

**Clinical trial results:**

A Phase 3, Randomized, Double-blind, Controlled Study Evaluating the Efficacy and Safety of VX-121 Combination Therapy in Subjects With Cystic Fibrosis Who Are Homozygous for F508del, Heterozygous for F508del and a Gating (F/G) or Residual Function (F/RF) Mutation, or Have At Least 1 Other Triple Combination Responsive CFTR Mutation and No F508del Mutation

Summary

| | |
|--------------------------|-------------------------------------|
| EudraCT number | 2021-000694-85 |
| Trial protocol | NO SE DE DK IE IT GR BE AT NL PL HU |
| Global end of trial date | 30 November 2023 |

Results information

| | |
|--------------------------------|--------------|
| Result version number | v1 (current) |
| This version publication date | 01 June 2024 |
| First version publication date | 01 June 2024 |

Trial information**Trial identification**

| | |
|-----------------------|--------------|
| Sponsor protocol code | VX20-121-103 |
|-----------------------|--------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT05076149 |
| 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-003052-PIP01-21 |
| 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 | 15 December 2023 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 18 May 2023 |
| Global end of trial reached? | Yes |
| Global end of trial date | 30 November 2023 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of VX-121/tezacaftor/deutivacaftor (VX-121/TEZ/D-IVA) in cystic fibrosis (CF) subjects who are homozygous for F508del, heterozygous for F508del and a gating (F/G) or residual function (F/RF) mutation, or have at least 1 other triple combination responsive (TCR) CFTR mutation and no F508del mutation

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 | 27 October 2021 |
| 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 | Netherlands: 13 |
| Country: Number of subjects enrolled | Norway: 5 |
| Country: Number of subjects enrolled | Poland: 13 |
| Country: Number of subjects enrolled | Sweden: 20 |
| Country: Number of subjects enrolled | Austria: 10 |
| Country: Number of subjects enrolled | Belgium: 31 |
| Country: Number of subjects enrolled | Denmark: 11 |
| Country: Number of subjects enrolled | France: 50 |
| Country: Number of subjects enrolled | Germany: 52 |
| Country: Number of subjects enrolled | Greece: 6 |
| Country: Number of subjects enrolled | Hungary: 18 |
| Country: Number of subjects enrolled | Ireland: 12 |
| Country: Number of subjects enrolled | Italy: 25 |
| Country: Number of subjects enrolled | Australia: 28 |
| Country: Number of subjects enrolled | Canada: 29 |
| Country: Number of subjects enrolled | New Zealand: 25 |

| | |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | Israel: 5 |
| Country: Number of subjects enrolled | Switzerland: 8 |
| Country: Number of subjects enrolled | United States: 202 |
| Country: Number of subjects enrolled | United Kingdom: 34 |
| Worldwide total number of subjects | 597 |
| EEA total number of subjects | 266 |

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) | 82 |
| Adults (18-64 years) | 513 |
| From 65 to 84 years | 2 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

This study was conducted in cystic fibrosis (CF) subjects aged 12 years or older. It was pre-specified in the protocol to combine the data from this study with study VX20-121-102 (NCT05033080) for selected endpoints.

Pre-assignment

Screening details:

A total of 597 subjects were enrolled in this study, of which 24 were included in the run-in period but were not dosed in treatment period. Therefore, results are presented for only 573 subjects dosed in the treatment period.

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 | ELX/TEZ/IVA |

Arm description:

Following elexacftor/tezacaftor/ivacaftor (ELX/TEZ/IVA) run-in period of 4 weeks, subjects received ELX 200 milligram (mg) once daily (qd) /TEZ 100 mg qd/IVA 150 mg every 12 hours (q12h) in the treatment period for 52 weeks.

| | |
|--|---------------------------------|
| Arm type | Active comparator |
| Investigational medicinal product name | ELX/TEZ/IVA |
| Investigational medicinal product code | VX-445/VX-661/VX-770 |
| Other name | Elxacaftor/Tezacaftor/Ivacaftor |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Subjects received ELX/TEZ/IVA fixed-dose combination (FDC) 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 once daily in the evening.

| | |
|------------------|------------------|
| Arm title | VX-121/TEZ/D-IVA |
|------------------|------------------|

Arm description:

Following ELX/TEZ/IVA run-in period of 4 weeks, subjects received VX-121 20 mg qd/TEZ 100 mg qd/D-IVA 250 mg qd in the treatment period for 52 weeks.

| | |
|--|---------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | VX-121/TEZ/D-IVA |
| Investigational medicinal product code | VX-121/VX-661/VX-561 |
| Other name | VX-121/tezacaftor/deutivacaftor |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Subjects received VX-121/TEZ/D-IVA fixed-dose combination (FDC) once daily in the morning.

| Number of subjects in period 1^[1] | ELX/TEZ/IVA | VX-121/TEZ/D-IVA |
|---|-------------|------------------|
| Started | 289 | 284 |
| Completed | 279 | 264 |
| Not completed | 10 | 20 |
| Physician decision | - | 1 |
| Other non compliance | 1 | 1 |
| Adverse Event | 3 | 9 |
| Other | 5 | 4 |
| Lost to follow-up | - | 1 |
| Withdrawal of consent (not due to AE) | 1 | 3 |
| Commercial drug is available for subject | - | 1 |

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 597 subjects were enrolled in the study, of which 24 were included in the run-in period but were not dosed in treatment period. Therefore, results are presented for only 573 subjects dosed in the treatment period.

Baseline characteristics

Reporting groups

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

Reporting group description:

Following elexacftor/tezacaftor/ivacaftor (ELX/TEZ/IVA) run-in period of 4 weeks, subjects received ELX 200 milligram (mg) once daily (qd) /TEZ 100 mg qd/IVA 150 mg every 12 hours (q12h) in the treatment period for 52 weeks.

| | |
|-----------------------|------------------|
| Reporting group title | VX-121/TEZ/D-IVA |
|-----------------------|------------------|

Reporting group description:

Following ELX/TEZ/IVA run-in period of 4 weeks, subjects received VX-121 20 mg qd/TEZ 100 mg qd/D-IVA 250 mg qd in the treatment period for 52 weeks.

| Reporting group values | ELX/TEZ/IVA | VX-121/TEZ/D-IVA | Total |
|------------------------|-------------|------------------|-------|
| Number of subjects | 289 | 284 | 573 |
| Age categorical | | | |
| Units: Subjects | | | |

| | | | |
|---|--------|--------|-----|
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 34.0 | 33.3 | |
| standard deviation | ± 12.4 | ± 12.6 | - |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 145 | 135 | 280 |
| Male | 144 | 149 | 293 |
| Ethnicity | | | |
| Units: Subjects | | | |
| Hispanic or Latino | 5 | 4 | 9 |
| Not Hispanic or Latino | 261 | 265 | 526 |
| Not Collected per Local Regulations | 23 | 15 | 38 |
| Race | | | |
| Units: Subjects | | | |
| White | 262 | 270 | 532 |
| Asian | 1 | 1 | 2 |
| American Indian or Alaska Native | 1 | 0 | 1 |
| Other | 1 | 1 | 2 |
| Not Collected per Local Regulations | 23 | 10 | 33 |
| More than one race | 1 | 2 | 3 |
| Percent Predicted Forced Expiratory Volume in 1 Second (ppFEV1) | | | |
| FEV1 is the volume of air that can forcibly be blown out in one second, after full inspiration. | | | |
| Units: Percentage points | | | |
| arithmetic mean | 66.4 | 67.2 | |
| standard deviation | ± 14.9 | ± 14.6 | - |

End points

End points reporting groups

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

Reporting group description:

Following elexacftor/tezacaftor/ivacaftor (ELX/TEZ/IVA) run-in period of 4 weeks, subjects received ELX 200 milligram (mg) once daily (qd) /TEZ 100 mg qd/IVA 150 mg every 12 hours (q12h) in the treatment period for 52 weeks.

| | |
|-----------------------|------------------|
| Reporting group title | VX-121/TEZ/D-IVA |
|-----------------------|------------------|

Reporting group description:

Following ELX/TEZ/IVA run-in period of 4 weeks, subjects received VX-121 20 mg qd/TEZ 100 mg qd/D-IVA 250 mg qd in the treatment period for 52 weeks.

| | |
|----------------------------|--|
| Subject analysis set title | ELX/TEZ/IVA (pooled analysis with 121-102) |
|----------------------------|--|

| | |
|---------------------------|--------------|
| Subject analysis set type | Per protocol |
|---------------------------|--------------|

Subject analysis set description:

The Pooled Full Analysis Set (PFAS) included all randomized subjects from this study (VX20-121-103) and from Study VX20-121-102 who carried the intended CFTR mutation(s) and received at least 1 dose of study drug during the Treatment Period. The PFAS will be used only for pooled analysis of selected endpoints.

| | |
|----------------------------|---|
| Subject analysis set title | VX-121/TEZ/D-IVA (pooled analysis with 121-102) |
|----------------------------|---|

| | |
|---------------------------|--------------|
| Subject analysis set type | Per protocol |
|---------------------------|--------------|

Subject analysis set description:

The Pooled Full Analysis Set (PFAS) included all randomized subjects from this study (VX20-121-103) and from Study VX20-121-102 who carried the intended CFTR mutation(s) and received at least 1 dose of study drug during the Treatment Period. The PFAS will be used only for pooled analysis of selected endpoints.

Primary: Absolute Change in Percent Predicted Forced Expiratory Volume in 1second (ppFEV1)

| | |
|-----------------|---|
| End point title | Absolute Change in Percent Predicted Forced Expiratory Volume in 1second (ppFEV1) |
|-----------------|---|

End point description:

FEV1 is the volume of air that can forcibly be blown out in one second, after full inspiration. The Full Analysis Set (FAS) all randomized subjects who carried the intended CFTR mutation(s) and received at least 1 dose of study drug during the Treatment Period.

Here "Number of Subjects Analyzed" signifies those subjects who were evaluated for this specific end point.

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

End point timeframe:

From Baseline Through Week 24

| End point values | ELX/TEZ/IVA | VX-121/TEZ/D-IVA | | |
|--|-------------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 276 | 268 | | |
| Units: percentage points | | | | |
| least squares mean (confidence interval 95%) | 0.0 (-0.5 to 0.5) | 0.2 (-0.3 to 0.7) | | |

Statistical analyses

| | |
|---|--------------------------------|
| Statistical analysis title | Statistical Analysis 1 |
| Comparison groups | ELX/TEZ/IVA v VX-121/TEZ/D-IVA |
| Number of subjects included in analysis | 544 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority |
| P-value | < 0.0001 |
| Method | Mixed Model Repeated Measures |
| Parameter estimate | LS Mean difference |
| Point estimate | 0.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.5 |
| upper limit | 0.9 |

Secondary: Absolute Change in Sweat Chloride (SwCl)

| | |
|------------------------|--|
| End point title | Absolute Change in Sweat Chloride (SwCl) |
| End point description: | Sweat samples were collected using an approved collection device. FAS. |
| End point type | Secondary |
| End point timeframe: | From Baseline Through Week 24 |

| | | | | |
|--|---------------------|---------------------|--|--|
| End point values | ELX/TEZ/IVA | VX-121/TEZ/D-IVA | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 276 | 270 | | |
| Units: millimole per liter (mmol/L) | | | | |
| least squares mean (confidence interval 95%) | -2.3 (-3.6 to -0.9) | -5.1 (-6.4 to -3.7) | | |

Statistical analyses

| | |
|---|--------------------------------|
| Statistical analysis title | Statistical Analysis 1 |
| Comparison groups | ELX/TEZ/IVA v VX-121/TEZ/D-IVA |
| Number of subjects included in analysis | 546 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0034 |
| Method | Mixed Model Repeated Measures |
| Parameter estimate | LS Mean difference |
| Point estimate | -2.8 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -4.7 |
| upper limit | -0.9 |

Secondary: Percentage of subjects with SwCl <60 mmol/L (pooled with data from Study VX20-121-102)

| | |
|-----------------|--|
| End point title | Percentage of subjects with SwCl <60 mmol/L (pooled with data from Study VX20-121-102) |
|-----------------|--|

End point description:

The Pooled Full Analysis Set (PFAS) included all randomized subjects from this study (VX20-121-103) and from Study VX20-121-102 who carried the intended CFTR mutation(s) and received at least 1 dose of study drug during the Treatment Period. The PFAS will be used only for pooled analysis of selected endpoints. Here "Number of Subjects Analyzed" signifies those subjects who were evaluated for this specific end point.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From Baseline Through Week 24

| End point values | ELX/TEZ/IVA (pooled analysis with 121-102) | VX-121/TEZ/D- IVA (pooled analysis with 121-102) | | |
|-------------------------------|---|---|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 479 | 465 | | |
| Units: percentage of subjects | | | | |
| number (not applicable) | 76.6 | 85.8 | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Statistical Analysis 1 |
| Comparison groups | ELX/TEZ/IVA (pooled analysis with 121-102) v VX-121/TEZ/D-IVA (pooled analysis with 121-102) |
| Number of subjects included in analysis | 944 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.0001 |
| Method | Generalized Estimated Equation Model |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 2.21 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.55 |
| upper limit | 3.15 |

Secondary: Percentage of subjects with SwCl <30 mmol/L (pooled with data from Study VX20-121-102)

| | |
|-----------------|--|
| End point title | Percentage of subjects with SwCl <30 mmol/L (pooled with data from Study VX20-121-102) |
|-----------------|--|

End point description:

PFAS. The PFAS will be used only for pooled analysis of selected endpoints. Here "Number of Subjects Analyzed" signifies those subjects who were evaluated for this specific end point.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From Baseline Through Week 24

| End point values | ELX/TEZ/IVA (pooled analysis with 121-102) | VX-121/TEZ/D- IVA (pooled analysis with 121-102) | | |
|-------------------------------|---|---|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 479 | 465 | | |
| Units: percentage of subjects | | | | |
| number (not applicable) | 22.5 | 30.5 | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Statistical Analysis 1 |
| Comparison groups | ELX/TEZ/IVA (pooled analysis with 121-102) v VX-121/TEZ/D-IVA (pooled analysis with 121-102) |
| Number of subjects included in analysis | 944 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.0001 |
| Method | Generalized Estimated Equation Model |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 2.87 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 2 |
| upper limit | 4.12 |

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Day 1 up to Safety follow-up (up to 52 weeks)

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 26.1 |
|--------------------|------|

Reporting groups

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

Reporting group description:

Following ELX/TEZ/IVA run-in period of 4 weeks, participants received ELX 200 mg qd /TEZ 100 mg qd/IVA 150 mg q12h in the treatment period for 52 weeks

| | |
|-----------------------|------------------|
| Reporting group title | VX-121/TEZ/D-IVA |
|-----------------------|------------------|

Reporting group description:

Following ELX/TEZ/IVA run-in period of 4 weeks, subjects received VX-121 20 mg qd/TEZ 100 mg qd/D-IVA 250 mg qd in the treatment period for 52 weeks.

| Serious adverse events | ELX/TEZ/IVA | VX-121/TEZ/D-IVA | |
|--|-------------------|-------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 40 / 289 (13.84%) | 40 / 284 (14.08%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | | | |
| General disorders and administration site conditions | | | |
| Chest pain | | | |
| subjects affected / exposed | 0 / 289 (0.00%) | 1 / 284 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Reproductive system and breast disorders | | | |
| Intermenstrual bleeding | | | |
| subjects affected / exposed | 1 / 289 (0.35%) | 0 / 284 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vaginal cyst | | | |
| subjects affected / exposed | 1 / 289 (0.35%) | 0 / 284 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal | | | |

| | | | |
|---|-----------------|-----------------|--|
| disorders | | | |
| Haemoptysis | | | |
| subjects affected / exposed | 1 / 289 (0.35%) | 1 / 284 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Psychiatric disorders | | | |
| Suicidal ideation | | | |
| subjects affected / exposed | 1 / 289 (0.35%) | 0 / 284 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Acute stress disorder | | | |
| subjects affected / exposed | 0 / 289 (0.00%) | 1 / 284 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Depression | | | |
| subjects affected / exposed | 0 / 289 (0.00%) | 1 / 284 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Product issues | | | |
| Device leakage | | | |
| subjects affected / exposed | 0 / 289 (0.00%) | 1 / 284 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Investigations | | | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 0 / 289 (0.00%) | 2 / 284 (0.70%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 0 / 289 (0.00%) | 2 / 284 (0.70%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood bilirubin increased | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 289 (0.00%) | 1 / 284 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood creatine phosphokinase increased | | | |
| subjects affected / exposed | 0 / 289 (0.00%) | 1 / 284 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gamma-glutamyltransferase increased | | | |
| subjects affected / exposed | 0 / 289 (0.00%) | 2 / 284 (0.70%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Glycosylated haemoglobin increased | | | |
| subjects affected / exposed | 1 / 289 (0.35%) | 0 / 284 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Ankle fracture | | | |
| subjects affected / exposed | 1 / 289 (0.35%) | 0 / 284 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Craniocerebral injury | | | |
| subjects affected / exposed | 1 / 289 (0.35%) | 0 / 284 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skull fractured base | | | |
| subjects affected / exposed | 0 / 289 (0.00%) | 1 / 284 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin laceration | | | |
| subjects affected / exposed | 0 / 289 (0.00%) | 1 / 284 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|--|-----------------|-----------------|--|
| Post procedural haematoma subjects affected / exposed | 0 / 289 (0.00%) | 1 / 284 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hand fracture subjects affected / exposed | 1 / 289 (0.35%) | 0 / 284 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Fall subjects affected / exposed | 0 / 289 (0.00%) | 1 / 284 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders Seizure subjects affected / exposed | 1 / 289 (0.35%) | 1 / 284 (0.35%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Psychomotor hyperactivity subjects affected / exposed | 1 / 289 (0.35%) | 0 / 284 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Post-traumatic headache subjects affected / exposed | 0 / 289 (0.00%) | 1 / 284 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemorrhage intracranial subjects affected / exposed | 0 / 289 (0.00%) | 1 / 284 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Disturbance in attention subjects affected / exposed | 1 / 289 (0.35%) | 0 / 284 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |

| | | | |
|---|-----------------|-----------------|--|
| Leukocytosis | | | |
| subjects affected / exposed | 1 / 289 (0.35%) | 0 / 284 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Eye disorders | | | |
| Vision blurred | | | |
| subjects affected / exposed | 0 / 289 (0.00%) | 1 / 284 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Pancreatic cyst | | | |
| subjects affected / exposed | 0 / 289 (0.00%) | 1 / 284 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Melaena | | | |
| subjects affected / exposed | 0 / 289 (0.00%) | 1 / 284 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastritis | | | |
| subjects affected / exposed | 1 / 289 (0.35%) | 0 / 284 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abdominal pain | | | |
| subjects affected / exposed | 1 / 289 (0.35%) | 0 / 284 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Faecaloma | | | |
| subjects affected / exposed | 1 / 289 (0.35%) | 0 / 284 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Distal intestinal obstruction syndrome | | | |
| subjects affected / exposed | 2 / 289 (0.69%) | 1 / 284 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| Constipation | | | |
| subjects affected / exposed | 1 / 289 (0.35%) | 0 / 284 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Flatulence | | | |
| subjects affected / exposed | 1 / 289 (0.35%) | 0 / 284 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Fatty liver alcoholic | | | |
| subjects affected / exposed | 1 / 289 (0.35%) | 0 / 284 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholelithiasis | | | |
| subjects affected / exposed | 2 / 289 (0.69%) | 0 / 284 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholangitis | | | |
| subjects affected / exposed | 1 / 289 (0.35%) | 0 / 284 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Nephrolithiasis | | | |
| subjects affected / exposed | 2 / 289 (0.69%) | 0 / 284 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Osteoarthritis | | | |
| subjects affected / exposed | 1 / 289 (0.35%) | 0 / 284 (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 | | | |
| Metapneumovirus pneumonia | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 1 / 289 (0.35%) | 0 / 284 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lower respiratory tract infection bacterial | | | |
| subjects affected / exposed | 1 / 289 (0.35%) | 0 / 284 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Influenza | | | |
| subjects affected / exposed | 2 / 289 (0.69%) | 4 / 284 (1.41%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infective pulmonary exacerbation of cystic fibrosis | | | |
| subjects affected / exposed | 12 / 289 (4.15%) | 18 / 284 (6.34%) | |
| occurrences causally related to treatment / all | 0 / 13 | 0 / 25 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infective exacerbation of bronchiectasis | | | |
| subjects affected / exposed | 0 / 289 (0.00%) | 1 / 284 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Erysipelas | | | |
| subjects affected / exposed | 0 / 289 (0.00%) | 1 / 284 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| COVID-19 | | | |
| subjects affected / exposed | 1 / 289 (0.35%) | 1 / 284 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia | | | |
| subjects affected / exposed | 6 / 289 (2.08%) | 2 / 284 (0.70%) | |
| occurrences causally related to treatment / all | 0 / 7 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary tract infection | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 289 (0.35%) | 0 / 284 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory tract infection viral | | | |
| subjects affected / exposed | 0 / 289 (0.00%) | 1 / 284 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyelonephritis | | | |
| subjects affected / exposed | 1 / 289 (0.35%) | 0 / 284 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Type 3 diabetes mellitus | | | |
| subjects affected / exposed | 0 / 289 (0.00%) | 1 / 284 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Malnutrition | | | |
| subjects affected / exposed | 1 / 289 (0.35%) | 0 / 284 (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 | ELX/TEZ/IVA | VX-121/TEZ/D-IVA | |
|---|--------------------|--------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 253 / 289 (87.54%) | 252 / 284 (88.73%) | |
| Investigations | | | |
| Blood creatine phosphokinase increased | | | |
| subjects affected / exposed | 17 / 289 (5.88%) | 24 / 284 (8.45%) | |
| occurrences (all) | 18 | 27 | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 18 / 289 (6.23%) | 19 / 284 (6.69%) | |
| occurrences (all) | 20 | 20 | |
| Alanine aminotransferase increased | | | |

| | | | |
|---|---|---|--|
| subjects affected / exposed occurrences (all) | 18 / 289 (6.23%) 22 | 24 / 284 (8.45%) 25 | |
| Nervous system disorders Headache subjects affected / exposed occurrences (all) | 41 / 289 (14.19%) 98 | 51 / 284 (17.96%) 60 | |
| General disorders and administration site conditions Pyrexia subjects affected / exposed occurrences (all) Fatigue subjects affected / exposed occurrences (all) | 29 / 289 (10.03%) 38 30 / 289 (10.38%) 40 | 28 / 284 (9.86%) 43 33 / 284 (11.62%) 38 | |
| Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all) Constipation subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) | 23 / 289 (7.96%) 30 19 / 289 (6.57%) 23 44 / 289 (15.22%) 49 19 / 289 (6.57%) 24 13 / 289 (4.50%) 14 | 15 / 284 (5.28%) 18 15 / 284 (5.28%) 18 37 / 284 (13.03%) 46 12 / 284 (4.23%) 14 22 / 284 (7.75%) 23 | |
| Respiratory, thoracic and mediastinal disorders Oropharyngeal pain subjects affected / exposed occurrences (all) Productive cough subjects affected / exposed occurrences (all) | 37 / 289 (12.80%) 50 19 / 289 (6.57%) 24 | 45 / 284 (15.85%) 58 16 / 284 (5.63%) 24 | |

| | | | |
|---|-------------------|-------------------|--|
| Rhinorrhoea | | | |
| subjects affected / exposed | 22 / 289 (7.61%) | 16 / 284 (5.63%) | |
| occurrences (all) | 25 | 19 | |
| Sinus congestion | | | |
| subjects affected / exposed | 10 / 289 (3.46%) | 18 / 284 (6.34%) | |
| occurrences (all) | 10 | 25 | |
| Sputum increased | | | |
| subjects affected / exposed | 29 / 289 (10.03%) | 27 / 284 (9.51%) | |
| occurrences (all) | 38 | 30 | |
| Nasal congestion | | | |
| subjects affected / exposed | 23 / 289 (7.96%) | 29 / 284 (10.21%) | |
| occurrences (all) | 29 | 36 | |
| Haemoptysis | | | |
| subjects affected / exposed | 22 / 289 (7.61%) | 16 / 284 (5.63%) | |
| occurrences (all) | 36 | 23 | |
| Dyspnoea | | | |
| subjects affected / exposed | 21 / 289 (7.27%) | 11 / 284 (3.87%) | |
| occurrences (all) | 21 | 14 | |
| Cough | | | |
| subjects affected / exposed | 60 / 289 (20.76%) | 63 / 284 (22.18%) | |
| occurrences (all) | 88 | 94 | |
| Skin and subcutaneous tissue disorders | | | |
| Rash | | | |
| subjects affected / exposed | 13 / 289 (4.50%) | 25 / 284 (8.80%) | |
| occurrences (all) | 15 | 30 | |
| Psychiatric disorders | | | |
| Anxiety | | | |
| subjects affected / exposed | 6 / 289 (2.08%) | 16 / 284 (5.63%) | |
| occurrences (all) | 7 | 17 | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 25 / 289 (8.65%) | 14 / 284 (4.93%) | |
| occurrences (all) | 26 | 15 | |
| Back pain | | | |
| subjects affected / exposed | 15 / 289 (5.19%) | 16 / 284 (5.63%) | |
| occurrences (all) | 15 | 20 | |

| | | | |
|---|-------------------|-------------------|--|
| Infections and infestations | | | |
| COVID-19 | | | |
| subjects affected / exposed | 72 / 289 (24.91%) | 57 / 284 (20.07%) | |
| occurrences (all) | 79 | 60 | |
| Infective pulmonary exacerbation of cystic fibrosis | | | |
| subjects affected / exposed | 85 / 289 (29.41%) | 70 / 284 (24.65%) | |
| occurrences (all) | 125 | 109 | |
| Influenza | | | |
| subjects affected / exposed | 14 / 289 (4.84%) | 29 / 284 (10.21%) | |
| occurrences (all) | 14 | 30 | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 60 / 289 (20.76%) | 57 / 284 (20.07%) | |
| occurrences (all) | 119 | 84 | |
| Viral upper respiratory tract infection | | | |
| subjects affected / exposed | 17 / 289 (5.88%) | 20 / 284 (7.04%) | |
| occurrences (all) | 19 | 26 | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 40 / 289 (13.84%) | 55 / 284 (19.37%) | |
| occurrences (all) | 59 | 71 | |
| Sinusitis | | | |
| subjects affected / exposed | 26 / 289 (9.00%) | 9 / 284 (3.17%) | |
| occurrences (all) | 31 | 11 | |

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