



## Clinical trial results:

### An Open-Label Safety and Efficacy Study for Patients With Nonsense Mutation Cystic Fibrosis Previously Treated With Ataluren (PTC 124)

#### Summary

|                          |                   |
|--------------------------|-------------------|
| EudraCT number           | 2013-005449-35    |
| Trial protocol           | BE SE IT DE ES FR |
| Global end of trial date | 05 June 2017      |

#### Results information

|                                |               |
|--------------------------------|---------------|
| Result version number          | v1 (current)  |
| This version publication date  | 27 March 2020 |
| First version publication date | 27 March 2020 |

#### Trial information

##### Trial identification

|                       |                  |
|-----------------------|------------------|
| Sponsor protocol code | PTC124-GD-023-CF |
|-----------------------|------------------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT02107859 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | PTC Therapeutics, Inc.   |
| Sponsor organisation address | 100 Corporate Court, South Plainfield, United States, NJ 07080                                 |
| Public contact               | Medical Information, PTC Therapeutics, Inc., +011 44 1-866-562-4620, medinfo@ptcbio.com        |
| Scientific contact           | Medical Information, PTC Therapeutics International Limited, +353 19068700, medinfo@ptcbio.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                       | 31 July 2017 |
| Is this the analysis of the primary completion data? | Yes          |
| Primary completion date                              | 05 June 2017 |
| Global end of trial reached?                         | Yes          |
| Global end of trial date                             | 05 June 2017 |
| Was the trial ended prematurely?                     | Yes          |

Notes:

## General information about the trial

Main objective of the trial:

The primary objective was to determine the long-term safety and tolerability of 10, 10, 20 milligrams/kilogram (mg/kg) ataluren in participants with nonsense mutation cystic fibrosis (nmCF) who completed participation in the double-blind study PTC124-GD-009-CF (NCT00803205) as assessed by adverse events and laboratory abnormalities.

Protection of trial subjects:

The study was conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki (revised version of Edinburgh, Scotland, 2000) and in conformance with the International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidance documents.

Background therapy: -

Evidence for comparator: -

|   |             |
|---|-------------|
| Actual start date of recruitment                          | 23 May 2014 |
| 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: 20 |
| Country: Number of subjects enrolled | Israel: 17        |
| Country: Number of subjects enrolled | Belgium: 8        |
| Country: Number of subjects enrolled | France: 7         |
| Country: Number of subjects enrolled | Italy: 6          |
| Country: Number of subjects enrolled | Sweden: 2         |
| Country: Number of subjects enrolled | Spain: 1          |
| Worldwide total number of subjects   | 61                |
| EEA total number of subjects         | 24                |

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          | 0 |

|                           |    |
|---------------------------|----|
| months)                   |    |
| Children (2-11 years)     | 2  |
| Adolescents (12-17 years) | 7  |
| Adults (18-64 years)      | 52 |
| From 65 to 84 years       | 0  |
| 85 years and over         | 0  |

## Subject disposition

### Recruitment

Recruitment details:

Participants with nmCF who had completed the double-blind study PTC124-GD-009-CF (NCT00803205) were enrolled and treated in this open-label extension study.

### Pre-assignment

Screening details:

On 2 March 2017, it was announced that the Phase 3 double-blind study PTC124-GD-021-CF (NCT02139306) did not achieve its primary or secondary endpoints. Based on these results, clinical development of ataluren in cystic fibrosis was discontinued and this ongoing open-label extension study was closed.

### Period 1

|                              |                                |
|------------------------------|--------------------------------|
| Period 1 title               | Overall Study (overall period) |
| Is this the baseline period? | Yes                            |
| Allocation method            | Not applicable                 |
| Blinding used                | Not blinded                    |

### Arms

|           |          |
|-----------|----------|
| Arm title | Ataluren |
|-----------|----------|

Arm description:

Participants received ataluren suspension orally 3 times a day (TID), 10mg/kg at morning, 10 mg/kg at midday, and 20 mg/kg at evening (total daily dose 40 mg/kg) for 192 weeks.

|  |                 |
|--|-----------------|
| Arm type                               | Experimental    |
| Investigational medicinal product name | Ataluren        |
| Investigational medicinal product code | PTC124          |
| Other name                             |                 |
| Pharmaceutical forms                   | Oral suspension |
| Routes of administration               | Oral use        |

Dosage and administration details:

Ataluren will be administered per dose and schedule specified in the arm.

| Number of subjects in period 1   | Ataluren |
|----------------------------------|----------|
| Started                          | 61       |
| As-treated population            | 61       |
| Intent-to-treat (ITT) population | 60       |
| Completed                        | 0        |
| Not completed                    | 61       |
| Consent withdrawn by subject     | 14       |
| Adverse event, non-fatal         | 3        |
| Other than specified             | 3        |
| Study closure                    | 41       |



## Baseline characteristics

### Reporting groups

|                       |          |
|-----------------------|----------|
| Reporting group title | Ataluren |
|-----------------------|----------|

Reporting group description:

Participants received ataluren suspension orally 3 times a day (TID), 10mg/kg at morning, 10 mg/kg at midday, and 20 mg/kg at evening (total daily dose 40 mg/kg) for 192 weeks.

| Reporting group values     | Ataluren | Total |  |
|----------------------------|----------|-------|--|
| Number of subjects         | 61       | 61    |  |
| Age categorical            |          |       |  |
| Units: Subjects            |          |       |  |
| Children (2-11 years)      | 2        | 2     |  |
| Adolescents (12-17 years)  | 7        | 7     |  |
| Adults (18-64 years)       | 52       | 52    |  |
| Age Continuous             |          |       |  |
| Units: years               |          |       |  |
| arithmetic mean            | 27.5     |       |  |
| standard deviation         | ± 10.73  | -     |  |
| Sex: Female, Male          |          |       |  |
| Units: participants        |          |       |  |
| Female                     | 34       | 34    |  |
| Male                       | 27       | 27    |  |
| Race/Ethnicity, Customized |          |       |  |
| Units: Subjects            |          |       |  |
| White-White/Caucasian      | 61       | 61    |  |
| Ethnicity (NIH/OMB)        |          |       |  |
| Units: Subjects            |          |       |  |
| Hispanic or Latino         | 1        | 1     |  |
| Not Hispanic or Latino     | 60       | 60    |  |
| Unknown or Not Reported    | 0        | 0     |  |

## End points

### End points reporting groups

|  |          |
|--|----------|
| Reporting group title  | Ataluren |
| Reporting group description:   |          |
| Participants received ataluren suspension orally 3 times a day (TID), 10mg/kg at morning, 10 mg/kg at midday, and 20 mg/kg at evening (total daily dose 40 mg/kg) for 192 weeks. |          |

### Primary: Number of Participants With Treatment-Emergent Adverse Events (TEAEs)

|                 |  |
|-----------------|--|
| End point title | Number of Participants With Treatment-Emergent Adverse Events (TEAEs) <sup>[1]</sup> |
|-----------------|--|

End point description:

AE: any untoward medical occurrence in a participant who received study drug without regard to possibility of causal relationship. Severity of an AE was classified as: mild (does not interfere with usual function), moderate (interferes to some extent with usual function), severe (interferes significantly with usual function), life threatening, and fatal AEs. Drug-related AEs: AEs with a possible or probable relationship to study drug. Serious AEs: death, a life-threatening AE, inpatient hospitalization or prolongation of existing hospitalization, persistent or significant disability or incapacity, a congenital anomaly or birth defect, or an important medical event required medical intervention. TEAE: AE that occurred or worsened from first dose of study drug to 4 weeks after last dose. A summary of other non-serious AEs and all serious AEs, regardless of causality is located in Reported AE section. As-treated population: all participants who received at least 1 dose of ataluren.

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

End point timeframe:

Baseline (Day 1) up to end of study (Week 196)

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: Safety analyses were descriptive in nature.

| End point values                 | Ataluren        |  |  |  |
|----------------------------------|-----------------|--|--|--|
| Subject group type               | Reporting group |  |  |  |
| Number of subjects analysed      | 61              |  |  |  |
| Units: participants              |                 |  |  |  |
| Any TEAEs                        | 61              |  |  |  |
| Mild AEs                         | 4               |  |  |  |
| Moderate AEs                     | 26              |  |  |  |
| Severe AEs                       | 30              |  |  |  |
| Life-threatening AEs             | 0               |  |  |  |
| Fatal AEs                        | 1               |  |  |  |
| AEs unrelated to ataluren        | 35              |  |  |  |
| AEs unlikely related to ataluren | 12              |  |  |  |
| AEs possible related to ataluren | 13              |  |  |  |
| AEs probable related to ataluren | 1               |  |  |  |
| Serious TEAEs                    | 36              |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Primary: Number of Participants With Clinically Significant Laboratory Abnormalities

|                 |  |
|-----------------|--|
| End point title | Number of Participants With Clinically Significant Laboratory Abnormalities <sup>[2]</sup> |
|-----------------|--|

End point description:

Laboratory parameters tests included hematology, biochemistry assay (hepatic, renal, and serum electrolyte values), adrenal assays, and urinalysis. Clinical significance was defined as per investigator's judgement. As-treated population included all participants who received at least 1 dose of ataluren.

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

End point timeframe:

Baseline (Day 1) up to end of study (Week 196)

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: Safety analyses were descriptive in nature.

|                             |                 |  |  |  |
|-----------------------------|-----------------|--|--|--|
| <b>End point values</b>     | Ataluren        |  |  |  |
| Subject group type          | Reporting group |  |  |  |
| Number of subjects analysed | 61              |  |  |  |
| Units: participants         | 0               |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change From Baseline in Percent Predicted Forced Expiratory Volume in 1 Second (FEV1) at the End of Treatment (Week 192), as Assessed by Spirometry

|                 |   |
|-----------------|---|
| End point title | Change From Baseline in Percent Predicted Forced Expiratory Volume in 1 Second (FEV1) at the End of Treatment (Week 192), as Assessed by Spirometry |
|-----------------|---|

End point description:

FEV1 is the volume of air that can forcibly be blown out in one second, after full inspiration. Percent of predicted FEV1 = (observed value)/(predicted value) \* 100%. Change from baseline in percent predicted FEV1 at the end of treatment was reported. ITT population included all participants who had at least 1 post-baseline efficacy assessment. Here, 'Overall number of participants analyzed' signifies participants evaluable for this outcome measure. 'n' signifies participants evaluable at specified timepoint.

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

End point timeframe:

Baseline, Week 192

|                                      |                    |  |  |  |
|--------------------------------------|--------------------|--|--|--|
| <b>End point values</b>              | Ataluren           |  |  |  |
| Subject group type                   | Reporting group    |  |  |  |
| Number of subjects analysed          | 59                 |  |  |  |
| Units: percentage of predicted FEV1  |                    |  |  |  |
| arithmetic mean (standard deviation) |                    |  |  |  |
| Baseline (n = 59)                    | 56.203 (± 17.2964) |  |  |  |



|                            |                        |  |  |  |
|----------------------------|------------------------|--|--|--|
| Change at Week 192 (n = 7) | -1.214 ( $\pm$ 3.6384) |  |  |  |
|----------------------------|------------------------|--|--|--|

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Participants With Pulmonary Exacerbation, As Assessed by Modified Fuchs Criteria

|   |  |
|---|--|
| End point title   | Percentage of Participants With Pulmonary Exacerbation, As Assessed by Modified Fuchs Criteria |
| End point description:<br>The modified Fuchs' criteria defined exacerbation as the presence of at least 4 of the following 12 Fuchs' signs and symptoms without the requirement for treatment with antibiotics: change in sputum; new or increased hemoptysis; increased cough; increased dyspnea; fatigue; temperature greater than (>) 38 degrees celsius (°C); anorexia; sinus pain; change in sinus discharge; change in physical examination of the chest; decrease in pulmonary function by 10 percent or more from a previously recorded value; or radiographic changes indicative of pulmonary function. ITT population included all participants who had at least 1 post-baseline efficacy assessment. |  |
| End point type  | Secondary  |
| End point timeframe:<br>Baseline up to Week 192   |  |

| End point values                  | Ataluren        |  |  |  |
|-----------------------------------|-----------------|--|--|--|
| Subject group type                | Reporting group |  |  |  |
| Number of subjects analysed       | 60              |  |  |  |
| Units: percentage of participants |                 |  |  |  |
| number (not applicable)           | 68.3            |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Participants With Pulmonary Exacerbation, As Assessed by Expanded Fuchs' Criteria

|  |   |
|--|---|
| End point title  | Percentage of Participants With Pulmonary Exacerbation, As Assessed by Expanded Fuchs' Criteria |
| End point description:<br>The expanded Fuchs' criteria defined exacerbation as the presence of at least 4 of the following 12 Fuchs' signs and symptoms requiring any form of antibiotic treatment (inhaled, oral, or intravenous): change in sputum; new or increased hemoptysis; increased cough; increased dyspnea; fatigue; temperature >38°C; anorexia; sinus pain; change in sinus discharge; change in physical examination of the chest; decrease in pulmonary function by 10 percent or more from a previously recorded value; or radiographic changes indicative of pulmonary function. ITT population included all participants who had at least 1 post-baseline efficacy assessment. |   |
| End point type   | Secondary   |

End point timeframe:  
Baseline up to Week 192

|                                   |                 |  |  |  |
|-----------------------------------|-----------------|--|--|--|
| <b>End point values</b>           | Ataluren        |  |  |  |
| Subject group type                | Reporting group |  |  |  |
| Number of subjects analysed       | 60              |  |  |  |
| Units: percentage of participants |                 |  |  |  |
| number (not applicable)           | 68.3            |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Participants With Pulmonary Exacerbation, As Assessed by Classic Fuchs' Criteria

|                 |  |
|-----------------|--|
| End point title | Percentage of Participants With Pulmonary Exacerbation, As Assessed by Classic Fuchs' Criteria |
|-----------------|--|

End point description:

The Classic Fuchs' criteria defined exacerbation as the presence of at least 4 of the following 12 Fuchs' signs and symptoms requiring treatment with parenteral antibiotics: change in sputum; new or increased hemoptysis; increased cough; increased dyspnea; fatigue; temperature >38°C; anorexia; sinus pain; change in sinus discharge; change in physical examination of the chest; decrease in pulmonary function by 10 percent or more from a previously recorded value; or radiographic changes indicative of pulmonary function. ITT population included all participants who had at least 1 post-baseline efficacy assessment.

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

End point timeframe:

Baseline up to Week 192

|                                   |                 |  |  |  |
|-----------------------------------|-----------------|--|--|--|
| <b>End point values</b>           | Ataluren        |  |  |  |
| Subject group type                | Reporting group |  |  |  |
| Number of subjects analysed       | 60              |  |  |  |
| Units: percentage of participants |                 |  |  |  |
| number (not applicable)           | 58.3            |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change From Baseline in 12-Lead Electrocardiogram (ECG) Parameters at Final Visit (Week 196)

|                 |  |
|-----------------|--|
| End point title | Change From Baseline in 12-Lead Electrocardiogram (ECG) Parameters at Final Visit (Week 196) |
|-----------------|--|

End point description:

ECG parameters included RR duration, PR duration, QRS duration, QT duration, QTcB (Bazett's correction formula) duration, QTcF (Fridericia's correction formula) duration. As-treated population included all participants who received at least 1 dose of ataluren. Here, 'Overall number of participants analyzed' signifies participants evaluable for this outcome measure. 'n' signifies participants evaluable for specified categories.

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

End point timeframe:

Baseline, Week 196

| End point values                         | Ataluren               |  |  |  |
|--|------------------------|--|--|--|
| Subject group type                       | Reporting group        |  |  |  |
| Number of subjects analysed              | 59                     |  |  |  |
| Units: milliseconds                      |                        |  |  |  |
| arithmetic mean (standard deviation)     |                        |  |  |  |
| Baseline: RR duration (n=59)             | 828.17 ( $\pm$ 132.15) |  |  |  |
| Change at Week 196: RR duration (n=55)   | -14.27 ( $\pm$ 115.62) |  |  |  |
| Baseline: PR duration (n=59)             | 145.02 ( $\pm$ 19.29)  |  |  |  |
| Change at Week 196: PR duration (n=55)   | -2.69 ( $\pm$ 12.25)   |  |  |  |
| Baseline: QRS duration (n=59)            | 83.90 ( $\pm$ 8.00)    |  |  |  |
| Change at Week 196: QRS duration (n=55)  | 0.33 ( $\pm$ 6.12)     |  |  |  |
| Baseline: QT duration (n=59)             | 370.71 ( $\pm$ 28.11)  |  |  |  |
| Change at Week 196: QT duration (n=55)   | -4.38 ( $\pm$ 25.63)   |  |  |  |
| Baseline: QTcB duration (n=59)           | 408.92 ( $\pm$ 22.05)  |  |  |  |
| Change at Week 196: QTcB duration (n=55) | -0.71 ( $\pm$ 17.96)   |  |  |  |
| Baseline: QTcF duration (n=59)           | 395.47 ( $\pm$ 19.23)  |  |  |  |
| Change at Week 196: QTcF duration (n=59) | -2.27 ( $\pm$ 17.13)   |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline in Heart Rate at Final Visit (Week 196), as Assessed by 12-Lead ECG

|                 |  |
|-----------------|--|
| End point title | Change From Baseline in Heart Rate at Final Visit (Week 196), as Assessed by 12-Lead ECG |
|-----------------|--|

End point description:

Heart rate was measured using 12-lead ECG. As-treated population included all participants who received at least 1 dose of ataluren. Here, 'Overall number of participants analyzed' signifies participants evaluable for this outcome measure. 'n' signifies participants evaluable for specified categories.

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

End point timeframe:

Baseline, Week 196

|                                      |                      |  |  |  |
|--------------------------------------|----------------------|--|--|--|
| <b>End point values</b>              | Ataluren             |  |  |  |
| Subject group type                   | Reporting group      |  |  |  |
| Number of subjects analysed          | 59                   |  |  |  |
| Units: beats/minute                  |                      |  |  |  |
| arithmetic mean (standard deviation) |                      |  |  |  |
| Baseline (n = 59)                    | 74.31 ( $\pm$ 12.06) |  |  |  |
| Change at Week 196 (n = 55)          | 2.04 ( $\pm$ 10.11)  |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change From Baseline in Vital Signs at Final Visit (Week 196)

|                 |   |
|-----------------|---|
| End point title | Change From Baseline in Vital Signs at Final Visit (Week 196) |
|-----------------|---|

End point description:

Vital Signs included systolic blood pressure (SBP), diastolic blood pressure (DBP). As-treated population included all participants who received at least 1 dose of ataluren. Here, 'n' signifies participants evaluable for specified categories.

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

End point timeframe:

Baseline, Week 196

|                                      |                     |  |  |  |
|--------------------------------------|---------------------|--|--|--|
| <b>End point values</b>              | Ataluren            |  |  |  |
| Subject group type                   | Reporting group     |  |  |  |
| Number of subjects analysed          | 61                  |  |  |  |
| Units: millimeters of mercury (mmHg) |                     |  |  |  |
| arithmetic mean (standard deviation) |                     |  |  |  |
| Baseline: SBP (n=61)                 | 114.8 ( $\pm$ 9.10) |  |  |  |
| Change at Week 196: SBP (n=59)       | 0.6 ( $\pm$ 12.62)  |  |  |  |
| Baseline: DBP (n=61)                 | 71.2 ( $\pm$ 8.93)  |  |  |  |
| Change at Week 196: DBP (n=59)       | -0.3 ( $\pm$ 9.93)  |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Other pre-specified: Change From Baseline in Percent Predicted Forced Vital

**Capacity (FVC) at the End of Treatment (Week 192), as Assessed by Spirometry**

|  |   |
|--|---|
| End point title  | Change From Baseline in Percent Predicted Forced Vital Capacity (FVC) at the End of Treatment (Week 192), as Assessed by Spirometry |
| End point description:<br>FVC is the volume of air that can forcibly be blown out after full inspiration in the upright position. Percent of predicted FVC = (observed value)/(predicted value) * 100%. Change from baseline in percent predicted FVC at the end of treatment was reported. ITT population included all participants who had at least 1 post-baseline efficacy assessment. Here, 'Overall number of participants analyzed' signifies participants evaluable for this outcome measure. 'n' signifies participants evaluable at specified timepoint. |   |
| End point type   | Other pre-specified   |
| End point timeframe:<br>Baseline, Week 192   |   |

| End point values                     | Ataluren           |  |  |  |
|--------------------------------------|--------------------|--|--|--|
| Subject group type                   | Reporting group    |  |  |  |
| Number of subjects analysed          | 59                 |  |  |  |
| Units: percentage of predicted FVC   |                    |  |  |  |
| arithmetic mean (standard deviation) |                    |  |  |  |
| Baseline (n = 59)                    | 73.576 (± 14.6552) |  |  |  |
| Change at Week 192 (n = 7)           | -2.286 (± 4.5722)  |  |  |  |

**Statistical analyses**

No statistical analyses for this end point

**Other pre-specified: Change From Baseline in Percent Predicted Forced Expiratory Flow Between 25% and 75% of Expiration (FEF25-75) at the End of Treatment (Week 192), as Assessed by Spirometry**

|  |   |
|--|---|
| End point title  | Change From Baseline in Percent Predicted Forced Expiratory Flow Between 25% and 75% of Expiration (FEF25-75) at the End of Treatment (Week 192), as Assessed by Spirometry |
| End point description:<br>FEF25-75 is the forced expiratory flow between 25 and 75% of vital capacity. |   |
| End point type   | Other pre-specified   |
| End point timeframe:<br>Baseline, Week 192   |   |

|                                      |                  |  |  |  |
|--------------------------------------|------------------|--|--|--|
| <b>End point values</b>              | Ataluren         |  |  |  |
| Subject group type                   | Reporting group  |  |  |  |
| Number of subjects analysed          | 0 <sup>[3]</sup> |  |  |  |
| Units: percent predicted FEV1        |                  |  |  |  |
| arithmetic mean (standard deviation) | ( )              |  |  |  |

Notes:

[3] - Due to change in planned analysis FEV25-75 was not calculated and summarized.

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Baseline up to end of study (Week 196)

Adverse event reporting additional description:

As-treated population included all participants who received at least 1 dose of ataluren.

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 17.0 |
|--------------------|------|

### Reporting groups

|                       |          |
|-----------------------|----------|
| Reporting group title | Ataluren |
|-----------------------|----------|

Reporting group description:

Participants received ataluren suspension orally TID, 10 mg/kg at morning, 10 mg/kg at midday, and 20 mg/kg at evening (total daily dose 40 mg/kg) for 192 weeks.

| Serious adverse events  | Ataluren         |  |  |
|---|------------------|--|--|
| Total subjects affected by serious adverse events                   |                  |  |  |
| subjects affected / exposed   | 36 / 61 (59.02%) |  |  |
| number of deaths (all causes)                                       | 1                |  |  |
| number of deaths resulting from adverse events                      |                  |  |  |
| Investigations  |                  |  |  |
| Blood creatine increased  |                  |  |  |
| subjects affected / exposed   | 1 / 61 (1.64%)   |  |  |
| occurrences causally related to treatment / all                     | 0 / 1            |  |  |
| deaths causally related to treatment / all                          | 0 / 0            |  |  |
| Forced expiratory volume decreased                                  |                  |  |  |
| subjects affected / exposed   | 2 / 61 (3.28%)   |  |  |
| occurrences causally related to treatment / all                     | 0 / 2            |  |  |
| deaths causally related to treatment / all                          | 0 / 0            |  |  |
| Pulmonary function test decreased                                   |                  |  |  |
| subjects affected / exposed   | 1 / 61 (1.64%)   |  |  |
| occurrences causally related to treatment / all                     | 0 / 1            |  |  |
| deaths causally related to treatment / all                          | 0 / 0            |  |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                  |  |  |
| Colon cancer  |                  |  |  |

|   |                |  |  |
|---|----------------|--|--|
| subjects affected / exposed                     | 1 / 61 (1.64%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Injury, poisoning and procedural complications  |                |  |  |
| Femur fracture                                  |                |  |  |
| subjects affected / exposed                     | 1 / 61 (1.64%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Congenital, familial and genetic disorders      |                |  |  |
| Cystic fibrosis                                 |                |  |  |
| subjects affected / exposed                     | 1 / 61 (1.64%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Vascular disorders                              |                |  |  |
| Deep vein thrombosis                            |                |  |  |
| subjects affected / exposed                     | 1 / 61 (1.64%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Gastrointestinal disorders                      |                |  |  |
| Constipation                                    |                |  |  |
| subjects affected / exposed                     | 1 / 61 (1.64%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Distal ileal obstruction syndrome               |                |  |  |
| subjects affected / exposed                     | 1 / 61 (1.64%) |  |  |
| occurrences causally related to treatment / all | 0 / 3          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Distal intestinal obstruction syndrome          |                |  |  |
| subjects affected / exposed                     | 3 / 61 (4.92%) |  |  |
| occurrences causally related to treatment / all | 0 / 3          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Intestinal obstruction                          |                |  |  |



|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                     | 1 / 61 (1.64%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Respiratory, thoracic and mediastinal disorders |                 |  |  |
| Dyspnoea  |                 |  |  |
| subjects affected / exposed                     | 1 / 61 (1.64%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Haemoptysis                                     |                 |  |  |
| subjects affected / exposed                     | 7 / 61 (11.48%) |  |  |
| occurrences causally related to treatment / all | 0 / 8           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Pneumothorax                                    |                 |  |  |
| subjects affected / exposed                     | 1 / 61 (1.64%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Respiratory failure                             |                 |  |  |
| subjects affected / exposed                     | 1 / 61 (1.64%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Hepatobiliary disorders                         |                 |  |  |
| Gallbladder pain                                |                 |  |  |
| subjects affected / exposed                     | 1 / 61 (1.64%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Renal and urinary disorders                     |                 |  |  |
| Renal failure                                   |                 |  |  |
| subjects affected / exposed                     | 1 / 61 (1.64%)  |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Renal failure acute                             |                 |  |  |
| subjects affected / exposed                     | 1 / 61 (1.64%)  |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |

|   |                  |  |  |
|---|------------------|--|--|
| Infections and infestations                         |                  |  |  |
| Appendicitis  |                  |  |  |
| subjects affected / exposed                         | 1 / 61 (1.64%)   |  |  |
| occurrences causally related to treatment / all     | 0 / 1            |  |  |
| deaths causally related to treatment / all          | 0 / 0            |  |  |
| Cellulitis  |                  |  |  |
| subjects affected / exposed                         | 1 / 61 (1.64%)   |  |  |
| occurrences causally related to treatment / all     | 0 / 1            |  |  |
| deaths causally related to treatment / all          | 0 / 0            |  |  |
| Clostridium difficile infection                     |                  |  |  |
| subjects affected / exposed                         | 1 / 61 (1.64%)   |  |  |
| occurrences causally related to treatment / all     | 0 / 1            |  |  |
| deaths causally related to treatment / all          | 0 / 1            |  |  |
| Device related infection                            |                  |  |  |
| subjects affected / exposed                         | 1 / 61 (1.64%)   |  |  |
| 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                         | 27 / 61 (44.26%) |  |  |
| occurrences causally related to treatment / all     | 1 / 70           |  |  |
| deaths causally related to treatment / all          | 0 / 0            |  |  |
| Viral upper respiratory tract infection             |                  |  |  |
| subjects affected / exposed                         | 1 / 61 (1.64%)   |  |  |
| 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 %

|   |                   |  |  |
|---|-------------------|--|--|
| <b>Non-serious adverse events</b>                     | Ataluren          |  |  |
| Total subjects affected by non-serious adverse events |                   |  |  |
| subjects affected / exposed                           | 61 / 61 (100.00%) |  |  |
| Nervous system disorders                              |                   |  |  |
| Headache  |                   |  |  |

|   |   |  |  |
|---|---|--|--|
| subjects affected / exposed<br>occurrences (all)  | 5 / 61 (8.20%)<br>12  |  |  |
| Immune system disorders<br>Drug hypersensitivity<br>subjects affected / exposed<br>occurrences (all)  | 5 / 61 (8.20%)<br>5   |  |  |
| Gastrointestinal disorders<br>Abdominal pain<br>subjects affected / exposed<br>occurrences (all)<br><br>Abdominal pain upper<br>subjects affected / exposed<br>occurrences (all)<br><br>Constipation<br>subjects affected / exposed<br>occurrences (all)<br><br>Diarrhoea<br>subjects affected / exposed<br>occurrences (all)<br><br>Haemorrhoids<br>subjects affected / exposed<br>occurrences (all)<br><br>Nausea<br>subjects affected / exposed<br>occurrences (all)<br><br>Vomiting<br>subjects affected / exposed<br>occurrences (all) | 6 / 61 (9.84%)<br>6<br><br>5 / 61 (8.20%)<br>8<br><br>7 / 61 (11.48%)<br>9<br><br>8 / 61 (13.11%)<br>8<br><br>4 / 61 (6.56%)<br>4<br><br>6 / 61 (9.84%)<br>7<br><br>4 / 61 (6.56%)<br>4 |  |  |
| Respiratory, thoracic and mediastinal disorders<br>Cough<br>subjects affected / exposed<br>occurrences (all)<br><br>Haemoptysis<br>subjects affected / exposed<br>occurrences (all)   | 9 / 61 (14.75%)<br>39<br><br>12 / 61 (19.67%)<br>22   |  |  |
| Musculoskeletal and connective tissue disorders   |   |  |  |

|   |                  |  |  |
|---|------------------|--|--|
| Arthralgia  |                  |  |  |
| subjects affected / exposed                         | 5 / 61 (8.20%)   |  |  |
| occurrences (all)                                   | 6                |  |  |
| Back pain   |                  |  |  |
| subjects affected / exposed                         | 5 / 61 (8.20%)   |  |  |
| occurrences (all)                                   | 5                |  |  |
| Musculoskeletal chest pain                          |                  |  |  |
| subjects affected / exposed                         | 4 / 61 (6.56%)   |  |  |
| occurrences (all)                                   | 4                |  |  |
| Infections and infestations                         |                  |  |  |
| Gastroenteritis                                     |                  |  |  |
| subjects affected / exposed                         | 5 / 61 (8.20%)   |  |  |
| occurrences (all)                                   | 6                |  |  |
| Infective pulmonary exacerbation of cystic fibrosis |                  |  |  |
| subjects affected / exposed                         | 50 / 61 (81.97%) |  |  |
| occurrences (all)                                   | 147              |  |  |
| Influenza   |                  |  |  |
| subjects affected / exposed                         | 4 / 61 (6.56%)   |  |  |
| occurrences (all)                                   | 4                |  |  |
| Nasopharyngitis                                     |                  |  |  |
| subjects affected / exposed                         | 5 / 61 (8.20%)   |  |  |
| occurrences (all)                                   | 9                |  |  |
| Oral candidiasis                                    |                  |  |  |
| subjects affected / exposed                         | 4 / 61 (6.56%)   |  |  |
| occurrences (all)                                   | 5                |  |  |
| Sinusitis   |                  |  |  |
| subjects affected / exposed                         | 6 / 61 (9.84%)   |  |  |
| occurrences (all)                                   | 6                |  |  |
| Upper respiratory tract infection                   |                  |  |  |
| subjects affected / exposed                         | 9 / 61 (14.75%)  |  |  |
| occurrences (all)                                   | 19               |  |  |
| Viral upper respiratory tract infection             |                  |  |  |
| subjects affected / exposed                         | 22 / 61 (36.07%) |  |  |
| occurrences (all)                                   | 34               |  |  |



## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment  |
|------------------|--|
| 24 February 2015 | <p>It included following changes:</p> <ul style="list-style-type: none"><li>• Treatment duration as changed from 48 to 96 weeks to allow participants prolonged access to study drug and possibility of weight-based dose adjustment at Week 64 was added.</li><li>• The approximate number of enrolled participants was changed from 80 to 70.</li><li>• An inclusion criterion was clarified to reflect that all screening laboratory results were to be received, reviewed, and deemed acceptable for study participation prior to enrollment.</li><li>• The assessment of adrenocorticotrophic hormone (ACTH), found to be obsolete and for which no relevant change had been found, was removed.</li><li>• A table of required laboratory values at screening was deleted and the inclusion criterion revised to reflect that values were to be within the central laboratory reference range.</li><li>• Exclusion criteria were modified to clarify exclusion for chronic use of inhaled or systemic tobramycin within 4 weeks prior to screening and for evidence of pulmonary exacerbation between screening and enrollment.</li><li>• Serum electrolyte parameters were removed from the table of safety monitoring laboratory parameters to allow participants to continue in study at the investigator's discretion.</li><li>• The Schedule of Events was updated to clarify visit windows.</li><li>• Long-term follow-up period was removed based upon lack of safety issues identified in previous studies.</li><li>• Total bilirubin was added to the list of serum biochemistry assessments.</li><li>• Concomitant medication information collection was clarified.</li><li>• Sputum data collection requirements were clarified.</li><li>• Instructions to withhold short-acting beta agonists (SABAs) and long-acting beta agonists (LABAs) prior to spirometry testing were added.</li><li>• Clarification was provided for reporting of pulmonary exacerbations and pregnancy outcomes as serious adverse events (SAEs).</li><li>• Text was updated to reflect electronic data capture (EDC) as the primary method for SAE reporting for sites.</li></ul> |
| 08 February 2016 | <p>It included following changes:</p> <ul style="list-style-type: none"><li>• Treatment duration as changed from 96 to 192 weeks to allow participants extended access to study drug, and additional weight-based dose adjustment timepoints were added. Text was updated throughout the protocol to reflect the new duration.</li><li>• Respiratory event evaluation was added to Phone Visit 5a.</li><li>• Five-year long-term follow-up assessment for non-CF AEs was removed.</li><li>• Contact information was updated to reflect change in the contract research organization (CRO).</li><li>• Minor text editorial and administrative changes were made for consistency and accuracy throughout.</li></ul>  |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Based on the results of study PTC124-GD-021-CF (NCT02139306) (did not achieve its primary or secondary endpoints), clinical development of ataluren in cystic fibrosis was discontinued and this ongoing open-label extension study was closed.

Notes: