUM/IVA | Part B: LUM/IVA |  |
|---|------------------|-----------------|--|
| Total subjects affected by serious adverse events   |                  |                 |  |
| subjects affected / exposed                         | 0 / 14 (0.00%)   | 5 / 46 (10.87%) |  |
| number of deaths (all causes)                       | 0                | 0               |  |
| number of deaths resulting from adverse events      |                  |                 |  |
| Injury, poisoning and procedural complications      |                  |                 |  |
| Post procedural fever                               |                  |                 |  |
| subjects affected / exposed                         | 0 / 14 (0.00%)   | 1 / 46 (2.17%)  |  |
| occurrences causally related to treatment / all     | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all          | 0 / 0            | 0 / 0           |  |
| Gastrointestinal disorders                          |                  |                 |  |
| Distal intestinal obstruction syndrome              |                  |                 |  |
| subjects affected / exposed                         | 0 / 14 (0.00%)   | 1 / 46 (2.17%)  |  |
| occurrences causally related to treatment / all     | 0 / 0            | 1 / 1           |  |
| deaths causally related to treatment / all          | 0 / 0            | 0 / 0           |  |
| Infections and infestations                         |                  |                 |  |
| Infective pulmonary exacerbation of cystic fibrosis |                  |                 |  |

|   |                |                |  |
|---|----------------|----------------|--|
| subjects affected / exposed                     | 0 / 14 (0.00%) | 3 / 46 (6.52%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 4          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |

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

| <b>Non-serious adverse events</b>                     | Part A : LUM/IVA | Part B: LUM/IVA  |  |
|---|------------------|------------------|--|
| Total subjects affected by non-serious adverse events |                  |                  |  |
| subjects affected / exposed                           | 12 / 14 (85.71%) | 42 / 46 (91.30%) |  |
| Investigations  |                  |                  |  |
| Alanine aminotransferase increased                    |                  |                  |  |
| subjects affected / exposed                           | 0 / 14 (0.00%)   | 4 / 46 (8.70%)   |  |
| occurrences (all)                                     | 0                | 4                |  |
| Pseudomonas test positive                             |                  |                  |  |
| subjects affected / exposed                           | 0 / 14 (0.00%)   | 5 / 46 (10.87%)  |  |
| occurrences (all)                                     | 0                | 5                |  |
| Injury, poisoning and procedural complications        |                  |                  |  |
| Lip injury  |                  |                  |  |
| subjects affected / exposed                           | 1 / 14 (7.14%)   | 0 / 46 (0.00%)   |  |
| occurrences (all)                                     | 1                | 0                |  |
| General disorders and administration site conditions  |                  |                  |  |
| Crying  |                  |                  |  |
| subjects affected / exposed                           | 1 / 14 (7.14%)   | 0 / 46 (0.00%)   |  |
| occurrences (all)                                     | 1                | 0                |  |
| Pyrexia   |                  |                  |  |
| subjects affected / exposed                           | 1 / 14 (7.14%)   | 10 / 46 (21.74%) |  |
| occurrences (all)                                     | 1                | 15               |  |
| Gastrointestinal disorders                            |                  |                  |  |
| Abdominal pain  |                  |                  |  |
| subjects affected / exposed                           | 0 / 14 (0.00%)   | 3 / 46 (6.52%)   |  |
| occurrences (all)                                     | 0                | 3                |  |
| Constipation  |                  |                  |  |
| subjects affected / exposed                           | 1 / 14 (7.14%)   | 5 / 46 (10.87%)  |  |
| occurrences (all)                                     | 1                | 7                |  |
| Diarrhoea   |                  |                  |  |

|  |                      |                        |  |
|--|----------------------|------------------------|--|
| subjects affected / exposed<br>occurrences (all)   | 0 / 14 (0.00%)<br>0  | 3 / 46 (6.52%)<br>3    |  |
| Vomiting<br>subjects affected / exposed<br>occurrences (all)   | 0 / 14 (0.00%)<br>0  | 8 / 46 (17.39%)<br>9   |  |
| Flatulence<br>subjects affected / exposed<br>occurrences (all)   | 1 / 14 (7.14%)<br>1  | 1 / 46 (2.17%)<br>1    |  |
| Respiratory, thoracic and mediastinal disorders<br>Cough<br>subjects affected / exposed<br>occurrences (all) | 4 / 14 (28.57%)<br>4 | 16 / 46 (34.78%)<br>27 |  |
| Nasal congestion<br>subjects affected / exposed<br>occurrences (all)   | 1 / 14 (7.14%)<br>1  | 4 / 46 (8.70%)<br>6    |  |
| Rhinorrhoea<br>subjects affected / exposed<br>occurrences (all)  | 5 / 14 (35.71%)<br>5 | 5 / 46 (10.87%)<br>9   |  |
| Skin and subcutaneous tissue disorders<br>Rash<br>subjects affected / exposed<br>occurrences (all)           | 3 / 14 (21.43%)<br>4 | 4 / 46 (8.70%)<br>4    |  |
| Psychiatric disorders<br>Insomnia<br>subjects affected / exposed<br>occurrences (all)                        | 1 / 14 (7.14%)<br>1  | 1 / 46 (2.17%)<br>1    |  |
| Infections and infestations<br>Ear infection<br>subjects affected / exposed<br>occurrences (all)             | 0 / 14 (0.00%)<br>0  | 5 / 46 (10.87%)<br>5   |  |
| Infective pulmonary exacerbation of cystic fibrosis<br>subjects affected / exposed<br>occurrences (all)      | 0 / 14 (0.00%)<br>0  | 8 / 46 (17.39%)<br>12  |  |
| Influenza<br>subjects affected / exposed<br>occurrences (all)  | 2 / 14 (14.29%)<br>2 | 0 / 46 (0.00%)<br>0    |  |

|  |                     |                      |  |
|--|---------------------|----------------------|--|
| Nasopharyngitis<br>subjects affected / exposed<br>occurrences (all)  | 0 / 14 (0.00%)<br>0 | 4 / 46 (8.70%)<br>4  |  |
| Upper respiratory tract infection<br>subjects affected / exposed<br>occurrences (all)                        | 1 / 14 (7.14%)<br>1 | 6 / 46 (13.04%)<br>9 |  |
| Viral upper respiratory tract infection<br>subjects affected / exposed<br>occurrences (all)                  | 0 / 14 (0.00%)<br>0 | 5 / 46 (10.87%)<br>6 |  |
| Metabolism and nutrition disorders<br>Decreased appetite<br>subjects affected / exposed<br>occurrences (all) | 1 / 14 (7.14%)<br>1 | 1 / 46 (2.17%)<br>1  |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment  |
|------------------|--|
| 04 December 2019 | Amended to update the planned dosing regimen to add lower dose of LUM/IVA in Parts A and B and, to adjust the weight bound of LUM/IVA in Part B. |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported