



## Clinical trial results:

### A Phase 3 Efficacy and Safety Study of PTC124 as an Oral Treatment for Nonsense-Mutation-Mediated Cystic Fibrosis

#### Summary

|                          |                         |
|--------------------------|-------------------------|
| EudraCT number           | 2008-003924-52          |
| Trial protocol           | SE NL BE ES FR GB IT DE |
| Global end of trial date | 12 November 2011        |

#### Results information

|                                |              |
|--------------------------------|--------------|
| Result version number          | v2 (current) |
| This version publication date  | 06 June 2020 |
| First version publication date | 03 May 2020  |
| Version creation reason        |              |

#### Trial information

##### Trial identification

|                       |                  |
|-----------------------|------------------|
| Sponsor protocol code | PTC124-GD-009-CF |
|-----------------------|------------------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT00803205 |
| 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 1-906-8700, medinfo@ptcbio.com |

Notes:

#### Paediatric regulatory details

|  |                     |
|--|---------------------|
| Is trial part of an agreed paediatric investigation plan (PIP)       | Yes                 |
| EMA paediatric investigation plan number(s)                          | EMA-000115-PIP02-09 |
| 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                       | 17 May 2013      |
| Is this the analysis of the primary completion data? | Yes              |
| Primary completion date                              | 12 November 2011 |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 12 November 2011 |
| Was the trial ended prematurely?                     | No               |

Notes:

## General information about the trial

Main objective of the trial:

To evaluate the ability of ataluren to improve pulmonary function as assessed by forced expiratory volume in 1 second (FEV1).

Protection of trial subjects:

This study was conducted in accordance with International Conference on Harmonisation (ICH) Good Clinical Practice, and the principles of the Declaration of Helsinki, in addition to following the laws and regulations of the country or countries in which a study is conducted.

Background therapy: -

Evidence for comparator: -

|   |                   |
|---|-------------------|
| Actual start date of recruitment                          | 08 September 2009 |
| Long term follow-up planned                               | Yes               |
| Long term follow-up rationale                             | Safety            |
| Long term follow-up duration                              | 5 Years           |
| Independent data monitoring committee (IDMC) involvement? | Yes               |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                   |
|--------------------------------------|-------------------|
| Country: Number of subjects enrolled | United States: 84 |
| Country: Number of subjects enrolled | France: 40        |
| Country: Number of subjects enrolled | Israel: 34        |
| Country: Number of subjects enrolled | Belgium: 25       |
| Country: Number of subjects enrolled | Italy: 25         |
| Country: Number of subjects enrolled | Netherlands: 12   |
| Country: Number of subjects enrolled | Germany: 6        |
| Country: Number of subjects enrolled | Sweden: 5         |
| Country: Number of subjects enrolled | Spain: 3          |
| Country: Number of subjects enrolled | United Kingdom: 3 |
| Country: Number of subjects enrolled | Canada: 1         |
| Worldwide total number of subjects   | 238               |
| EEA total number of subjects         | 119               |

Notes:

| <b>Subjects enrolled per age group</b>    |     |
|---|-----|
| 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)                     | 17  |
| Adolescents (12-17 years)                 | 58  |
| Adults (18-64 years)                      | 163 |
| From 65 to 84 years                       | 0   |
| 85 years and over                         | 0   |

## Subject disposition

### Recruitment

Recruitment details:

A total of 299 male and female participants with nonsense-mutation-mediated cystic fibrosis (nmCF) aged  $\geq 6$  years (y) signed the informed consent form and were screened for eligibility, of which 61 did not meet entry criteria to participate in the study.

### Pre-assignment

Screening details:

A total of 238 participants were randomized in a 1:1 ratio to either ataluren or placebo. Six participants (4 in the ataluren arm; 2 in the placebo arm) were excluded from the Intent-to-Treat (ITT) population because they did not have at least 1 post-Baseline (BL) forced expiratory volume (FEV1) assessment by Week 8.

### Period 1

|                              |  |
|------------------------------|--|
| Period 1 title               | Overall Study (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                 |
| <b>Arm title</b>             | Ataluren As-Treated |

Arm description:

Participants received ataluren 3 times daily (TID): 10 milligrams/kilogram (mg/kg) of body weight with breakfast, 10 mg/kg with lunch, and 20 mg/kg with dinner (total daily dose 40 mg/kg). Treatment continued for 48 weeks, after which participants were followed for 4 weeks.

|  |                                      |
|--|--------------------------------------|
| Arm type                               | Experimental                         |
| Investigational medicinal product name | Ataluren                             |
| Investigational medicinal product code |                                      |
| Other name                             | PTC124, Translarna                   |
| Pharmaceutical forms                   | Granules for oral solution in sachet |
| Routes of administration               | Oral use                             |

Dosage and administration details:

Ataluren was provided as a vanilla-flavored powder and was mixed with water. Participants received 10 mg/kg of body weight with breakfast, 10 mg/kg with lunch, and 20 mg/kg with dinner (total daily dose 40 mg/kg).

|                  |                    |
|------------------|--------------------|
| <b>Arm title</b> | Placebo As-Treated |
|------------------|--------------------|

Arm description:

Participants received placebo TID: 10 mg/kg of body weight with breakfast, 10 mg/kg with lunch, and 20 mg/kg with dinner (total daily dose 40 mg/kg). Treatment continued for 48 weeks, after which participants were followed for 4 weeks.

|  |                                      |
|--|--------------------------------------|
| Arm type                               | Placebo                              |
| Investigational medicinal product name | Placebo                              |
| Investigational medicinal product code |                                      |
| Other name                             |                                      |
| Pharmaceutical forms                   | Granules for oral solution in sachet |
| Routes of administration               | Oral use                             |

Dosage and administration details:

Placebo matching to ataluren was provided. Participants received 10 mg/kg of body weight with breakfast, 10 mg/kg with lunch, and 20 mg/kg with dinner (total daily dose 40 mg/kg).

| <b>Number of subjects in period 1</b> | Ataluren As-Treated | Placebo As-Treated |
|---------------------------------------|---------------------|--------------------|
| Started                               | 120                 | 118                |
| Completed Week 16                     | 107                 | 113                |
| Completed Week 24                     | 103                 | 110                |
| As-Treated Population*                | 120                 | 118                |
| Intent-to-Treat (ITT) Population      | 116                 | 116                |
| Per Protocol Population               | 100                 | 103 <sup>[1]</sup> |
| Completed                             | 100                 | 104                |
| Not completed                         | 20                  | 14                 |
| Medical Monitor Decision              | 1                   | -                  |
| Consent withdrawn by subject          | 9                   | 9                  |
| Physician decision                    | 1                   | -                  |
| Acquired a Lung Infection             | -                   | 1                  |
| Adverse event, non-fatal              | 7                   | 2                  |
| Sponsor Decision                      | -                   | 1                  |
| Lost to follow-up                     | 1                   | -                  |
| Protocol deviation                    | 1                   | 1                  |

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Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: One participant did not contribute data for FEV1 at Week 48.

## Baseline characteristics

### Reporting groups

|  |                     |
|--|---------------------|
| Reporting group title  | Ataluren As-Treated |
| Reporting group description:<br>Participants received ataluren 3 times daily (TID): 10 milligrams/kilogram (mg/kg) of body weight with breakfast, 10 mg/kg with lunch, and 20 mg/kg with dinner (total daily dose 40 mg/kg). Treatment continued for 48 weeks, after which participants were followed for 4 weeks. |                     |
| Reporting group title  | Placebo As-Treated  |
| Reporting group description:<br>Participants received placebo TID: 10 mg/kg of body weight with breakfast, 10 mg/kg with lunch, and 20 mg/kg with dinner (total daily dose 40 mg/kg). Treatment continued for 48 weeks, after which participants were followed for 4 weeks.  |                     |

| Reporting group values  | Ataluren As-Treated | Placebo As-Treated | Total |
|---|---------------------|--------------------|-------|
| Number of subjects  | 120                 | 118                | 238   |
| Age, Customized<br>Units: Subjects                                      |                     |                    |       |
| Participants aged 6 (min) to 53 (max) years old                         | 120                 | 118                | 238   |
| Age Continuous<br>Units: years<br>arithmetic mean<br>standard deviation | 23.0<br>± 10.06     | 23.2<br>± 9.24     | -     |
| Sex: Female, Male<br>Units: Subjects                                    |                     |                    |       |
| Female  | 58                  | 59                 | 117   |
| Male  | 62                  | 59                 | 121   |

### Subject analysis sets

|   |                    |
|---|--------------------|
| Subject analysis set title  | Ataluren ITT       |
| Subject analysis set type   | Intention-to-treat |
| Subject analysis set description:<br>Participants received ataluren TID: 10 mg/kg of body weight with breakfast, 10 mg/kg with lunch, and 20 mg/kg with dinner (total daily dose 40 mg/kg). Treatment continued for 48 weeks, after which participants were followed for 4 weeks. The ITT population included randomized participants with FEV1 data at Baseline and at least 1 post-Baseline assessment by Week 8. |                    |
| Subject analysis set title  | Placebo ITT        |
| Subject analysis set type   | Intention-to-treat |
| Subject analysis set description:<br>Participants received placebo TID: 10 mg/kg of body weight with breakfast, 10 mg/kg with lunch, and 20 mg/kg with dinner (total daily dose 40 mg/kg). Treatment continued for 48 weeks, after which participants were followed for 4 weeks. The ITT population included randomized participants with FEV1 data at Baseline and at least 1 post-Baseline assessment by Week 8.  |                    |

| Reporting group values                          | Ataluren ITT | Placebo ITT |  |
|---|--------------|-------------|--|
| Number of subjects                              | 116          | 116         |  |
| Age, Customized<br>Units: Subjects              |              |             |  |
| Participants aged 6 (min) to 53 (max) years old | 116          | 116         |  |

|                    |         |        |  |
|--------------------|---------|--------|--|
| Age Continuous     |         |        |  |
| Units: years       |         |        |  |
| arithmetic mean    | 22.8    | 23.2   |  |
| standard deviation | ± 10.18 | ± 9.32 |  |
| Sex: Female, Male  |         |        |  |
| Units: Subjects    |         |        |  |
| Female             | 56      | 58     |  |
| Male               | 60      | 58     |  |

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## End points

### End points reporting groups

|   |                     |
|---|---------------------|
| Reporting group title   | Ataluren As-Treated |
| Reporting group description:<br>Participants received ataluren 3 times daily (TID): 10 milligrams/kilogram (mg/kg) of body weight with breakfast, 10 mg/kg with lunch, and 20 mg/kg with dinner (total daily dose 40 mg/kg). Treatment continued for 48 weeks, after which participants were followed for 4 weeks.  |                     |
| Reporting group title   | Placebo As-Treated  |
| Reporting group description:<br>Participants received placebo TID: 10 mg/kg of body weight with breakfast, 10 mg/kg with lunch, and 20 mg/kg with dinner (total daily dose 40 mg/kg). Treatment continued for 48 weeks, after which participants were followed for 4 weeks.   |                     |
| Subject analysis set title  | Ataluren ITT        |
| Subject analysis set type   | Intention-to-treat  |
| Subject analysis set description:<br>Participants received ataluren TID: 10 mg/kg of body weight with breakfast, 10 mg/kg with lunch, and 20 mg/kg with dinner (total daily dose 40 mg/kg). Treatment continued for 48 weeks, after which participants were followed for 4 weeks. The ITT population included randomized participants with FEV1 data at Baseline and at least 1 post-Baseline assessment by Week 8. |                     |
| Subject analysis set title  | Placebo ITT         |
| Subject analysis set type   | Intention-to-treat  |
| Subject analysis set description:<br>Participants received placebo TID: 10 mg/kg of body weight with breakfast, 10 mg/kg with lunch, and 20 mg/kg with dinner (total daily dose 40 mg/kg). Treatment continued for 48 weeks, after which participants were followed for 4 weeks. The ITT population included randomized participants with FEV1 data at Baseline and at least 1 post-Baseline assessment by Week 8.  |                     |

### Primary: Percentage of Predicted Function (Percent-Predicted) of Forced Expiratory Volume in One Second (FEV1) at Baseline

|  |   |
|--|---|
| End point title  | Percentage of Predicted Function (Percent-Predicted) of Forced Expiratory Volume in One Second (FEV1) at Baseline |
| End point description:<br>Spirometry was used to assess pulmonary function by measuring the percentage of predicted function, which was determined on the basis of the height value obtained at the same study visit, for FEV1 (the amount of air that can be exhaled in 1 second). Spirometry was assessed by using current guidelines of the American Thoracic Society (ATS) and European Respiratory Society (ERS). Baseline was the average of percent-predicted FEV1 at screening and randomization. Here, 'Number analyzed' signifies participants evaluable for this outcome measure. |   |
| End point type   | Primary   |
| End point timeframe:<br>Baseline (Week 1)  |   |

| End point values                     | Ataluren ITT            | Placebo ITT             |  |  |
|--------------------------------------|-------------------------|-------------------------|--|--|
| Subject group type                   | Subject analysis set    | Subject analysis set    |  |  |
| Number of subjects analysed          | 116                     | 116                     |  |  |
| Units: percentage of predicted FEV1  |                         |                         |  |  |
| arithmetic mean (standard deviation) | 62.092 ( $\pm$ 13.6159) | 60.232 ( $\pm$ 15.1437) |  |  |



## Statistical analyses

|   |                                     |
|---|-------------------------------------|
| <b>Statistical analysis title</b>       | Ataluren, Placebo Baseline Analysis |
| Comparison groups                       | Ataluren ITT v Placebo ITT          |
| Number of subjects included in analysis | 232                                 |
| Analysis specification                  | Pre-specified                       |
| Analysis type                           | superiority                         |
| P-value                                 | = 0.3264                            |
| Method                                  | ANOVA                               |

## Primary: Percentage Change From Baseline in Percent-Predicted of FEV1 at Week 48

|                 |   |
|-----------------|---|
| End point title | Percentage Change From Baseline in Percent-Predicted of FEV1 at Week 48 |
|-----------------|---|

End point description:

Spirometry was used to assess pulmonary function by measuring the percentage of predicted function, which was determined on the basis of the height value obtained at the same study visit, for FEV1 (the amount of air that can be exhaled in 1 second). Spirometry was assessed by using current guidelines of the American Thoracic Society (ATS) and European Respiratory Society (ERS). The percentage of change in percent-predicted of FEV1 was calculated as follows:  $([\text{percent-predicted FEV1} - \text{Baseline percent-predicted FEV1}] / \text{Baseline percent-predicted FEV1}) * 100$ . Baseline was the average of percent-predicted FEV1 at screening and randomization. A negative change from Baseline indicates that percent-predicted of FEV1 decreased. Here, 'Number analyzed' signifies participants evaluable for this outcome measure.

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

End point timeframe:

End of Treatment (EOT) (Week 48)

|                                      |                         |                         |  |  |
|--------------------------------------|-------------------------|-------------------------|--|--|
| <b>End point values</b>              | Ataluren ITT            | Placebo ITT             |  |  |
| Subject group type                   | Subject analysis set    | Subject analysis set    |  |  |
| Number of subjects analysed          | 100                     | 103                     |  |  |
| Units: percent change                |                         |                         |  |  |
| arithmetic mean (standard deviation) | -2.534 ( $\pm$ 13.2452) | -5.500 ( $\pm$ 12.5595) |  |  |

## Statistical analyses

|                                   |   |
|-----------------------------------|---|
| <b>Statistical analysis title</b> | Analysis of Percent-Predicted FEV1 At Week 48 |
|-----------------------------------|---|

Statistical analysis description:

Least squares (LS) mean estimates based on mixed model for repeated measures (Weeks 8, 16, 24, 32, 40 and 48) of relative change in percent-predicted FEV1 as the dependent variable; independent variables including Baseline percent-predicted FEV1, treatment, visit, interactions between treatment and visit and between Baseline percent-predicted FEV1 and visit; and stratification factors of Baseline age, Baseline inhaled antibiotics, and Baseline percent-predicted FEV1.

|                   |                            |
|-------------------|----------------------------|
| Comparison groups | Ataluren ITT v Placebo ITT |
|-------------------|----------------------------|

|   |                                |
|---|--------------------------------|
| Number of subjects included in analysis | 203                            |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           |                                |
| P-value                                 | = 0.1235 <sup>[1]</sup>        |
| Method                                  | Mixed models analysis          |
| Parameter estimate                      | Mean difference (final values) |
| Point estimate                          | 2.754                          |
| Confidence interval                     |                                |
| level                                   | 95 %                           |
| sides                                   | 2-sided                        |
| lower limit                             | -0.756                         |
| upper limit                             | 6.264                          |
| Variability estimate                    | Standard error of the mean     |
| Dispersion value                        | 1.78124                        |

Notes:

[1] - The p-value is the LS-mean for the comparison between active treatment and placebo. The level of significance was 0.04998.

### Secondary: Rate of Pulmonary Exacerbations as Defined by Modified Fuch's Criteria Over 48 Weeks

|                 |  |
|-----------------|--|
| End point title | Rate of Pulmonary Exacerbations as Defined by Modified Fuch's Criteria Over 48 Weeks |
|-----------------|--|

End point description:

A Respiratory Event Form, which collected data on various signs, symptoms, and effects for each event, was completed by the Investigator when informed by the participant of a respiratory event. Pulmonary exacerbations were assessed by using the modified Fuchs' criteria, which defines an exacerbation as a respiratory event requiring treatment with parenteral antibiotics for any 4 of the following 12 symptoms, with or without intravenous 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% or more from a previously recorded value; or radiographic changes indicative of pulmonary function. The 48-week exacerbation rate was determined by adding the weekly rates for each arm and dividing the sum by 48.

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

End point timeframe:

Baseline to EOT (Week 48)

| End point values                          | Ataluren ITT         | Placebo ITT          |  |  |
|---|----------------------|----------------------|--|--|
| Subject group type                        | Subject analysis set | Subject analysis set |  |  |
| Number of subjects analysed               | 116                  | 116                  |  |  |
| Units: exacerbations                      |                      |                      |  |  |
| arithmetic mean (confidence interval 95%) | 1.42 (1.05 to 1.79)  | 1.78 (1.38 to 2.17)  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change From Baseline in Awake Cough Hourly Rate at Week 48

|                 |  |
|-----------------|--|
| End point title | Change From Baseline in Awake Cough Hourly Rate at Week 48 |
|-----------------|--|

End point description:

The frequency of awake cough was measured using the LifeShirt, which incorporates motion-sensing transducers, electrodes, a microphone, and a 3-axis accelerometer into a lightweight vest. The rate was determined by dividing the total number of coughs by 24 (the number of hours of the observation period). Baseline was the latest, valid assessment prior to the treatment. A negative change from Baseline indicates that coughing decreased. Here, 'Number analyzed' signifies participants evaluable for this outcome measure.

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

End point timeframe:

Baseline, EOT (Week 48)

| End point values                     | Ataluren ITT         | Placebo ITT          |  |  |
|--------------------------------------|----------------------|----------------------|--|--|
| Subject group type                   | Subject analysis set | Subject analysis set |  |  |
| Number of subjects analysed          | 116                  | 116                  |  |  |
| Units: coughs/hour                   |                      |                      |  |  |
| arithmetic mean (standard deviation) |                      |                      |  |  |
| Baseline (n=115, 114)                | 28.218 (± 20.2726)   | 24.472 (± 16.7828)   |  |  |
| Change From Baseline (n=97, 100)     | -0.595 (± 18.3221)   | 0.882 (± 14.3936)    |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline in the Respiratory Domain Score of the Revised Cystic Fibrosis Questionnaire (CFQ-R) at Week 48

|                 |  |
|-----------------|--|
| End point title | Change From Baseline in the Respiratory Domain Score of the Revised Cystic Fibrosis Questionnaire (CFQ-R) at Week 48 |
|-----------------|--|

End point description:

The CFQ-R consists of 44 items, including generic scales of physical functioning, role functioning, vitality, health perceptions, emotional functioning, and social functioning, and CF-specific scales of respiratory and digestive symptoms, body image, eating disturbances, and treatment burden. Each domain score ranges from 1 to 4. Scores were linearly transformed to a 0 to 100 scale, with higher scores indicating better health. Domain scores were calculated by using the following formula:  $100 * (\text{sum of responses} - \text{minimum possible sum}) / (\text{maximum possible sum} - \text{minimum possible sum})$ . The minimum possible sum = number of questions \* 1; the maximum possible = the number of questions \* 4. Baseline was the latest, valid assessment prior to the treatment. A negative change from Baseline indicates that health has worsened. Participants may have switched age groups during the study. Here, 'Number analyzed' signifies participants evaluable for this outcome measure.

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

End point timeframe:

Baseline, EOT (Week 48)

| End point values                                | Ataluren ITT         | Placebo ITT          |  |  |
|---|----------------------|----------------------|--|--|
| Subject group type                              | Subject analysis set | Subject analysis set |  |  |
| Number of subjects analysed                     | 116                  | 116                  |  |  |
| Units: units on a scale                         |                      |                      |  |  |
| arithmetic mean (standard deviation)            |                      |                      |  |  |
| Aged 6-13 years, Baseline (n=18, 13)            | 77.78 (± 11.070)     | 79.49 (± 16.879)     |  |  |
| Aged 6-13 years, Change From Baseline (n=12, 7) | -0.69 (± 12.028)     | -3.57 (± 21.973)     |  |  |
| Age ≥14 years, Baseline (n=95, 101)             | 70.06 (± 15.678)     | 65.95 (± 16.771)     |  |  |
| Age ≥14 years, Change From Baseline (n=81, 92)  | -2.81 (± 18.365)     | -3.32 (± 16.245)     |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Percent-Predicted of Forced Vital Capacity (FVC) at Baseline

|  |  |
|--|--|
| End point title  | Percent-Predicted of Forced Vital Capacity (FVC) at Baseline |
| End point description:   |  |
| Spirometry was used to assess pulmonary function by measuring the percentage of predicted function, which was determined on the basis of the height value obtained at the same study visit, for FVC (the amount of air that can be exhaled after taking a deep breath). Spirometry was assessed by using current guidelines of the ATS and ERS. Baseline was the average of percent-predicted FVC at screening and randomization. Here, 'Number analyzed' signifies participants evaluable for this outcome measure. |  |
| End point type   | Secondary  |
| End point timeframe:   |  |
| Baseline (Week 1)  |  |

| End point values                     | Ataluren ITT         | Placebo ITT          |  |  |
|--------------------------------------|----------------------|----------------------|--|--|
| Subject group type                   | Subject analysis set | Subject analysis set |  |  |
| Number of subjects analysed          | 116                  | 116                  |  |  |
| Units: percentage of predicted FVC   |                      |                      |  |  |
| arithmetic mean (standard deviation) | 78.332 (± 13.1825)   | 76.609 (± 13.3711)   |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage Change From Baseline in Percent-Predicted of FVC at Week 48

|                 |  |
|-----------------|--|
| End point title | Percentage Change From Baseline in Percent-Predicted of FVC at Week 48 |
|-----------------|--|

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**End point description:**

Spirometry was used to assess pulmonary function by measuring the percentage of predicted function, which was determined on the basis of the height value obtained at the same study visit, for FVC (the amount of air that can be exhaled after taking a deep breath). Spirometry was assessed by using current guidelines of the ATS and ERS. The percentage of change in percent-predicted of FVC was calculated as follows:  $((\text{percent-predicted FVC} - \text{Baseline percent-predicted FVC}) / \text{Baseline percent-predicted FVC}) * 100$ . Baseline was the average of percent-predicted FVC at screening and randomization. A negative change from Baseline indicates that percent-predicted of FVC decreased. Here, 'Number analyzed' signifies participants evaluable for this outcome measure.

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

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End point timeframe:

EOT (Week 48)

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| End point values                     | Ataluren ITT            | Placebo ITT            |  |  |
|--------------------------------------|-------------------------|------------------------|--|--|
| Subject group type                   | Subject analysis set    | Subject analysis set   |  |  |
| Number of subjects analysed          | 100                     | 103                    |  |  |
| Units: percent change                |                         |                        |  |  |
| arithmetic mean (standard deviation) | -2.139 ( $\pm$ 10.0463) | -3.484 ( $\pm$ 9.9304) |  |  |

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**Statistical analyses**

No statistical analyses for this end point

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**Other pre-specified: Percentage of Participants With Treatment-Emergent Adverse Events (TEAE)**

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|                 |  |
|-----------------|--|
| End point title | Percentage of Participants With Treatment-Emergent Adverse Events (TEAE) |
|-----------------|--|

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End point description:

A TEAE was any untoward medical occurrence in a participant who received study drug without regard to possibility of causal relationship that occurred or worsened in the period extending from first dose of study drug to 4 weeks after the last dose of study drug. A serious adverse event (SAE) was an AE resulting in any of the following outcomes or deemed significant for any other reason: death; initial or prolonged inpatient hospitalization; life-threatening experience (immediate risk of dying); persistent or significant disability/incapacity; congenital anomaly. AEs included both SAEs and non-serious AEs. AE severity was graded as follows: Grade 1: mild; Grade 2: moderate; Grade 3: severe; Grade 4: life-threatening; Grade 5: fatal. A TEAE was considered related if in the opinion of the Investigator it was possibly or probably caused by the study drug. A summary of other non-serious AEs and all SAEs, regardless of causality is located in the Adverse Events module.

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|                |                     |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

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End point timeframe:

Baseline up to 4 Weeks Post-Treatment (Week 52) or Premature Discontinuation (PD)

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| End point values               | Ataluren As-Treated | Placebo As-Treated |  |  |
|--------------------------------|---------------------|--------------------|--|--|
| Subject group type             | Reporting group     | Reporting group    |  |  |
| Number of subjects analysed    | 120                 | 118                |  |  |
| Units: percent of participants |                     |                    |  |  |
| number (not applicable)        |                     |                    |  |  |
| At least 1 TEAE                | 98.3                | 97.5               |  |  |
| Grade 1 TEAE                   | 15.0                | 16.9               |  |  |
| Grade 2 TEAE                   | 67.5                | 55.1               |  |  |
| Grade 3 TEAE                   | 15.8                | 25.4               |  |  |
| Grade 4 TEAE                   | 0                   | 0                  |  |  |
| Grade 5 TEAE                   | 0                   | 0                  |  |  |
| Unrelated TEAE                 | 25.0                | 35.6               |  |  |
| Unlikely related TEAE          | 32.5                | 26.3               |  |  |
| Possibly related TEAE          | 28.3                | 29.7               |  |  |
| Probably related TEAE          | 12.5                | 5.9                |  |  |
| Discontinuation due to TEAE    | 6.7                 | 2.5                |  |  |
| Serious TEAE                   | 37.5                | 40.7               |  |  |

## Statistical analyses

No statistical analyses for this end point

## Other pre-specified: Rate of Study Drug Compliance by Drug Accountability

|                 |  |
|-----------------|--|
| End point title | Rate of Study Drug Compliance by Drug Accountability |
|-----------------|--|

End point description:

Study drug compliance was assessed by using a Pharmacy Subject Study Drug Accountability Log (completed by the investigational site personnel). The rate of compliance was defined as 100 \* (number of sachets taken/number of planned sachets) during the study. All calculations were based on the records of the first dose date to the last dose date. To differentiate dose strengths while maintaining the blind, each kit had a unique kit number and had prominent lettering "A" and "B." Each kit contained 65 packets of 1 of the dose strengths (125, 250, or 1000 mg or matching placebo). Labeling for active drug and placebo was identical.

|                |                     |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

Baseline up to EOT (Week 48)

| End point values              | Ataluren As-Treated      | Placebo As-Treated       |  |  |
|-------------------------------|--------------------------|--------------------------|--|--|
| Subject group type            | Reporting group          | Reporting group          |  |  |
| Number of subjects analysed   | 120                      | 118                      |  |  |
| Units: percent of doses taken |                          |                          |  |  |
| median (full range (min-max)) |                          |                          |  |  |
| Drug Kit A                    | 90.149 (18.24 to 109.24) | 85.119 (28.36 to 125.79) |  |  |
| Drug Kit B                    | 90.830 (13.27 to 116.67) | 86.614 (25.22 to 107.60) |  |  |

## Statistical analyses

No statistical analyses for this end point

### Other pre-specified: Rate of Study Drug Compliance by Patient-Reported Data

|                 |  |
|-----------------|--|
| End point title | Rate of Study Drug Compliance by Patient-Reported Data |
|-----------------|--|

End point description:

Patient-reported data were obtained from the participant's electronic daily diary, which was completed by the participant or the caregiver. During study treatment, the electronic daily diary was to be completed by the participant or caregiver each day for each dose. For each participant, compliance is described in terms of the percentage of study drug actually taken. All calculations were based on the records of the first dose date to the last dose date. To differentiate dose strengths while maintaining the blind, each kit had a unique kit number and had prominent lettering "A" and "B." Each kit contained 65 packets of 1 of the dose strengths (125, 250, or 1000 mg or matching placebo). Labeling for active drug and placebo was identical.

|                |                     |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

Baseline up to EOT (Week 48)

| End point values              | Ataluren As-Treated | Placebo As-Treated  |  |  |
|-------------------------------|---------------------|---------------------|--|--|
| Subject group type            | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed   | 120                 | 118                 |  |  |
| Units: percent of doses taken |                     |                     |  |  |
| median (full range (min-max)) | 71.48 (0 to 98.5)   | 69.27 (6.4 to 98.9) |  |  |

## Statistical analyses

No statistical analyses for this end point

### Other pre-specified: Concentration of Ataluren

|                 |  |
|-----------------|--|
| End point title | Concentration of Ataluren <sup>[2]</sup> |
|-----------------|--|

End point description:

Blood samples were drawn immediately before administration of the first daily dose (dose taken with breakfast) of study drug and 2 hours after the first daily dose. Whenever possible, the pre-dose sample was to be obtained within 15 minutes of drug administration. Participants in the Placebo arm did not receive Ataluren and are not included in this End Point. Here, 'Number analyzed' signifies participants evaluable for this outcome measure.

|                |                     |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

Predose and 2 Hours Postdose at Week 1, Week 16, Week 32, EOT (Week 48)

Notes:

[2] - 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: Participants in the Placebo arm did not receive Ataluren and are not included in this End Point.

| End point values                     | Ataluren As-Treated    |  |  |  |
|--------------------------------------|------------------------|--|--|--|
| Subject group type                   | Reporting group        |  |  |  |
| Number of subjects analysed          | 120                    |  |  |  |
| Units: micrograms/milliliter (ug/mL) |                        |  |  |  |
| median (full range (min-max))        |                        |  |  |  |
| Week 1 Predose (n=119)               | 0 (0 to 0)             |  |  |  |
| Week 1 Postdose (n=117)              | 14.100 (1.42 to 56.40) |  |  |  |
| Week 16 Predose (n=103)              | 4.350 (0 to 52.60)     |  |  |  |
| Week 16 Postdose (n=104)             | 11.900 (0.80 to 41.90) |  |  |  |
| Week 32 Predose (n=99)               | 4.630 (0 to 29.20)     |  |  |  |
| Week 32 Postdose (n=97)              | 13.400 (2.37 to 36.30) |  |  |  |
| Week 48 Predose (n= 97)              | 3.970 (0 to 27.00)     |  |  |  |
| Week 48 Postdose (n=96)              | 10.500 (0 to 39.10)    |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Other pre-specified: Rate of Interventions for Respiratory Symptoms

|   |  |
|---|--|
| End point title   | Rate of Interventions for Respiratory Symptoms |
| End point description:<br>During treatment, any intervention including hospitalization or use of oral, inhaled, or intravenous antibiotics was documented if it was due to an exacerbation-like episode. Participants and caregivers recorded interventions in an electronic diary. The rate of interventions was defined as the total days with interventions divided by the total study duration. |  |
| End point type  | Other pre-specified                            |
| End point timeframe:<br>Baseline up to EOT (Week 48)  |  |

| End point values                                | Ataluren ITT         | Placebo ITT          |  |  |
|---|----------------------|----------------------|--|--|
| Subject group type                              | Subject analysis set | Subject analysis set |  |  |
| Number of subjects analysed                     | 116                  | 116                  |  |  |
| Units: days with interventions during the study |                      |                      |  |  |
| arithmetic mean (standard deviation)            |                      |                      |  |  |
| Hospitalization                                 | 0.010 (± 0.0222)     | 0.021 (± 0.0469)     |  |  |



|                    |                       |                       |  |  |
|--------------------|-----------------------|-----------------------|--|--|
| Use of Antibiotics | 0.220 ( $\pm$ 0.2284) | 0.245 ( $\pm$ 0.2380) |  |  |
|--------------------|-----------------------|-----------------------|--|--|

## Statistical analyses

No statistical analyses for this end point

## Other pre-specified: Rate of Disruptions in Activities of Daily Living Because of Pulmonary Symptoms

|   |   |
|---|---|
| End point title   | Rate of Disruptions in Activities of Daily Living Because of Pulmonary Symptoms |
| End point description:<br>During treatment, any disruption in the activities of daily living, such as missed school or work, was documented if it was due to an exacerbation-like episode. Participants and caregivers recorded all disruptions in an electronic diary. The rate of disruptions was defined as the total days with disruptions to daily living divided by the total study duration. |   |
| End point type  | Other pre-specified   |
| End point timeframe:<br>Baseline up to EOT (Week 48)  |   |

| End point values                             | Ataluren ITT          | Placebo ITT           |  |  |
|--|-----------------------|-----------------------|--|--|
| Subject group type                           | Subject analysis set  | Subject analysis set  |  |  |
| Number of subjects analysed                  | 116                   | 116                   |  |  |
| Units: days with disruption during the study |                       |                       |  |  |
| arithmetic mean (standard deviation)         | 0.037 ( $\pm$ 0.0550) | 0.047 ( $\pm$ 0.0755) |  |  |

## Statistical analyses

No statistical analyses for this end point

## Other pre-specified: Change From Baseline in Body Weight at Week 48

|   |  |
|---|--|
| End point title   | Change From Baseline in Body Weight at Week 48 |
| End point description:<br>Participants were weighed, and the weight was recorded at Baseline and then every 8 weeks during the treatment period. Baseline was the latest valid assessment prior to the treatment. A positive change from Baseline indicates that weight increased. Here, 'Number analyzed' signifies participants evaluable for this outcome measure. |  |
| End point type  | Other pre-specified                            |
| End point timeframe:<br>Baseline, EOT (Week 48)   |  |

| End point values                     | Ataluren ITT         | Placebo ITT          |  |  |
|--------------------------------------|----------------------|----------------------|--|--|
| Subject group type                   | Subject analysis set | Subject analysis set |  |  |
| Number of subjects analysed          | 116                  | 116                  |  |  |
| Units: kg                            |                      |                      |  |  |
| arithmetic mean (standard deviation) |                      |                      |  |  |
| Baseline (n=116, 116)                | 53.46 (± 13.941)     | 56.01 (± 13.149)     |  |  |
| Change From Baseline (n=100, 104)    | 0.87 (± 3.342)       | 0.83 (± 3.101)       |  |  |

## Statistical analyses

No statistical analyses for this end point

## Other pre-specified: Change From Baseline in the Concentration of Interleukin-8 (IL-8) in Serum and Sputum at Week 48

|   |  |
|---|--|
| End point title   | Change From Baseline in the Concentration of Interleukin-8 (IL-8) in Serum and Sputum at Week 48 |
| End point description:  |  |
| Expression of IL-8 was measured in serum and in sputum. Sputum was spontaneously produced and tested by using standardized procedures developed by the Cystic Fibrosis Foundation Therapeutics, Inc. Therapeutics Development Network (CFFT-TDN). Baseline was the latest valid assessment prior to the treatment. A negative change from Baseline indicates that the concentration of IL-8 decreased. Here, 'Number analyzed' signifies participants evaluable for this outcome measure. |  |
| End point type  | Other pre-specified  |
| End point timeframe:  |  |
| Baseline, EOT (Week 48)   |  |

| End point values                        | Ataluren ITT             | Placebo ITT              |  |  |
|---|--------------------------|--------------------------|--|--|
| Subject group type                      | Subject analysis set     | Subject analysis set     |  |  |
| Number of subjects analysed             | 116                      | 116                      |  |  |
| Units: picograms/mL                     |                          |                          |  |  |
| arithmetic mean (standard deviation)    |                          |                          |  |  |
| Serum, Baseline (n=115, 116)            | 39.537 (± 14.1697)       | 55.845 (± 131.8505)      |  |  |
| Serum, Change From Baseline (n=96, 103) | -2.334 (± 13.2141)       | -16.197 (± 138.3108)     |  |  |
| Sputum, Baseline (n=94, 95)             | 267629.93 (± 259089.569) | 250170.95 (± 180581.976) |  |  |
| Sputum, Change From Baseline (n=73, 81) | 28882.79 (± 199160.845)  | 9957.24 (± 166348.660)   |  |  |

## Statistical analyses

No statistical analyses for this end point

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**Other pre-specified: Change From Baseline in the Concentration of Neutrophil Elastase in Sputum at Week 48**

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|                 |   |
|-----------------|---|
| End point title | Change From Baseline in the Concentration of Neutrophil Elastase in Sputum at Week 48 |
|-----------------|---|

End point description:

Expression of neutrophil elastase was measured in sputum. Sputum was spontaneously produced and tested by using standardized procedures developed by the CFFT-TDN. Baseline was the latest valid assessment prior to the treatment. A positive change from Baseline indicates that the concentration of neutrophil elastase increased. Here, 'Number analyzed' signifies participants evaluable for this outcome measure.

|                |                     |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

Baseline, EOT (Week 48)

---

| End point values                     | Ataluren ITT         | Placebo ITT          |  |  |
|--------------------------------------|----------------------|----------------------|--|--|
| Subject group type                   | Subject analysis set | Subject analysis set |  |  |
| Number of subjects analysed          | 94 <sup>[3]</sup>    | 94 <sup>[4]</sup>    |  |  |
| Units: ug/mL                         |                      |                      |  |  |
| arithmetic mean (standard deviation) |                      |                      |  |  |
| Baseline (n=94, 94)                  | 183.64 (± 221.901)   | 227.35 (± 227.881)   |  |  |
| Change From Baseline (n=73, 80)      | 5.45 (± 232.824)     | -8.67 (± 296.105)    |  |  |

Notes:

[3] - Twenty-two participants in the ataluren group were not evaluable.

[4] - Twenty-two participants in the placebo group were not evaluable.

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**Statistical analyses**

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No statistical analyses for this end point

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**Other pre-specified: Change From Baseline in the Concentration of C-Reactive Protein (CRP) in Serum at Week 48**

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|                 |   |
|-----------------|---|
| End point title | Change From Baseline in the Concentration of C-Reactive Protein (CRP) in Serum at Week 48 |
|-----------------|---|

End point description:

Expression of CRP was measured in serum. Baseline was the latest valid assessment prior to the treatment. A positive change from Baseline indicates that CRP concentration increased. Here, 'Number analyzed' signifies participants evaluable for this outcome measure.

|                |                     |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

Baseline, EOT (Week 48)

---

| End point values                     | Ataluren ITT         | Placebo ITT          |  |  |
|--------------------------------------|----------------------|----------------------|--|--|
| Subject group type                   | Subject analysis set | Subject analysis set |  |  |
| Number of subjects analysed          | 116                  | 116                  |  |  |
| Units: mg/liter (L)                  |                      |                      |  |  |
| arithmetic mean (standard deviation) |                      |                      |  |  |
| Baseline (n=115, 116)                | 6.899 (± 11.5869)    | 7.037 (± 8.4411)     |  |  |
| Change From Baseline (n=96, 103)     | 2.420 (± 10.5162)    | 2.031 (± 10.1202)    |  |  |

### Statistical analyses

No statistical analyses for this end point

### Other pre-specified: Change From Baseline in the Total Lung Score as Assessed by Computed Tomography (CT) at Week 48

|   |   |
|---|---|
| End point title   | Change From Baseline in the Total Lung Score as Assessed by Computed Tomography (CT) at Week 48 |
| End point description:  |   |
| Lungs were imaged by using non-contrast, spiral CT. The total lung score for each CT scan was established by the sum of 5 characteristics from the Brody scoring system, with scores ranging from 0 to 40.5, with lower scores indicating better lung function. The characteristics scored were bronchiectasis (score range 0 – 12), mucus plugging (score range 0 – 6), peribronchial thickening (score range 0 – 9), parenchyma (score range 0 – 9), and hyperinflation (score range 0 – 4.5). Baseline was the latest valid assessment prior to the treatment. A positive change from Baseline indicates that lung function worsened. Here, 'Number analyzed' signifies participants evaluable for this outcome measure. |   |
| End point type  | Other pre-specified   |
| End point timeframe:  |   |
| Baseline, EOT (Week 48)   |   |

| End point values                     | Ataluren ITT         | Placebo ITT          |  |  |
|--------------------------------------|----------------------|----------------------|--|--|
| Subject group type                   | Subject analysis set | Subject analysis set |  |  |
| Number of subjects analysed          | 105 <sup>[5]</sup>   | 106 <sup>[6]</sup>   |  |  |
| Units: units on a scale              |                      |                      |  |  |
| arithmetic mean (standard deviation) |                      |                      |  |  |
| Baseline (n=105, 106)                | 9.531 (± 3.7526)     | 9.619 (± 3.4244)     |  |  |
| Change From Baseline (n=99, 104)     | 0.282 (± 1.3441)     | 0.560 (± 1.5602)     |  |  |

Notes:

[5] - Eleven participants in the ataluren group were not evaluable.

[6] - Ten participants in the placebo group were not evaluable.

### Statistical analyses

No statistical analyses for this end point

### Other pre-specified: Change From Baseline in Total Nasal Chloride Transport as Assessed by Transepithelial Potential Difference (TEPD) at Week 48

|                 |   |
|-----------------|---|
| End point title | Change From Baseline in Total Nasal Chloride Transport as |
|-----------------|---|

End point description:

TEPD was assessed in each nostril using standardized equipment, techniques, and solutions. Assessments were made on the nasal epithelium cells lining the inferior turbinate. Warmed solutions of Ringer's solution, amiloride, chloride-free gluconate, isoproterenol, and adenosine triphosphate (ATP) were perfused for  $\geq 3$ -minute sequentially through a nasal catheter while a voltage tracing was recorded. Total chloride transport was computed for each nostril. The total chloride transport values were calculated by subtracting the voltages at the end of a perfusion from the voltage at the end of an earlier perfusion (isoproterenol-amiloride). The average of the values for each nostril was computed. If the assessment was available in only 1 nostril, this value was used as if it were the average of both nostrils. A positive change from Baseline indicates that nasal chloride transport increased. Here, 'Number analyzed' signifies participants evaluable for this outcome measure.

|                |                     |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

Baseline, EOT (Week 48)

| End point values                     | Ataluren ITT          | Placebo ITT           |  |  |
|--------------------------------------|-----------------------|-----------------------|--|--|
| Subject group type                   | Subject analysis set  | Subject analysis set  |  |  |
| Number of subjects analysed          | 116                   | 116                   |  |  |
| Units: millivolts                    |                       |                       |  |  |
| arithmetic mean (standard deviation) |                       |                       |  |  |
| Baseline (n=116, 116)                | 1.578 ( $\pm$ 3.8786) | 1.950 ( $\pm$ 3.5462) |  |  |
| Change From Baseline (n=100, 104)    | 0.312 ( $\pm$ 5.0574) | 0.139 ( $\pm$ 5.8139) |  |  |

## Statistical analyses

No statistical analyses for this end point

## Other pre-specified: Change From Baseline in Sweat Chloride Concentration at Week 48

|                 |   |
|-----------------|---|
| End point title | Change From Baseline in Sweat Chloride Concentration at Week 48 |
|-----------------|---|

End point description:

Sweat was collected, from each arm, by using pilocarpine iontophoresis. The chloride concentration in the sweat was quantified for each arm by using standard laboratory methods. Tests were also considered valid if the sweat collection time was  $\leq 35$  minutes; tests with longer collection times were also considered valid if extra time was needed to obtain sufficient volume ( $\geq 15\mu\text{L}$ ) for analysis. For analysis purposes, the average of the values from each arm were computed. If the assessment was valid and/or available in only 1 arm, this value was used as if it were the average of both arms. The method used was consistent with the CFFT-TDN guidelines. Baseline was the latest, valid assessment prior to the treatment. A negative change from Baseline indicates that sweat chloride concentration decreased. Here, 'Number analyzed' signifies participants evaluable for this outcome measure.

|                |                     |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

Baseline, EOT (Week 48)

| <b>End point values</b>              | Ataluren ITT         | Placebo ITT          |  |  |
|--------------------------------------|----------------------|----------------------|--|--|
| Subject group type                   | Subject analysis set | Subject analysis set |  |  |
| Number of subjects analysed          | 114 <sup>[7]</sup>   | 111 <sup>[8]</sup>   |  |  |
| Units: millimoles/L                  |                      |                      |  |  |
| arithmetic mean (standard deviation) |                      |                      |  |  |
| Baseline (n=114, 111)                | 100.140 (± 14.2170)  | 96.586 (± 15.9279)   |  |  |
| Change From Baseline (n=97, 97)      | -1.325 (± 8.9431)    | -0.619 (± 10.2657)   |  |  |

Notes:

[7] - Two participants in the ataluren group were not evaluable.

[8] - Five participants in the placebo group were not evaluable.

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Baseline up to 4 Weeks Post-Treatment (Week 52) or Premature Discontinuation (PD)

Adverse event reporting additional description:

The As-Treated Population: all randomized participants who received at least 1 dose of study drug.

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 12.0 |
|--------------------|------|

### Reporting groups

|                       |         |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

Participants received placebo TID: 10 mg/kg of body weight with breakfast, 10 mg/kg with lunch, and 20 mg/kg with dinner (total daily dose 40 mg/kg). Treatment continued for 48 weeks, after which participants were followed for 4 weeks.

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

Reporting group description:

Participants received ataluren TID: 10 mg/kg of body weight with breakfast, 10 mg/kg with lunch, and 20 mg/kg with dinner (total daily dose 40 mg/kg). Treatment continued for 48 weeks, after which participants were followed for 4 weeks.

| Serious adverse events  | Placebo           | Ataluren          |  |
|---|-------------------|-------------------|--|
| Total subjects affected by serious adverse events                   |                   |                   |  |
| subjects affected / exposed   | 50 / 118 (42.37%) | 46 / 120 (38.33%) |  |
| number of deaths (all causes)                                       | 0                 | 0                 |  |
| number of deaths resulting from adverse events                      |                   |                   |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                   |                   |  |
| Malignant melanoma  |                   |                   |  |
| subjects affected / exposed   | 1 / 118 (0.85%)   | 0 / 120 (0.00%)   |  |
| occurrences causally related to treatment / all                     | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all                          | 0 / 0             | 0 / 0             |  |
| Vascular disorders  |                   |                   |  |
| Thrombosis  |                   |                   |  |
| subjects affected / exposed   | 1 / 118 (0.85%)   | 0 / 120 (0.00%)   |  |
| occurrences causally related to treatment / all                     | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all                          | 0 / 0             | 0 / 0             |  |
| General disorders and administration site conditions                |                   |                   |  |
| Pyrexia   |                   |                   |  |

|   |                   |                   |  |
|---|-------------------|-------------------|--|
| subjects affected / exposed                     | 0 / 118 (0.00%)   | 1 / 120 (0.83%)   |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Drug withdrawal syndrome                        |                   |                   |  |
| subjects affected / exposed                     | 1 / 118 (0.85%)   | 0 / 120 (0.00%)   |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Immune system disorders                         |                   |                   |  |
| Drug hypersensitivity                           |                   |                   |  |
| subjects affected / exposed                     | 1 / 118 (0.85%)   | 1 / 120 (0.83%)   |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Respiratory, thoracic and mediastinal disorders |                   |                   |  |
| Cystic fibrosis long                            |                   |                   |  |
| subjects affected / exposed                     | 41 / 118 (34.75%) | 34 / 120 (28.33%) |  |
| occurrences causally related to treatment / all | 0 / 66            | 0 / 47            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Haemoptysis                                     |                   |                   |  |
| subjects affected / exposed                     | 3 / 118 (2.54%)   | 2 / 120 (1.67%)   |  |
| occurrences causally related to treatment / all | 0 / 3             | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Nasal polyps                                    |                   |                   |  |
| subjects affected / exposed                     | 1 / 118 (0.85%)   | 0 / 120 (0.00%)   |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Psychiatric disorders                           |                   |                   |  |
| Depression                                      |                   |                   |  |
| subjects affected / exposed                     | 1 / 118 (0.85%)   | 0 / 120 (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  |                   |                   |  |
| Post procedural haemorrhage                     |                   |                   |  |



|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 118 (0.00%) | 1 / 120 (0.83%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Joint injury                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 118 (0.85%) | 0 / 120 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastrointestinal disorders                      |                 |                 |  |
| Haematemesis                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 118 (0.00%) | 1 / 120 (0.83%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Intussusception                                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 118 (0.00%) | 1 / 120 (0.83%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pancreatitis                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 118 (0.85%) | 1 / 120 (0.83%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Abdominal pain                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 118 (0.85%) | 0 / 120 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Constipation                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 118 (0.85%) | 0 / 120 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastrointestinal obstruction                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 118 (0.85%) | 0 / 120 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hepatobiliary disorders                         |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| Biliary colic                                   |                 |                 |  |
| subjects affected / exposed                     | 0 / 118 (0.00%) | 1 / 120 (0.83%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cholelithiasis                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 118 (0.00%) | 1 / 120 (0.83%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Renal and urinary disorders                     |                 |                 |  |
| Renal failure                                   |                 |                 |  |
| subjects affected / exposed                     | 0 / 118 (0.00%) | 3 / 120 (2.50%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 2 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Renal failure acute                             |                 |                 |  |
| subjects affected / exposed                     | 0 / 118 (0.00%) | 3 / 120 (2.50%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Renal colic                                     |                 |                 |  |
| subjects affected / exposed                     | 0 / 118 (0.00%) | 1 / 120 (0.83%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Urinary retention                               |                 |                 |  |
| subjects affected / exposed                     | 0 / 118 (0.00%) | 1 / 120 (0.83%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Musculoskeletal and connective tissue disorders |                 |                 |  |
| Hypercreatinaemia                               |                 |                 |  |
| subjects affected / exposed                     | 0 / 118 (0.00%) | 1 / 120 (0.83%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Infections and infestations                     |                 |                 |  |
| Pneumonia                                       |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 118 (0.00%) | 2 / 120 (1.67%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Appendicitis                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 118 (0.00%) | 1 / 120 (0.83%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pneumonia mycoplasmal                           |                 |                 |  |
| subjects affected / exposed                     | 0 / 118 (0.00%) | 1 / 120 (0.83%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Urinary tract infection                         |                 |                 |  |
| subjects affected / exposed                     | 0 / 118 (0.00%) | 1 / 120 (0.83%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Bronchopulmonary aspergillosis allergic         |                 |                 |  |
| subjects affected / exposed                     | 1 / 118 (0.85%) | 0 / 120 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastroenteritis                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 118 (0.85%) | 0 / 120 (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                     | 1 / 118 (0.85%) | 0 / 120 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Mycobacterium abscessus infection               |                 |                 |  |
| subjects affected / exposed                     | 2 / 118 (1.69%) | 0 / 120 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Metabolism and nutrition disorders              |                 |                 |  |
| Dehydration                                     |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 118 (0.85%) | 1 / 120 (0.83%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| <b>Anorexia</b>                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 118 (0.85%) | 0 / 120 (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 %

| <b>Non-serious adverse events</b>                           | Placebo            | Ataluren           |  |
|---|--------------------|--------------------|--|
| Total subjects affected by non-serious adverse events       |                    |                    |  |
| subjects affected / exposed                                 | 115 / 118 (97.46%) | 118 / 120 (98.33%) |  |
| <b>Nervous system disorders</b>                             |                    |                    |  |
| Headache  |                    |                    |  |
| subjects affected / exposed                                 | 14 / 118 (11.86%)  | 20 / 120 (16.67%)  |  |
| occurrences (all)   | 34                 | 38                 |  |
| <b>General disorders and administration site conditions</b> |                    |                    |  |
| Pyrexia   |                    |                    |  |
| subjects affected / exposed                                 | 22 / 118 (18.64%)  | 17 / 120 (14.17%)  |  |
| occurrences (all)   | 30                 | 28                 |  |
| Fatigue   |                    |                    |  |
| subjects affected / exposed                                 | 11 / 118 (9.32%)   | 11 / 120 (9.17%)   |  |
| occurrences (all)   | 12                 | 12                 |  |
| <b>Gastrointestinal disorders</b>                           |                    |                    |  |
| Abdominal pain  |                    |                    |  |
| subjects affected / exposed                                 | 14 / 118 (11.86%)  | 20 / 120 (16.67%)  |  |
| occurrences (all)   | 20                 | 38                 |  |
| Vomiting  |                    |                    |  |
| subjects affected / exposed                                 | 11 / 118 (9.32%)   | 14 / 120 (11.67%)  |  |
| occurrences (all)   | 13                 | 16                 |  |
| Diarrhoea   |                    |                    |  |
| subjects affected / exposed                                 | 21 / 118 (17.80%)  | 13 / 120 (10.83%)  |  |
| occurrences (all)   | 27                 | 18                 |  |
| Abdominal pain upper  |                    |                    |  |

|   |                   |                   |  |
|---|-------------------|-------------------|--|
| subjects affected / exposed                     | 7 / 118 (5.93%)   | 11 / 120 (9.17%)  |  |
| occurrences (all)                               | 22                | 15                |  |
| Nausea  |                   |                   |  |
| subjects affected / exposed                     | 13 / 118 (11.02%) | 11 / 120 (9.17%)  |  |
| occurrences (all)                               | 19                | 13                |  |
| Constipation                                    |                   |                   |  |
| subjects affected / exposed                     | 9 / 118 (7.63%)   | 7 / 120 (5.83%)   |  |
| occurrences (all)                               | 10                | 9                 |  |
| Respiratory, thoracic and mediastinal disorders |                   |                   |  |
| Cystic fibrosis lung                            |                   |                   |  |
| subjects affected / exposed                     | 82 / 118 (69.49%) | 85 / 120 (70.83%) |  |
| occurrences (all)                               | 190               | 168               |  |
| Cough   |                   |                   |  |
| subjects affected / exposed                     | 35 / 118 (29.66%) | 28 / 120 (23.33%) |  |
| occurrences (all)                               | 70                | 47                |  |
| Productive cough                                |                   |                   |  |
| subjects affected / exposed                     | 11 / 118 (9.32%)  | 12 / 120 (10.00%) |  |
| occurrences (all)                               | 14                | 16                |  |
| Haemoptysis                                     |                   |                   |  |
| subjects affected / exposed                     | 16 / 118 (13.56%) | 9 / 120 (7.50%)   |  |
| occurrences (all)                               | 25                | 18                |  |
| Rales   |                   |                   |  |
| subjects affected / exposed                     | 6 / 118 (5.08%)   | 6 / 120 (5.00%)   |  |
| occurrences (all)                               | 7                 | 8                 |  |
| Respiratory tract congestion                    |                   |                   |  |
| subjects affected / exposed                     | 8 / 118 (6.78%)   | 5 / 120 (4.17%)   |  |
| occurrences (all)                               | 10                | 6                 |  |
| Oropharyngeal pain                              |                   |                   |  |
| subjects affected / exposed                     | 14 / 118 (11.86%) | 4 / 120 (3.33%)   |  |
| occurrences (all)                               | 20                | 5                 |  |
| Bronchospasm                                    |                   |                   |  |
| subjects affected / exposed                     | 6 / 118 (5.08%)   | 1 / 120 (0.83%)   |  |
| occurrences (all)                               | 6                 | 1                 |  |
| Renal and urinary disorders                     |                   |                   |  |

|   |                         |                         |  |
|---|-------------------------|-------------------------|--|
| Nephrolithiasis<br>subjects affected / exposed<br>occurrences (all)                         | 4 / 118 (3.39%)<br>4    | 8 / 120 (6.67%)<br>9    |  |
| Dysuria<br>subjects affected / exposed<br>occurrences (all)                                 | 1 / 118 (0.85%)<br>1    | 7 / 120 (5.83%)<br>8    |  |
| Musculoskeletal and connective tissue disorders   |                         |                         |  |
| Back pain<br>subjects affected / exposed<br>occurrences (all)                               | 6 / 118 (5.08%)<br>6    | 8 / 120 (6.67%)<br>8    |  |
| Hypercreatinaemia<br>subjects affected / exposed<br>occurrences (all)                       | 1 / 118 (0.85%)<br>1    | 8 / 120 (6.67%)<br>13   |  |
| Infections and infestations   |                         |                         |  |
| Viral upper respiratory tract infection<br>subjects affected / exposed<br>occurrences (all) | 32 / 118 (27.12%)<br>37 | 21 / 120 (17.50%)<br>27 |  |
| Sinusitis<br>subjects affected / exposed<br>occurrences (all)                               | 14 / 118 (11.86%)<br>25 | 15 / 120 (12.50%)<br>18 |  |
| Rhinitis<br>subjects affected / exposed<br>occurrences (all)                                | 13 / 118 (11.02%)<br>16 | 12 / 120 (10.00%)<br>13 |  |
| Nasopharyngitis<br>subjects affected / exposed<br>occurrences (all)                         | 8 / 118 (6.78%)<br>12   | 10 / 120 (8.33%)<br>15  |  |
| Pharyngitis<br>subjects affected / exposed<br>occurrences (all)                             | 4 / 118 (3.39%)<br>4    | 7 / 120 (5.83%)<br>7    |  |
| Upper respiratory tract infection<br>subjects affected / exposed<br>occurrences (all)       | 12 / 118 (10.17%)<br>16 | 5 / 120 (4.17%)<br>6    |  |
| Metabolism and nutrition disorders  |                         |                         |  |
| Abnormal loss of weight<br>subjects affected / exposed<br>occurrences (all)                 | 5 / 118 (4.24%)<br>5    | 10 / 120 (8.33%)<br>10  |  |



## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date           | Amendment   |
|----------------|---|
| 03 August 2010 | <p>This amendment introduced the following changes:</p> <ul style="list-style-type: none"><li>* Updates of results of Phase 1 and Phase 2 clinical studies in the cystic fibrosis and Duchene/Becker muscular dystrophy populations.</li><li>* Addition of endpoints related to the Exacerbations of Chronic Pulmonary Disease Tool (EXACT) questionnaire.</li><li>* Updates of eligibility criteria, frequency of laboratory assessment, treatment with concomitant medications, blood collection, and adverse events reporting.</li><li>* Updates of procedures for subject enrollment.</li><li>* Update to plans for statistical analyses and interim analyses, blinding, and unblinding.</li><li>* Inclusion of summary of findings related to renal dysfunction in this study.</li></ul> |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported

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### Online references

<http://www.ncbi.nlm.nih.gov/pubmed/24836205>