

**Clinical trial results:****A Phase 3 Extension Study of Ataluren (PTC124®) in Subjects With Nonsense-Mutation-Mediated Cystic Fibrosis****Summary**

|                          |                         |
|--------------------------|-------------------------|
| EudraCT number           | 2010-019692-30          |
| Trial protocol           | BE FR NL SE IT DE ES GB |
| Global end of trial date | 02 December 2013        |

**Results information**

|                                |                 |
|--------------------------------|-----------------|
| Result version number          | v1 (current)    |
| This version publication date  | 03 October 2020 |
| First version publication date | 03 October 2020 |

**Trial information****Trial identification**

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

**Additional study identifiers**

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT01140451 |
| 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)       | 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                       | 20 December 2013 |
| Is this the analysis of the primary completion data? | Yes              |
| Primary completion date                              | 02 December 2013 |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 02 December 2013 |
| Was the trial ended prematurely?                     | No               |

Notes:

## General information about the trial

Main objective of the trial:

To evaluate the long-term safety of ataluren in participants with nonsense-mutation-mediated cystic fibrosis (nmCF), as determined by adverse events and laboratory abnormalities.

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                          | 12 August 2010 |
| 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: 65 |
| Country: Number of subjects enrolled | France: 34        |
| Country: Number of subjects enrolled | Israel: 26        |
| Country: Number of subjects enrolled | Belgium: 23       |
| Country: Number of subjects enrolled | Italy: 19         |
| Country: Number of subjects enrolled | Germany: 6        |
| Country: Number of subjects enrolled | Netherlands: 8    |
| Country: Number of subjects enrolled | Sweden: 4         |
| Country: Number of subjects enrolled | Spain: 3          |
| Country: Number of subjects enrolled | United Kingdom: 2 |
| Country: Number of subjects enrolled | Canada: 1         |
| Worldwide total number of subjects   | 191               |
| EEA total number of subjects         | 99                |

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)                     | 13  |
| Adolescents (12-17 years)                 | 41  |
| Adults (18-64 years)                      | 137 |
| From 65 to 84 years                       | 0   |
| 85 years and over                         | 0   |

## Subject disposition

### Recruitment

Recruitment details:

This was a multicenter, open-label extension study of the safety and efficacy of ataluren in male and female participants with nmCF aged  $\geq 6$  years who successfully completed Study PTC124-GD-009-CF (NCT00803205 [Study 009]).

### Pre-assignment

Screening details:

Participants began the open-label extension study immediately after completing end-of-study visit (Week 48) in Study 009 to avoid interruption in treatment. Most assessments performed at Study 009's final visit were used as Baseline assessments in Study PTC124-GD-009e-CF (009e). Investigators and participants remained blinded to Study 009 dosing.

### Period 1

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

### Arms

|                              |                   |
|------------------------------|-------------------|
| Are arms mutually exclusive? | Yes               |
| <b>Arm title</b>             | Ataluren/Ataluren |

Arm description:

Participants who received double-blind ataluren during Study 009 continued to receive open-label ataluren taken 3 times per day (TID): 10 milligram (mg)/kilogram (kg) of body weight with breakfast, 10 mg/kg with lunch, and 20 mg/kg with dinner (total dose 40 mg/kg/day), for up to 96 weeks. Participants were followed for 4 weeks after treatment.

|                                        |                                      |
|----------------------------------------|--------------------------------------|
| Arm type                               | Open-Label                           |
| 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 dose 40 mg/kg/day).

|                  |                  |
|------------------|------------------|
| <b>Arm title</b> | Placebo/Ataluren |
|------------------|------------------|

Arm description:

Participants who received double-blind placebo during Study 009 received open-label ataluren TID: 10 mg/kg of body weight with breakfast, 10 mg/kg with lunch, and 20 mg/kg with dinner (total dose 40 mg/kg/day), for up to 96 weeks. Participants were followed for 4 weeks after treatment.

|                                        |                                      |
|----------------------------------------|--------------------------------------|
| Arm type                               | Open-Label                           |
| 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 dose 40 mg/kg/day).

| <b>Number of subjects in period 1</b> | Ataluren/Ataluren | Placebo/Ataluren |
|---------------------------------------|-------------------|------------------|
| Started                               | 95                | 96               |
| Completed 24 Weeks                    | 89                | 86               |
| Completed 48 Weeks                    | 78                | 70               |
| Completed 72 Weeks                    | 63                | 62               |
| Completed 96 Weeks                    | 57                | 54               |
| As-Treated Population*                | 95                | 96               |
| 96-Week Completer Population          | 78                | 70               |
| 144-Week Completer Population         | 57                | 54               |
| Completed                             | 57                | 54               |
| Not completed                         | 38                | 42               |
| Consent withdrawn by subject          | 26                | 33               |
| Physician decision                    | 5                 | 3                |
| Adverse Event                         | 2                 | 6                |
| Lost to follow-up                     | 2                 | -                |
| Participants Planning Pregnancy       | 3                 | -                |

## Baseline characteristics

### Reporting groups

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

Reporting group description:

Participants who received double-blind ataluren during Study 009 continued to receive open-label ataluren taken 3 times per day (TID): 10 milligram (mg)/kilogram (kg) of body weight with breakfast, 10 mg/kg with lunch, and 20 mg/kg with dinner (total dose 40 mg/kg/day), for up to 96 weeks. Participants were followed for 4 weeks after treatment.

|                       |                  |
|-----------------------|------------------|
| Reporting group title | Placebo/Ataluren |
|-----------------------|------------------|

Reporting group description:

Participants who received double-blind placebo during Study 009 received open-label ataluren TID: 10 mg/kg of body weight with breakfast, 10 mg/kg with lunch, and 20 mg/kg with dinner (total dose 40 mg/kg/day), for up to 96 weeks. Participants were followed for 4 weeks after treatment.

| Reporting group values                          | Ataluren/Ataluren | Placebo/Ataluren | Total |
|-------------------------------------------------|-------------------|------------------|-------|
| Number of subjects                              | 95                | 96               | 191   |
| Age categorical<br>Units: Subjects              |                   |                  |       |
| Participants aged 7 (min) to 54 (max) years old | 95                | 96               | 191   |
| Age Continuous<br>Units: years                  |                   |                  |       |
| arithmetic mean                                 | 22.9              | 24.9             |       |
| standard deviation                              | ± 10.04           | ± 9.29           | -     |
| Sex: Female, Male<br>Units: Subjects            |                   |                  |       |
| Female                                          | 48                | 49               | 97    |
| Male                                            | 47                | 47               | 94    |

## End points

### End points reporting groups

|                                                                                                                                                                                                                                                                                                                                                                                            |                   |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------|
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                      | Ataluren/Ataluren |
| Reporting group description:<br>Participants who received double-blind ataluren during Study 009 continued to receive open-label ataluren taken 3 times per day (TID): 10 milligram (mg)/kilogram (kg) of body weight with breakfast, 10 mg/kg with lunch, and 20 mg/kg with dinner (total dose 40 mg/kg/day), for up to 96 weeks. Participants were followed for 4 weeks after treatment. |                   |
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                      | Placebo/Ataluren  |
| Reporting group description:<br>Participants who received double-blind placebo during Study 009 received open-label ataluren TID: 10 mg/kg of body weight with breakfast, 10 mg/kg with lunch, and 20 mg/kg with dinner (total dose 40 mg/kg/day), for up to 96 weeks. Participants were followed for 4 weeks after treatment.                                                             |                   |

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

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                                                                          |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | Percentage of Participants With Treatment-Emergent Adverse Events (TEAEs) <sup>[1]</sup> |
| End point description:<br>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 the first dose of study drug to 6 weeks after the last dose of study drug. A serious adverse event (SAE) was an adverse event (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. |                                                                                          |
| End point type                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | Primary                                                                                  |
| End point timeframe:<br>Baseline (Week 1 [TSW 48]) up to 4 Weeks Post-Treatment (Week 100 [TSW 148]) or Premature Discontinuation (PD) (whichever occurred first)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                                                                          |

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: No analyses were completed for this safety endpoint.

| End point values               | Ataluren/Ataluren | Placebo/Ataluren |  |  |
|--------------------------------|-------------------|------------------|--|--|
| Subject group type             | Reporting group   | Reporting group  |  |  |
| Number of subjects analysed    | 95                | 96               |  |  |
| Units: percent of participants |                   |                  |  |  |
| number (not applicable)        |                   |                  |  |  |
| At least 1 TEAE                | 100.0             | 97.9             |  |  |
| Grade 1 TEAE                   | 14.7              | 18.8             |  |  |
| Grade 2 TEAE                   | 62.1              | 51.0             |  |  |
| Grade 3 TEAE                   | 23.2              | 26.0             |  |  |
| Grade 4 TEAE                   | 0                 | 1.0              |  |  |
| Grade 5 TEAE                   | 0                 | 1.0              |  |  |
| Unrelated TEAE                 | 29.5              | 26.0             |  |  |
| Unlikely related TEAE          | 37.9              | 33.3             |  |  |
| Possibly related TEAE          | 28.4              | 31.3             |  |  |

|                          |      |      |  |  |
|--------------------------|------|------|--|--|
| Probably related TEAE    | 4.2  | 7.3  |  |  |
| Discontinued due to TEAE | 2.1  | 6.3  |  |  |
| Serious TEAE             | 50.5 | 57.3 |  |  |

## Statistical analyses

No statistical analyses for this end point

### Primary: Number of Participants With any Treatment-Emergent Laboratory Abnormality (TELA)

|                 |                                                                                                 |
|-----------------|-------------------------------------------------------------------------------------------------|
| End point title | Number of Participants With any Treatment-Emergent Laboratory Abnormality (TELA) <sup>[2]</sup> |
|-----------------|-------------------------------------------------------------------------------------------------|

End point description:

A TELA was any abnormal laboratory value that started or worsened after administration of study drug. Abnormal values were defined as values outside normal range. Values considered abnormal included - Hepatic: Serum total bilirubin  $\geq 1.5 \times$  upper limit of normal (ULN); serum gamma glutamyl transferase  $> 2.5 \times$  ULN; serum alanine aminotransferase increase of  $> 150$  units/liter (U/L) without increased creatine kinase; -Adrenal: plasma adrenocorticotrophic hormone  $> \text{ULN}$  (normal cortisol); -Renal: serum cystatin C  $> 1.33$  mg/L; serum creatinine  $> \text{ULN} - 1.5 \times \text{ULN}$  for age; serum blood urea nitrogen  $\geq 1.5 \times \text{ULN}$ ; urine protein:creatinine  $> 0.40$  mg/deciliter (dL):mg/dL; urine protein:osmolality  $> 0.30$  mg/L: milliosmoles/kg; urine blood 2+; - Serum Electrolytes: serum sodium  $> 150$  millimoles (mmol)/L,  $< 130$  mmol/L; serum potassium  $> 5.5$ ,  $< 3.0$  mmol/L; serum magnesium  $> 1.23$  mmol/L,  $< 0.5$  mmol/L; total serum calcium  $> 2.9$  mmol/L,  $< 2.0$  mmol/L; serum phosphorous  $< 0.8$  mmol/L; serum biocarbonate- $< 16$  mmol/L.

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

End point timeframe:

Baseline (Week 1 [TSW 48]) up to 4 Weeks Post-Treatment (Week 100 [TSW 148]) or PD (whichever occurred first)

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: No analyses were completed for this safety endpoint.

| End point values                         | Ataluren/Ataluren | Placebo/Ataluren |  |  |
|------------------------------------------|-------------------|------------------|--|--|
| Subject group type                       | Reporting group   | Reporting group  |  |  |
| Number of subjects analysed              | 95                | 96               |  |  |
| Units: participants                      |                   |                  |  |  |
| Renal laboratory abnormality             | 13                | 18               |  |  |
| Serum electrolyte laboratory abnormality | 39                | 47               |  |  |
| Hepatic laboratory abnormality           | 44                | 49               |  |  |
| Adrenal laboratory abnormality           | 5                 | 3                |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Predicted Function (Percent-Predicted) of Forced Expiratory Volume in 1 Second (FEV1) at Baseline

|                 |                                                                                                                 |
|-----------------|-----------------------------------------------------------------------------------------------------------------|
| End point title | Percentage of Predicted Function (Percent-Predicted) of Forced Expiratory Volume in 1 Second (FEV1) at Baseline |
|-----------------|-----------------------------------------------------------------------------------------------------------------|

End point description:

Spirometry was used to assess pulmonary function by measuring the percent-predicted, 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 validated by using current guidelines of the American Thoracic Society (ATS) and European Respiratory Society (ERS). Baseline was defined as Week 1 or the most recent value of percent-predicted FEV1 prior to the first dose of open-label treatment in Study 009e. Here, 'Number Analyzed' signifies participants evaluable for the specified week.

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

End point timeframe:

Baseline (Week 1 [TSW 48])

| End point values                     | Ataluren/Ataluren | Placebo/Ataluren |  |  |
|--------------------------------------|-------------------|------------------|--|--|
| Subject group type                   | Reporting group   | Reporting group  |  |  |
| Number of subjects analysed          | 95                | 96               |  |  |
| Units: percentage of predicted FEV1  |                   |                  |  |  |
| arithmetic mean (standard deviation) | 60.61 (± 17.075)  | 56.49 (± 15.954) |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage Change From Baseline in Percent-Predicted of FEV1 at Weeks 48 and 96

|                 |                                                                                 |
|-----------------|---------------------------------------------------------------------------------|
| End point title | Percentage Change From Baseline in Percent-Predicted of FEV1 at Weeks 48 and 96 |
|-----------------|---------------------------------------------------------------------------------|

End point description:

Spirometry was used to assess pulmonary function by measuring the percent-predicted, 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 validated 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: ((percent-predicted FEV1-Baseline percent-predicted FEV1)/Baseline percent-predicted FEV1)\*100. Baseline was defined as Week 1 or the most recent value of percent-predicted FEV1 prior to the first dose of open-label treatment in Study 009e. A positive change from Baseline indicates that FEV1 improved. Here, 'n' signifies participants evaluable for the specified week.

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

End point timeframe:

Week 48 (TSW 96), End of Treatment (EOT) (Week 96 [TSW 144])

| End point values                     | Ataluren/Ataluren | Placebo/Ataluren |  |  |
|--------------------------------------|-------------------|------------------|--|--|
| Subject group type                   | Reporting group   | Reporting group  |  |  |
| Number of subjects analysed          | 95                | 96               |  |  |
| Units: percent change                |                   |                  |  |  |
| arithmetic mean (standard deviation) |                   |                  |  |  |

|                                               |                     |                     |  |  |
|-----------------------------------------------|---------------------|---------------------|--|--|
| Change From Baseline at Week 48<br>(n=75, 66) | -0.73 (±<br>12.170) | 1.09 (±<br>23.025)  |  |  |
| Change From Baseline at Week 96<br>(n=55, 50) | -3.09 (±<br>12.304) | -2.12 (±<br>16.893) |  |  |

## 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 %-predicted, 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 validated by using current guidelines of the ATS and ERS. Baseline was defined as Week 1 or the most recent value of percent-predicted FVC prior to the first dose of open-label treatment in Study 009e. Here, 'n' signifies participants evaluable for the specified week.

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

End point timeframe:

Baseline (Week 1 [TSW 48])

| End point values                     | Ataluren/Ataluren   | Placebo/Ataluren    |  |  |
|--------------------------------------|---------------------|---------------------|--|--|
| Subject group type                   | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed          | 95                  | 96                  |  |  |
| Units: percentage of predicted FVC   |                     |                     |  |  |
| arithmetic mean (standard deviation) | 76.37 (±<br>15.254) | 73.26 (±<br>14.133) |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage Change From Baseline in Percent-Predicted of FVC at Weeks 48 and 96

|                 |                                                                                |
|-----------------|--------------------------------------------------------------------------------|
| End point title | Percentage Change From Baseline in Percent-Predicted of FVC at Weeks 48 and 96 |
|-----------------|--------------------------------------------------------------------------------|

End point description:

Spirometry was used to assess pulmonary function by measuring the %-predicted, 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 validated by using current guidelines of the ATS and ERS. The percentage of change in %-predicted of FVC was calculated as follows: ((%-predicted FVC-baseline %-predicted FVC)/baseline %-predicted FVC)\*100. A positive change from Baseline indicates that FVC improved. Here, 'n' signifies participants evaluable for the specified week.

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

End point timeframe:

Week 48 (TSW 96), EOT (Week 96 [TSW 144])

| End point values                              | Ataluren/Ataluren   | Placebo/Ataluren    |  |  |
|-----------------------------------------------|---------------------|---------------------|--|--|
| Subject group type                            | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed                   | 95                  | 96                  |  |  |
| Units: percent change                         |                     |                     |  |  |
| arithmetic mean (standard deviation)          |                     |                     |  |  |
| Change From Baseline at Week 48<br>(n=75, 66) | 0.05 (±<br>10.690)  | 0.69 (±<br>15.658)  |  |  |
| Change From Baseline at Week 96<br>(n=55, 50) | -1.48 (±<br>11.080) | -1.17 (±<br>13.940) |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percent-Predicted of Forced Expiratory Flow Between 25% and 75% of Expiration (FEF25-75) at Baseline

|                 |                                                                                                      |
|-----------------|------------------------------------------------------------------------------------------------------|
| End point title | Percent-Predicted of Forced Expiratory Flow Between 25% and 75% of Expiration (FEF25-75) at Baseline |
|-----------------|------------------------------------------------------------------------------------------------------|

End point description:

Spirometry was used to assess pulmonary function by measuring the percent-predicted, which was determined on the basis of the height value obtained at the same study visit, for FEF25-75 (the rate of air flow during the middle part of an exhalation). Spirometry was validated by using current guidelines of the ATS and ERS. Baseline was defined as Week 1 or the most recent value of percent-predicted FEF25-75 prior to the first dose of open-label treatment in Study 009e. Here, 'n' signifies participants evaluable for the specified week.

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

End point timeframe:

Baseline (Week 1 [TSW 48])

| End point values                        | Ataluren/Ataluren   | Placebo/Ataluren    |  |  |
|-----------------------------------------|---------------------|---------------------|--|--|
| Subject group type                      | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed             | 95                  | 96                  |  |  |
| Units: percentage of predicted FEF25-75 |                     |                     |  |  |
| arithmetic mean (standard deviation)    | 38.16 (±<br>24.594) | 33.11 (±<br>23.775) |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage Change From Baseline in Percent-Predicted of FEF25-75 at Weeks 48 and 96

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                                                                     |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | Percentage Change From Baseline in Percent-Predicted of FEF25-75 at Weeks 48 and 96 |
| End point description:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                                                                     |
| Spirometry was used to assess pulmonary function by measuring the percent-predicted, which was determined on the basis of the height value obtained at the same study visit, for FEF25-75 (the rate of air flow during the middle part of an exhalation). Spirometry was validated by using current guidelines of the ATS and ERS. The percentage of change in percent-predicted of FEF25-75 was calculated as follows: ((percent-predicted FEF25-75-Baseline percent-predicted FEF25-75)/Baseline percent-predicted FEF25-75)*100. Baseline was defined as Week 1 or the most recent value of percent-predicted FEF25-75 prior to the first dose of open-label treatment in Study 009e. A positive change from Baseline indicates that FEF25-75 improved. Here, 'n' signifies participants evaluable for the specified week. |                                                                                     |
| End point type                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Secondary                                                                           |
| End point timeframe:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                                                     |
| Week 48 (TSW 96), EOT (Week 96 [TSW 144])                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                     |

| End point values                           | Ataluren/Ataluren | Placebo/Ataluren |  |  |
|--------------------------------------------|-------------------|------------------|--|--|
| Subject group type                         | Reporting group   | Reporting group  |  |  |
| Number of subjects analysed                | 95                | 96               |  |  |
| Units: percent change                      |                   |                  |  |  |
| arithmetic mean (standard deviation)       |                   |                  |  |  |
| Change From Baseline at Week 48 (n=75, 66) | -0.55 (± 22.447)  | 7.89 (± 58.780)  |  |  |
| Change From Baseline at Week 96 (n=55, 50) | -5.55 (± 24.043)  | -3.29 (± 25.283) |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Participants With Pulmonary Exacerbations as Defined by Modified Fuch's Criteria

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                                                            |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | Number of Participants With Pulmonary Exacerbations as Defined by Modified Fuch's Criteria |
| End point description:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                            |
| A Respiratory Event Form (REF), 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 (IV) 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; or decrease in pulmonary function by 10% or more from a previously recorded value; or radiographic changes indicative of pulmonary function. |                                                                                            |
| End point type                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | Secondary                                                                                  |
| End point timeframe:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                            |
| Baseline (Week 1 [TSW 48]) up to Week 48 and EOT (Week 96) (TSW 96 and 144)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                            |

| End point values            | Ataluren/Ataluren | Placebo/Ataluren |  |  |
|-----------------------------|-------------------|------------------|--|--|
| Subject group type          | Reporting group   | Reporting group  |  |  |
| Number of subjects analysed | 95                | 96               |  |  |
| Units: participants         |                   |                  |  |  |
| Week 1 up to Week 48        | 50                | 56               |  |  |
| Week 1 up to Week 96        | 57                | 68               |  |  |

## Statistical analyses

No statistical analyses for this end point

## 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:<br>A REF, 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 function was 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 treatment with IV 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 for each 48-week period and dividing the sum by 48. |                                                                                      |
| End point type                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | Secondary                                                                            |
| End point timeframe:<br>Baseline (Week 1 [TSW 48]) up to Week 48 (TSW 96)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                      |

| End point values                          | Ataluren/Ataluren      | Placebo/Ataluren       |  |  |
|-------------------------------------------|------------------------|------------------------|--|--|
| Subject group type                        | Reporting group        | Reporting group        |  |  |
| Number of subjects analysed               | 95                     | 96                     |  |  |
| Units: exacerbations                      |                        |                        |  |  |
| arithmetic mean (confidence interval 95%) | 1.150 (0.843 to 1.457) | 1.614 (1.163 to 2.064) |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Duration of Pulmonary Exacerbations as Defined by Modified Fuch's Criteria

|                 |                                                                            |
|-----------------|----------------------------------------------------------------------------|
| End point title | Duration of Pulmonary Exacerbations as Defined by Modified Fuch's Criteria |
|-----------------|----------------------------------------------------------------------------|

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**End point description:**

A REF, 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 function was assessed by using the modified Fuchs' criteria (a respiratory event requiring treatment with parenteral antibiotics for 4 of 12 symptoms with or without treatment with IV 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). Duration over a 5-week interval is presented. Duration was calculated as follows: estimated date of return to a stable state (as determined by the Investigator)-estimated date of onset of symptoms. 'n' signifies participants evaluable for the specified week.

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

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**End point timeframe:**

Weeks 43 up to 48 and Weeks 91 up to 96 (TSW 91 up to 96 and TSW 139 up to 144)

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| End point values                          | Ataluren/Ataluren      | Placebo/Ataluren       |  |  |
|-------------------------------------------|------------------------|------------------------|--|--|
| Subject group type                        | Reporting group        | Reporting group        |  |  |
| Number of subjects analysed               | 95                     | 96                     |  |  |
| Units: days                               |                        |                        |  |  |
| arithmetic mean (confidence interval 95%) |                        |                        |  |  |
| Week 43 up to Week 48 (n=80, 79)          | 3.675 (1.394 to 5.956) | 4.734 (2.258 to 7.210) |  |  |
| Week 91 up to Week 96 (n=60, 57)          | 3.567 (1.124 to 6.010) | 3.912 (1.742 to 6.083) |  |  |

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**Statistical analyses**

No statistical analyses for this end point

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**Secondary: Number of Participants With Severe Pulmonary Exacerbations as Defined by Modified Fuch's Criteria**

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|                 |                                                                                                   |
|-----------------|---------------------------------------------------------------------------------------------------|
| End point title | Number of Participants With Severe Pulmonary Exacerbations as Defined by Modified Fuch's Criteria |
|-----------------|---------------------------------------------------------------------------------------------------|

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**End point description:**

A REF, 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 function was assessed by using the modified Fuchs' criteria (a respiratory event requiring treatment with parenteral antibiotics for 4 of 12 symptoms with or without treatment with IV 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). Severity of pulmonary exacerbations over a 5-week interval is presented. The severity of pulmonary exacerbations were graded as mild, moderate, or severe. Here, 'n' signifies participants evaluable for the specified week.

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

---

**End point timeframe:**

Weeks 43 up to 48 and Weeks 91 up to 96 (TSW 91 up to 96 and TSW 139 up to 144)

---

| End point values                 | Ataluren/Ataluren | Placebo/Ataluren |  |  |
|----------------------------------|-------------------|------------------|--|--|
| Subject group type               | Reporting group   | Reporting group  |  |  |
| Number of subjects analysed      | 95                | 96               |  |  |
| Units: participants              |                   |                  |  |  |
| Week 43 up to Week 48 (n=71, 73) | 1                 | 1                |  |  |
| Week 91 up to Week 96 (n=53, 49) | 0                 | 1                |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline for the Respiratory Domain Score of the Cystic Fibrosis Questionnaire-Revised (CFQ-R) at Weeks 48 and 96

|                 |                                                                                                                               |
|-----------------|-------------------------------------------------------------------------------------------------------------------------------|
| End point title | Change From Baseline for the Respiratory Domain Score of the Cystic Fibrosis Questionnaire-Revised (CFQ-R) at Weeks 48 and 96 |
|-----------------|-------------------------------------------------------------------------------------------------------------------------------|

End point description:

The CFQ-R consists of 44 items, including generic scales (physical and role functioning, vitality, health perceptions, emotional and social functioning), and cystic fibrosis (CF)-specific scales (respiratory and digestive symptoms, body image, eating disturbances, and treatment burden). Scores range from 1 to 4; higher scores indicate better quality of life (QOL). For some questions, the scale was reversed, so that 1 indicated better QOL. Domain scores were linearly transformed to a 0-100 scale, so that higher scores indicate better QOL. Domain scores were calculated as follows:  $100 * (\text{sum of responses} - \text{minimum possible sum}) / (\text{maximum possible sum} - \text{minimum possible sum})$ . Minimum possible sum = number of questions \* 1; maximum possible = the number of questions \* 4. Baseline = Week 1. A negative change from Baseline indicates that health has worsened. Participants may have switched age groups during the study. 'n' signifies participants evaluable for specified categories. 99999 = Data Not Available

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

End point timeframe:

Baseline (Week 1 [TSW 48]), Week 48 (TSW 96), EOT (Week 96 [TSW 144])

| End point values                                | Ataluren/Ataluren   | Placebo/Ataluren   |  |  |
|-------------------------------------------------|---------------------|--------------------|--|--|
| Subject group type                              | Reporting group     | Reporting group    |  |  |
| Number of subjects analysed                     | 95                  | 96                 |  |  |
| Units: units on a scale                         |                     |                    |  |  |
| arithmetic mean (standard deviation)            |                     |                    |  |  |
| 6-11 years (y), Baseline (n=8, 3)               | 83.333 (± 8.9087)   | 86.111 (± 17.3472) |  |  |
| 6-11 y, Change From Baseline, Week 48 (n=7, 3)  | -13.095 (± 19.7538) | -0 (± 0)           |  |  |
| 6-11 y, Change From Baseline, Week 96 (n=6, 1)  | -5.556 (± 10.0922)  | 0 (± 99999)        |  |  |
| 12-13 y, Baseline (n=6, 3)                      | 75.000 (± 16.6667)  | 63.889 (± 4.8113)  |  |  |
| 12-13 y, Change From Baseline, Week 48 (n=2, 2) | 0 (± 11.7851)       | 16.667 (± 0)       |  |  |
| 12-13 y, Change From Baseline, Week 96 (n=0, 0) | 99999 (± 99999)     | 99999 (± 99999)    |  |  |
| ≥14 y, Baseline (n=80, 90)                      | 66.181 (± 20.5449)  | 65.123 (± 18.1322) |  |  |

|                                                    |                    |                    |  |  |
|----------------------------------------------------|--------------------|--------------------|--|--|
| ≥14 y, Change From Baseline, Week 48 (n=64, 64)    | 2.691 (± 17.4280)  | 3.819 (± 16.2311)  |  |  |
| ≥14 y, Change From Baseline, Week 96 (n=43, 51)    | 5.039 (± 16.4811)  | 1.307 (± 20.9228)  |  |  |
| All ages, Baseline (n=94, 96)                      | 68.203 (± 20.1408) | 65.567 (± 18.1927) |  |  |
| All ages, Change From Baseline, Week 48 (n=77, 70) | 0.722 (± 17.7087)  | 4.365 (± 16.0206)  |  |  |
| All ages, Change From Baseline, Week 96 (n=56, 53) | 3.274 (± 16.5408)  | 1.625 (± 20.6684)  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Rate of Study Drug Compliance

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                               |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | Rate of Study Drug Compliance |
| End point description:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                               |
| The rate of compliance was defined as the number of actual doses taken divided by the number of planned doses * 100. Participant-reported data were obtained from the participant's compliance log, which was completed by the participant or the caregiver. The participant or caregiver reported how many doses were taken. Compliance by drug accountability was determined by counting used and unused study drug sachets. All calculations were based on the records of the first dose date to the last dose date. Here, 'n' signifies participants evaluable for specified categories. |                               |
| End point type                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | Secondary                     |
| End point timeframe:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                               |
| Baseline (Week 1 [TSW 48]) up to EOT (Week 96 [TSW 144])                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                               |

| End point values                        | Ataluren/Ataluren        | Placebo/Ataluren     |  |  |
|-----------------------------------------|--------------------------|----------------------|--|--|
| Subject group type                      | Reporting group          | Reporting group      |  |  |
| Number of subjects analysed             | 95                       | 96                   |  |  |
| Units: percent of doses taken           |                          |                      |  |  |
| median (full range (min-max))           |                          |                      |  |  |
| By drug accountability (n=95, 96)       | 86.057 (27.03 to 106.06) | 80.118 (0 to 100.74) |  |  |
| By participant-reported data (n=91, 93) | 81.50 (0 to 99.9)        | 78.59 (0 to 99.7)    |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Predose Concentration of Ataluren

|                                                                                                                                                                                                           |                                   |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------|
| End point title                                                                                                                                                                                           | Predose Concentration of Ataluren |
| End point description:                                                                                                                                                                                    |                                   |
| Blood samples were drawn immediately before administration of the first daily dose (dose taken with breakfast) of ataluren. Whenever possible, the predose sample was to be obtained within 15 minutes of |                                   |

study ataluren administration. Here, 'n' signifies participants evaluable for the specified week.

|                                                                                                               |           |
|---------------------------------------------------------------------------------------------------------------|-----------|
| End point type                                                                                                | Secondary |
| End point timeframe:                                                                                          |           |
| Predose at Weeks 1, 16, 32, 48, 64, 80 and EOT (Week 96) (TSW 48, 64, 80 96, 112, 128, and 144, respectively) |           |

| End point values                     | Ataluren/Ataluren | Placebo/Ataluren |  |  |
|--------------------------------------|-------------------|------------------|--|--|
| Subject group type                   | Reporting group   | Reporting group  |  |  |
| Number of subjects analysed          | 95                | 96               |  |  |
| Units: micrograms/milliliter (ug/mL) |                   |                  |  |  |
| arithmetic mean (standard deviation) |                   |                  |  |  |
| Week 1 (n=6, 7)                      | 1.668 (± 3.6279)  | 0 (± 0)          |  |  |
| Week 16 (n=90, 90)                   | 5.744 (± 5.7198)  | 7.552 (± 8.3963) |  |  |
| Week 32 (n=80, 78)                   | 6.298 (± 7.1222)  | 7.694 (± 7.9796) |  |  |
| Week 48 (n=78, 69)                   | 5.874 (± 6.8533)  | 6.981 (± 6.8874) |  |  |
| Week 64 (n=65, 61)                   | 5.227 (± 4.7054)  | 5.703 (± 6.2718) |  |  |
| Week 80 (n=58, 59)                   | 6.126 (± 6.4939)  | 4.902 (± 5.9218) |  |  |
| Week 96 (n=57, 53)                   | 6.390 (± 6.8861)  | 5.435 (± 6.5315) |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Participants Who Required Interventions for Pulmonary Symptoms

|                                                                                                                                                                                                                                                                                                   |                                                                          |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                   | Number of Participants Who Required Interventions for Pulmonary Symptoms |
| End point description:                                                                                                                                                                                                                                                                            |                                                                          |
| During treatment, any interventions including hospitalization or use of oral, inhaled, or intravenous antibiotics was documented if it was due to an exacerbation-like episode. A summary of other non-serious AEs and all SAEs, regardless of causality is located in the Adverse Events module. |                                                                          |
| End point type                                                                                                                                                                                                                                                                                    | Secondary                                                                |
| End point timeframe:                                                                                                                                                                                                                                                                              |                                                                          |
| Baseline (Week 1 [TSW 48]) up to EOT (Week 96 [TSW 144])                                                                                                                                                                                                                                          |                                                                          |

| End point values               | Ataluren/Ataluren | Placebo/Ataluren |  |  |
|--------------------------------|-------------------|------------------|--|--|
| Subject group type             | Reporting group   | Reporting group  |  |  |
| Number of subjects analysed    | 95                | 96               |  |  |
| Units: participants            |                   |                  |  |  |
| Hospitalization                | 44                | 49               |  |  |
| Use of Inhaled Antibiotics     | 10                | 18               |  |  |
| Use of Intravenous Antibiotics | 80                | 80               |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Participants With Disruptions in Activities of Daily Living Because of Pulmonary Symptoms

|                 |                                                                                                     |
|-----------------|-----------------------------------------------------------------------------------------------------|
| End point title | Number of Participants With Disruptions in Activities of Daily Living Because of Pulmonary Symptoms |
|-----------------|-----------------------------------------------------------------------------------------------------|

End point description:

During treatment, participants reported when they missed school or work because of pulmonary symptoms. A summary of other non-serious AEs and all SAEs, regardless of causality is located in the Adverse Events module.

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

End point timeframe:

Baseline (Week 1 [TSW 48]) up to EOT (Week 96 [TSW 144])

| End point values                | Ataluren/Ataluren | Placebo/Ataluren |  |  |
|---------------------------------|-------------------|------------------|--|--|
| Subject group type              | Reporting group   | Reporting group  |  |  |
| Number of subjects analysed     | 95                | 96               |  |  |
| Units: participants             |                   |                  |  |  |
| Missed at Least 1 Day of School | 23                | 25               |  |  |
| Missed at Least 1 Day of Work   | 27                | 25               |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Duration of Disruptions in Activities of Daily Living Because of Pulmonary Symptoms

|                 |                                                                                     |
|-----------------|-------------------------------------------------------------------------------------|
| End point title | Duration of Disruptions in Activities of Daily Living Because of Pulmonary Symptoms |
|-----------------|-------------------------------------------------------------------------------------|

End point description:

During treatment, participants reported when they missed school or work because of pulmonary symptoms. If Event Date was before Day 1 (Baseline) Date, Study Day = Event Date – First Dose Date. If Event Date was on or after Day 1 Date, Study Day = Event Date – First Dose Date + 1. The Duration = Return to Stable Date – Onset Date. Participants with a respiratory event that was ongoing when the participant was discontinued from the study were considered as not evaluable. A summary of other non-

serious AEs and all SAEs, regardless of causality is located in the Adverse Events module.

|                                                          |           |
|----------------------------------------------------------|-----------|
| End point type                                           | Secondary |
| End point timeframe:                                     |           |
| Baseline (Week 1 [TSW 48]) up to EOT (Week 96 [TSW 144]) |           |

| End point values                | Ataluren/Ataluren | Placebo/Ataluren  |  |  |
|---------------------------------|-------------------|-------------------|--|--|
| Subject group type              | Reporting group   | Reporting group   |  |  |
| Number of subjects analysed     | 95 <sup>[3]</sup> | 96 <sup>[4]</sup> |  |  |
| Units: days                     |                   |                   |  |  |
| median (full range (min-max))   |                   |                   |  |  |
| Missed at Least 1 Day of School | 25.0 (7 to 187)   | 21.5 (4 to 112)   |  |  |
| Missed at Least 1 Day of Work   | 25.0 (1 to 161)   | 22.0 (1 to 131)   |  |  |

Notes:

[3] - Data were collected but not summarized for this endpoint.

[4] - Data were collected but not summarized for this endpoint.

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline in Body Weight at Weeks 48 and 96

|                                                                                                                                                                                                                                                                                 |                                                        |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                 | Change From Baseline in Body Weight at Weeks 48 and 96 |
| End point description:                                                                                                                                                                                                                                                          |                                                        |
| Participants were weighed, and the weight was recorded at Baseline and then every 8 weeks during the treatment period. Baseline was Week 1. A positive change from Baseline indicates that weight increased. Here, 'n' signifies participants evaluable for the specified week. |                                                        |
| End point type                                                                                                                                                                                                                                                                  | Secondary                                              |
| End point timeframe:                                                                                                                                                                                                                                                            |                                                        |
| Baseline (Week 1 [TSW 48]), Week 48 (TSW 96), EOT (Week 96 [TSW 144])                                                                                                                                                                                                           |                                                        |

| End point values                           | Ataluren/Ataluren  | Placebo/Ataluren   |  |  |
|--------------------------------------------|--------------------|--------------------|--|--|
| Subject group type                         | Reporting group    | Reporting group    |  |  |
| Number of subjects analysed                | 95                 | 96                 |  |  |
| Units: kg                                  |                    |                    |  |  |
| arithmetic mean (standard deviation)       |                    |                    |  |  |
| Baseline (n=95, 96)                        | 53.354 (± 13.5601) | 57.444 (± 11.7890) |  |  |
| Change From Baseline at Week 48 (n=78, 70) | 1.232 (± 2.8322)   | 0.540 (± 2.8287)   |  |  |
| Change From Baseline at Week 96 (n=57, 53) | 2.149 (± 5.0803)   | 0.830 (± 3.6440)   |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change From Baseline in Body Mass Index (BMI) at Weeks 48 and 96

|                 |                                                                  |
|-----------------|------------------------------------------------------------------|
| End point title | Change From Baseline in Body Mass Index (BMI) at Weeks 48 and 96 |
|-----------------|------------------------------------------------------------------|

End point description:

Participants were weighed and measured and the weight and height were recorded at each visit. The BMI was determined by dividing the participant's weight by his or her height. Baseline was Week 1. A positive change from Baseline indicates that BMI increased. Here, 'n' signifies participants evaluable for the specified week.

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

End point timeframe:

Baseline (Week 1 [TSW 48]), Week 48 (TSW 96), EOT (Week 96 [TSW 144])

| End point values                            | Ataluren/Ataluren | Placebo/Ataluren  |  |  |
|---------------------------------------------|-------------------|-------------------|--|--|
| Subject group type                          | Reporting group   | Reporting group   |  |  |
| Number of subjects analysed                 | 95                | 96                |  |  |
| Units: kg/square meter (kg/m <sup>2</sup> ) |                   |                   |  |  |
| arithmetic mean (standard deviation)        |                   |                   |  |  |
| Baseline (n=95, 96)                         | 20.023 (± 3.3136) | 21.044 (± 2.7735) |  |  |
| Change From Baseline at Week 48 (n=78, 70)  | 0.179 (± 0.8323)  | 0.102 (± 0.9179)  |  |  |
| Change From Baseline at Week 96 (n=57, 53)  | 0.144 (± 1.1404)  | 0.105 (± 1.1885)  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Total Lung Computed Tomography (CT) Score at Weeks 48 and 96

|                 |                                                              |
|-----------------|--------------------------------------------------------------|
| End point title | Total Lung Computed Tomography (CT) Score at Weeks 48 and 96 |
|-----------------|--------------------------------------------------------------|

End point description:

Lungs were imaged by using non-contrast, spiral CT. The administration of CT scans was discontinued for this study via a memorandum sent to all Investigators, based on the results of Study 009, which showed that this exploratory endpoint failed to discriminate active treatment from placebo over the 48-week study period. Therefore, this Endpoint was removed from the study as a Secondary Endpoint and the CT scans that were administered for this study were not reviewed or analyzed for this Endpoint. Here, 'Number analyzed' signifies the number of participants analyzed for the specified weeks for this Endpoint.

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

End point timeframe:

Week 48 (TSW 96) and EOT (Week 96 [TSW 144])

| End point values                     | Ataluren/Ataluren | Placebo/Ataluren |  |  |
|--------------------------------------|-------------------|------------------|--|--|
| Subject group type                   | Reporting group   | Reporting group  |  |  |
| Number of subjects analysed          | 0 <sup>[5]</sup>  | 0 <sup>[6]</sup> |  |  |
| Units: units on a scale              |                   |                  |  |  |
| arithmetic mean (standard deviation) |                   |                  |  |  |
| Week 48                              | ()                | ()               |  |  |
| Week 96                              | ()                | ()               |  |  |

Notes:

[5] - No CT data from this study were reviewed or analyzed.

[6] - No CT data from this study were reviewed or analyzed.

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline in the Nasal Transepithelial Potential Difference (TEPD) at Week 48

|                 |                                                                                          |
|-----------------|------------------------------------------------------------------------------------------|
| End point title | Change From Baseline in the Nasal Transepithelial Potential Difference (TEPD) at Week 48 |
|-----------------|------------------------------------------------------------------------------------------|

End point description:

TEPD was to be assessed in each nostril by using standardized equipment, techniques, and solutions. Collection of nasal TEPD tracings was discontinued for this study via a memorandum sent to all Investigators, based on the results of Study 009, which showed that this biomarker failed to discriminate active treatment from placebo over the 48-week study period. Therefore, this Endpoint was removed from the study as a Secondary Endpoint and none of the nasal TEPD tracings were reviewed or analyzed for this Endpoint. Here, 'Number analyzed' signifies the number of participants analyzed for the specified weeks for this Endpoint.

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

End point timeframe:

Baseline (Week 1 [TSW 48]) and Week 48 (TSW 96)

| End point values                     | Ataluren/Ataluren | Placebo/Ataluren |  |  |
|--------------------------------------|-------------------|------------------|--|--|
| Subject group type                   | Reporting group   | Reporting group  |  |  |
| Number of subjects analysed          | 0 <sup>[7]</sup>  | 0 <sup>[8]</sup> |  |  |
| Units: millivolts                    |                   |                  |  |  |
| arithmetic mean (standard deviation) |                   |                  |  |  |
| Baseline                             | ()                | ()               |  |  |
| Change From Baseline at Week 48      | ()                | ()               |  |  |

Notes:

[7] - None of the nasal TEPD tracings were reviewed or analyzed.

[8] - None of the nasal TEPD tracings were reviewed or analyzed.

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline in the Concentration of Sweat Chloride at Week 48

|                 |                                                                        |
|-----------------|------------------------------------------------------------------------|
| End point title | Change From Baseline in the Concentration of Sweat Chloride 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 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 ( $\geq 15$  uL) 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 guidelines of the Cystic Fibrosis Foundation Therapeutics - Therapeutic Development Network. Baseline was the most recent value of sweat chloride prior to treatment in Study 009e. A positive change from Baseline indicates that sweat chloride concentration increased. Here, 'n' signifies participants evaluable for the specified week.

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

**End point timeframe:**

Baseline (Week 1 [TSW 48]), Week 48 (TSW 96)

| End point values                           | Ataluren/Ataluren      | Placebo/Ataluren      |  |  |
|--------------------------------------------|------------------------|-----------------------|--|--|
| Subject group type                         | Reporting group        | Reporting group       |  |  |
| Number of subjects analysed                | 94 <sup>[9]</sup>      | 92 <sup>[10]</sup>    |  |  |
| Units: mmol/L                              |                        |                       |  |  |
| arithmetic mean (standard deviation)       |                        |                       |  |  |
| Baseline (n=94, 92)                        | 100.26 ( $\pm$ 13.602) | 97.88 ( $\pm$ 16.444) |  |  |
| Change From Baseline at Week 48 (n=48, 41) | 5.34 ( $\pm$ 10.062)   | 3.60 ( $\pm$ 14.422)  |  |  |

**Notes:**

[9] - One participant in the ataluren/ataluren group was not evaluable.

[10] - Four participants in the placebo/ataluren group were not evaluable.

**Statistical analyses**

No statistical analyses for this end point

**Post-hoc: Percent-Predicted of FEV1 in the 96-Week Completer Population at Baseline**

|                 |                                                                           |
|-----------------|---------------------------------------------------------------------------|
| End point title | Percent-Predicted of FEV1 in the 96-Week Completer Population at Baseline |
|-----------------|---------------------------------------------------------------------------|

**End point description:**

Spirometry was used to assess pulmonary function by measuring the percent-predicted (determined with the height value obtained at the same study visit) for FEV1 (the amount of air exhaled in 1 second). Spirometry was validated with current guidelines of the ATS and ERS. Baseline was defined as Week 1 or the most recent value of percent-predicted FEV1 prior to the first dose of open-label treatment in Study 009e. Analyses of the Study 009/009e 96-Week Completer Population, which included participants who completed 48 weeks of treatment with ataluren or placebo in Study 009 and  $\geq 48$  weeks of treatment with ataluren in Study 009e, complemented analyses of the Study 009e As-Treated population. 'n' signifies participants evaluable for the specified week.

|                |          |
|----------------|----------|
| End point type | Post-hoc |
|----------------|----------|

**End point timeframe:**

Baseline (Week 1 [TSW 48])

| End point values                     | Ataluren/Ataluren | Placebo/Ataluren |  |  |
|--------------------------------------|-------------------|------------------|--|--|
| Subject group type                   | Reporting group   | Reporting group  |  |  |
| Number of subjects analysed          | 78                | 70               |  |  |
| Units: percentage of predicted FEV1  |                   |                  |  |  |
| arithmetic mean (standard deviation) | 60.89 (± 13.320)  | 59.50 (± 15.622) |  |  |

## Statistical analyses

No statistical analyses for this end point

### Post-hoc: Percentage Change From Baseline in Percent-Predicted of FEV1 in the 96-Week Completer Population Over a Total of 96 Weeks of Treatment

|                 |                                                                                                                                        |
|-----------------|----------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Percentage Change From Baseline in Percent-Predicted of FEV1 in the 96-Week Completer Population Over a Total of 96 Weeks of Treatment |
|-----------------|----------------------------------------------------------------------------------------------------------------------------------------|

End point description:

Spirometry was used to assess pulmonary function by measuring the percent-predicted (determined with the height value obtained at the same study visit) for FEV1 (the amount of air exhaled in 1 second). Spirometry was validated with current guidelines of the ATS and ERS. The percentage of change in percent-predicted of FEV1 was calculated as follows: ((percent-predicted FEV1-Baseline percent-predicted FEV1)/Baseline percent-predicted FEV1)\*100. Baseline was defined as Week 1 or the most recent value of percent-predicted FEV1 prior to the first dose of open-label treatment in Study 009e. A positive change from Baseline indicates that FEV1 improved. Analyses of the Study 009/009e 96-Week Completer Population, which included participants who completed 48 weeks of treatment with ataluren or placebo in Study 009 and ≥48 weeks of treatment with ataluren in Study 009e, complemented analyses of the Study 009e As-Treated population. 'n' signifies participants evaluable for the specified week.

|                      |          |
|----------------------|----------|
| End point type       | Post-hoc |
| End point timeframe: |          |
| Week 48 (TSW 96)     |          |

| End point values                          | Ataluren/Ataluren | Placebo/Ataluren |  |  |
|-------------------------------------------|-------------------|------------------|--|--|
| Subject group type                        | Reporting group   | Reporting group  |  |  |
| Number of subjects analysed               | 78                | 70               |  |  |
| Units: percent change                     |                   |                  |  |  |
| arithmetic mean (standard deviation)      |                   |                  |  |  |
| Change From Baseline at TSW 96 (n=78, 70) | -1.63 (± 13.239)  | -5.13 (± 12.061) |  |  |

## Statistical analyses

No statistical analyses for this end point

### Post-hoc: Percent-Predicted of FEV1 in the 144-Week Completer Population at Baseline

|                 |                                                     |
|-----------------|-----------------------------------------------------|
| End point title | Percent-Predicted of FEV1 in the 144-Week Completer |
|-----------------|-----------------------------------------------------|

## End point description:

Spirometry was used to assess pulmonary function by measuring the percent-predicted (determined with the height value obtained at the same study visit) for FEV1 (the amount of air exhaled in 1 second). Spirometry was validated with current guidelines of the ATS and ERS. Baseline was defined as Week 1 or the most recent value of percent-predicted FEV1 prior to the first dose of open-label treatment in Study 009e. Analyses of the study 009/009e 144-Week Completer Population, which included participants who completed 48 weeks of treatment with ataluren or placebo in Study 009 and ≥96 weeks of treatment with ataluren in Study 009e, complemented analyses of the Study 009e As-Treated population. 'n' signifies participants evaluable for the specified week.

|                |          |
|----------------|----------|
| End point type | Post-hoc |
|----------------|----------|

## End point timeframe:

Baseline (Week 1 [TSW 48])

| End point values                     | Ataluren/Ataluren | Placebo/Ataluren |  |  |
|--------------------------------------|-------------------|------------------|--|--|
| Subject group type                   | Reporting group   | Reporting group  |  |  |
| Number of subjects analysed          | 57                | 54               |  |  |
| Units: percentage of predicted FEV1  |                   |                  |  |  |
| arithmetic mean (standard deviation) | 61.68 (± 13.790)  | 60.28 (± 16.202) |  |  |

## Statistical analyses

No statistical analyses for this end point

**Post-hoc: Percentage Change From Baseline in Percent-Predicted of FEV1 in the 144-week Completer Population Over a Total of 144 Weeks of Treatment**

|                 |                                                                                                                                          |
|-----------------|------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Percentage Change From Baseline in Percent-Predicted of FEV1 in the 144-week Completer Population Over a Total of 144 Weeks of Treatment |
|-----------------|------------------------------------------------------------------------------------------------------------------------------------------|

## End point description:

Spirometry was used to assess pulmonary function by measuring the percent-predicted (determined with the height value obtained at the same study visit) for FEV1 (the amount of air exhaled in 1 second). Spirometry was validated with current guidelines of the ATS and ERS. The percentage of change in percent-predicted of FEV1 was calculated as follows: ((percent-predicted FEV1-Baseline percent-predicted FEV1)/Baseline percent-predicted FEV1)\*100. Baseline was defined as Week 1 or the most recent value of percent-predicted FEV1 prior to the first dose of open-label treatment in Study 009e. A positive change from Baseline indicates that FEV1 improved. Analyses of the study 009/009e 144-Week Completer Population, which included participants who completed 48 weeks of treatment with ataluren or placebo in Study 009 and ≥96 weeks of treatment with ataluren in Study 009e, complemented analyses of the Study 009e As-Treated population. 'n' signifies participants evaluable for the specified week.

|                |          |
|----------------|----------|
| End point type | Post-hoc |
|----------------|----------|

## End point timeframe:

EOT (Week 96 [TSW 144])

| <b>End point values</b>                       | Ataluren/Ataluren   | Placebo/Ataluren    |  |  |
|-----------------------------------------------|---------------------|---------------------|--|--|
| Subject group type                            | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed                   | 57                  | 54                  |  |  |
| Units: percent change                         |                     |                     |  |  |
| arithmetic mean (standard deviation)          |                     |                     |  |  |
| Change From Baseline at TSW 144<br>(n=55, 50) | -3.69 (±<br>16.068) | -5.89 (±<br>14.854) |  |  |

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Baseline (Week 1 [TSW 48]) up to 4 Weeks Post-Treatment (Week 100 [TSW 148]) or PD (whichever occurred first)

Adverse event reporting additional description:

The Study 009e As-Treated Population: participants who received at least 1 dose of study drug.

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

### Dictionary used

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

|                    |    |
|--------------------|----|
| Dictionary version | 16 |
|--------------------|----|

### Reporting groups

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

Reporting group description:

Participants who received double-blind ataluren during Study 009 continued to receive open-label ataluren TID: 10 mg/kg of body weight with breakfast, 10 mg/kg with lunch, and 20 mg/kg with dinner (total dose 40 mg/kg/day), for up to 96 weeks. Participants were followed for 4 weeks after treatment.

|                       |                  |
|-----------------------|------------------|
| Reporting group title | Placebo/Ataluren |
|-----------------------|------------------|

Reporting group description:

Participants who received double-blind placebo during Study 009 received open-label ataluren TID: 10 mg/kg of body weight with breakfast, 10 mg/kg with lunch, and 20 mg/kg with dinner (total dose 40 mg/kg/day), for up to 96 weeks. Participants were followed for 4 weeks after treatment.

|                       |                    |
|-----------------------|--------------------|
| Reporting group title | Overall Population |
|-----------------------|--------------------|

Reporting group description:

Participants who received double-blind ataluren or placebo during Study 009 received open-label ataluren TID: 10 mg/kg of body weight with breakfast, 10 mg/kg with lunch, and 20 mg/kg with dinner (total dose 40 mg/kg/day), for up to 96 weeks. Participants were followed for 4 weeks after treatment.

| Serious adverse events                                              | Ataluren/Ataluren | Placebo/Ataluren | Overall Population |
|---------------------------------------------------------------------|-------------------|------------------|--------------------|
| Total subjects affected by serious adverse events                   |                   |                  |                    |
| subjects affected / exposed                                         | 48 / 95 (50.53%)  | 57 / 96 (59.38%) | 105 / 191 (54.97%) |
| number of deaths (all causes)                                       | 0                 | 1                | 1                  |
| number of deaths resulting from adverse events                      |                   |                  |                    |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                   |                  |                    |
| Bile duct cancer                                                    |                   |                  |                    |
| subjects affected / exposed                                         | 0 / 95 (0.00%)    | 1 / 96 (1.04%)   | 1 / 191 (0.52%)    |
| occurrences causally related to treatment / all                     | 0 / 0             | 0 / 1            | 0 / 1              |
| deaths causally related to treatment / all                          | 0 / 0             | 0 / 1            | 0 / 1              |
| Vascular disorders                                                  |                   |                  |                    |
| Axillary vein thrombosis                                            |                   |                  |                    |

|                                                      |                  |                  |                   |
|------------------------------------------------------|------------------|------------------|-------------------|
| subjects affected / exposed                          | 0 / 95 (0.00%)   | 1 / 96 (1.04%)   | 1 / 191 (0.52%)   |
| occurrences causally related to treatment / all      | 0 / 0            | 0 / 1            | 0 / 1             |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0            | 0 / 0             |
| General disorders and administration site conditions |                  |                  |                   |
| General physical health deterioration                |                  |                  |                   |
| subjects affected / exposed                          | 0 / 95 (0.00%)   | 1 / 96 (1.04%)   | 1 / 191 (0.52%)   |
| occurrences causally related to treatment / all      | 0 / 0            | 0 / 1            | 0 / 1             |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0            | 0 / 0             |
| Malaise                                              |                  |                  |                   |
| subjects affected / exposed                          | 1 / 95 (1.05%)   | 0 / 96 (0.00%)   | 1 / 191 (0.52%)   |
| occurrences causally related to treatment / all      | 0 / 1            | 0 / 0            | 0 / 1             |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0            | 0 / 0             |
| Respiratory, thoracic and mediastinal disorders      |                  |                  |                   |
| Cystic fibrosis lung                                 |                  |                  |                   |
| subjects affected / exposed                          | 41 / 95 (43.16%) | 45 / 96 (46.88%) | 86 / 191 (45.03%) |
| occurrences causally related to treatment / all      | 0 / 84           | 0 / 90           | 0 / 174           |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0            | 0 / 0             |
| Haemoptysis                                          |                  |                  |                   |
| subjects affected / exposed                          | 2 / 95 (2.11%)   | 1 / 96 (1.04%)   | 3 / 191 (1.57%)   |
| occurrences causally related to treatment / all      | 0 / 6            | 0 / 1            | 0 / 7             |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0            | 0 / 0             |
| Nasal polyps                                         |                  |                  |                   |
| subjects affected / exposed                          | 1 / 95 (1.05%)   | 1 / 96 (1.04%)   | 2 / 191 (1.05%)   |
| occurrences causally related to treatment / all      | 0 / 1            | 0 / 1            | 0 / 2             |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0            | 0 / 0             |
| Pneumothorax                                         |                  |                  |                   |
| subjects affected / exposed                          | 0 / 95 (0.00%)   | 1 / 96 (1.04%)   | 1 / 191 (0.52%)   |
| occurrences causally related to treatment / all      | 0 / 0            | 0 / 2            | 0 / 2             |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0            | 0 / 0             |
| Injury, poisoning and procedural complications       |                  |                  |                   |
| Overdose                                             |                  |                  |                   |

|                                                 |                |                |                 |
|-------------------------------------------------|----------------|----------------|-----------------|
| subjects affected / exposed                     | 1 / 95 (1.05%) | 0 / 96 (0.00%) | 1 / 191 (0.52%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Congenital, familial and genetic disorders      |                |                |                 |
| Cystic fibrosis related diabetes                |                |                |                 |
| subjects affected / exposed                     | 1 / 95 (1.05%) | 0 / 96 (0.00%) | 1 / 191 (0.52%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Nervous system disorders                        |                |                |                 |
| Cauda equina syndrome                           |                |                |                 |
| subjects affected / exposed                     | 0 / 95 (0.00%) | 1 / 96 (1.04%) | 1 / 191 (0.52%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Dysaesthesia                                    |                |                |                 |
| subjects affected / exposed                     | 0 / 95 (0.00%) | 1 / 96 (1.04%) | 1 / 191 (0.52%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Serotonin syndrome                              |                |                |                 |
| subjects affected / exposed                     | 0 / 95 (0.00%) | 1 / 96 (1.04%) | 1 / 191 (0.52%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Blood and lymphatic system disorders            |                |                |                 |
| Neutropenia                                     |                |                |                 |
| subjects affected / exposed                     | 0 / 95 (0.00%) | 1 / 96 (1.04%) | 1 / 191 (0.52%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Gastrointestinal disorders                      |                |                |                 |
| Distal intestinal obstruction syndrome          |                |                |                 |
| subjects affected / exposed                     | 0 / 95 (0.00%) | 2 / 96 (2.08%) | 2 / 191 (1.05%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 2          | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Abdominal pain                                  |                |                |                 |

|                                                 |                |                |                 |
|-------------------------------------------------|----------------|----------------|-----------------|
| subjects affected / exposed                     | 1 / 95 (1.05%) | 0 / 96 (0.00%) | 1 / 191 (0.52%) |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0          | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Annual fistula                                  |                |                |                 |
| subjects affected / exposed                     | 0 / 95 (0.00%) | 1 / 96 (1.04%) | 1 / 191 (0.52%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Crohn's disease                                 |                |                |                 |
| subjects affected / exposed                     | 0 / 95 (0.00%) | 1 / 96 (1.04%) | 1 / 191 (0.52%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Erosive oesophagitis                            |                |                |                 |
| subjects affected / exposed                     | 1 / 95 (1.05%) | 0 / 96 (0.00%) | 1 / 191 (0.52%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Gastric ulcer                                   |                |                |                 |
| subjects affected / exposed                     | 0 / 95 (0.00%) | 1 / 96 (1.04%) | 1 / 191 (0.52%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Haematemesis                                    |                |                |                 |
| subjects affected / exposed                     | 1 / 95 (1.05%) | 0 / 96 (0.00%) | 1 / 191 (0.52%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Ileus                                           |                |                |                 |
| subjects affected / exposed                     | 0 / 95 (0.00%) | 1 / 96 (1.04%) | 1 / 191 (0.52%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Intussusception                                 |                |                |                 |
| subjects affected / exposed                     | 0 / 95 (0.00%) | 1 / 96 (1.04%) | 1 / 191 (0.52%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Pancreatitis                                    |                |                |                 |

|                                                 |                |                |                 |
|-------------------------------------------------|----------------|----------------|-----------------|
| subjects affected / exposed                     | 1 / 95 (1.05%) | 0 / 96 (0.00%) | 1 / 191 (0.52%) |
| occurrences causally related to treatment / all | 1 / 3          | 0 / 0          | 1 / 3           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Pancreatitis acute                              |                |                |                 |
| subjects affected / exposed                     | 0 / 95 (0.00%) | 1 / 96 (1.04%) | 1 / 191 (0.52%) |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Hepatobiliary disorders                         |                |                |                 |
| Jaundice                                        |                |                |                 |
| subjects affected / exposed                     | 0 / 95 (0.00%) | 1 / 96 (1.04%) | 1 / 191 (0.52%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Renal and urinary disorders                     |                |                |                 |
| Calculus ureteric                               |                |                |                 |
| subjects affected / exposed                     | 1 / 95 (1.05%) | 1 / 96 (1.04%) | 2 / 191 (1.05%) |
| occurrences causally related to treatment / all | 1 / 1          | 1 / 1          | 2 / 2           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Nephrolithiasis                                 |                |                |                 |
| subjects affected / exposed                     | 0 / 95 (0.00%) | 2 / 96 (2.08%) | 2 / 191 (1.05%) |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 2          | 1 / 2           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Haematuria                                      |                |                |                 |
| subjects affected / exposed                     | 1 / 95 (1.05%) | 0 / 96 (0.00%) | 1 / 191 (0.52%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Hydronephrosis                                  |                |                |                 |
| subjects affected / exposed                     | 0 / 95 (0.00%) | 1 / 96 (1.04%) | 1 / 191 (0.52%) |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Hypercreatininaemia                             |                |                |                 |
| subjects affected / exposed                     | 0 / 95 (0.00%) | 1 / 96 (1.04%) | 1 / 191 (0.52%) |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Nephritis interstitial                          |                |                |                 |

|                                                 |                |                |                 |
|-------------------------------------------------|----------------|----------------|-----------------|
| subjects affected / exposed                     | 0 / 95 (0.00%) | 1 / 96 (1.04%) | 1 / 191 (0.52%) |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Renal failure                                   |                |                |                 |
| subjects affected / exposed                     | 1 / 95 (1.05%) | 0 / 96 (0.00%) | 1 / 191 (0.52%) |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0          | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Renal failure acute                             |                |                |                 |
| subjects affected / exposed                     | 0 / 95 (0.00%) | 1 / 96 (1.04%) | 1 / 191 (0.52%) |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Dysuria                                         |                |                |                 |
| subjects affected / exposed                     | 1 / 95 (1.05%) | 0 / 96 (0.00%) | 1 / 191 (0.52%) |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0          | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Musculoskeletal and connective tissue disorders |                |                |                 |
| Back pain                                       |                |                |                 |
| subjects affected / exposed                     | 1 / 95 (1.05%) | 0 / 96 (0.00%) | 1 / 191 (0.52%) |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0          | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Musculoskeletal pain                            |                |                |                 |
| subjects affected / exposed                     | 1 / 95 (1.05%) | 0 / 96 (0.00%) | 1 / 191 (0.52%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Infections and infestations                     |                |                |                 |
| Acute sinusitis                                 |                |                |                 |
| subjects affected / exposed                     | 1 / 95 (1.05%) | 1 / 96 (1.04%) | 2 / 191 (1.05%) |
| occurrences causally related to treatment / all | 0 / 2          | 0 / 1          | 0 / 3           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Mycobacterium abscessus infection               |                |                |                 |
| subjects affected / exposed                     | 1 / 95 (1.05%) | 1 / 96 (1.04%) | 2 / 191 (1.05%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 1          | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |

|                                                 |                |                |                 |
|-------------------------------------------------|----------------|----------------|-----------------|
| Anal abscess                                    |                |                |                 |
| subjects affected / exposed                     | 0 / 95 (0.00%) | 1 / 96 (1.04%) | 1 / 191 (0.52%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Bronchopulmonary aspergillosis allergic         |                |                |                 |
| subjects affected / exposed                     | 0 / 95 (0.00%) | 1 / 96 (1.04%) | 1 / 191 (0.52%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Burkholderia cepacia infection                  |                |                |                 |
| subjects affected / exposed                     | 1 / 95 (1.05%) | 0 / 96 (0.00%) | 1 / 191 (0.52%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Catheter sepsis                                 |                |                |                 |
| subjects affected / exposed                     | 1 / 95 (1.05%) | 0 / 96 (0.00%) | 1 / 191 (0.52%) |
| occurrences causally related to treatment / all | 0 / 2          | 0 / 0          | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Cellulitis                                      |                |                |                 |
| subjects affected / exposed                     | 1 / 95 (1.05%) | 0 / 96 (0.00%) | 1 / 191 (0.52%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Gastroenteritis                                 |                |                |                 |
| subjects affected / exposed                     | 0 / 95 (0.00%) | 1 / 96 (1.04%) | 1 / 191 (0.52%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Influenza                                       |                |                |                 |
| subjects affected / exposed                     | 1 / 95 (1.05%) | 0 / 96 (0.00%) | 1 / 191 (0.52%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Lobar pneumonia                                 |                |                |                 |
| subjects affected / exposed                     | 1 / 95 (1.05%) | 0 / 96 (0.00%) | 1 / 191 (0.52%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Lung infection pseudomonal                      |                |                |                 |

|                                                 |                |                |                 |
|-------------------------------------------------|----------------|----------------|-----------------|
| subjects affected / exposed                     | 0 / 95 (0.00%) | 1 / 96 (1.04%) | 1 / 191 (0.52%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Parainfluenzae virus infection                  |                |                |                 |
| subjects affected / exposed                     | 0 / 95 (0.00%) | 1 / 96 (1.04%) | 1 / 191 (0.52%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Pneumonia                                       |                |                |                 |
| subjects affected / exposed                     | 1 / 95 (1.05%) | 0 / 96 (0.00%) | 1 / 191 (0.52%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Respiratory tract infection bacterial           |                |                |                 |
| subjects affected / exposed                     | 1 / 95 (1.05%) | 0 / 96 (0.00%) | 1 / 191 (0.52%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Sepsis                                          |                |                |                 |
| subjects affected / exposed                     | 0 / 95 (0.00%) | 1 / 96 (1.04%) | 1 / 191 (0.52%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Sinusitis                                       |                |                |                 |
| subjects affected / exposed                     | 1 / 95 (1.05%) | 0 / 96 (0.00%) | 1 / 191 (0.52%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Viral infection                                 |                |                |                 |
| subjects affected / exposed                     | 0 / 95 (0.00%) | 1 / 96 (1.04%) | 1 / 191 (0.52%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Viral pharyngitis                               |                |                |                 |
| subjects affected / exposed                     | 1 / 95 (1.05%) | 0 / 96 (0.00%) | 1 / 191 (0.52%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Viral upper respiratory tract infection         |                |                |                 |

|                                                 |                |                |                 |
|-------------------------------------------------|----------------|----------------|-----------------|
| subjects affected / exposed                     | 1 / 95 (1.05%) | 0 / 96 (0.00%) | 1 / 191 (0.52%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Metabolism and nutrition disorders              |                |                |                 |
| Hyperglycaemia                                  |                |                |                 |
| subjects affected / exposed                     | 1 / 95 (1.05%) | 0 / 96 (0.00%) | 1 / 191 (0.52%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Hyponatraemia                                   |                |                |                 |
| subjects affected / exposed                     | 1 / 95 (1.05%) | 0 / 96 (0.00%) | 1 / 191 (0.52%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |

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

| <b>Non-serious adverse events</b>                     | Ataluren/Ataluren | Placebo/Ataluren | Overall Population |
|-------------------------------------------------------|-------------------|------------------|--------------------|
| Total subjects affected by non-serious adverse events |                   |                  |                    |
| subjects affected / exposed                           | 95 / 95 (100.00%) | 94 / 96 (97.92%) | 189 / 191 (98.95%) |
| Investigations                                        |                   |                  |                    |
| Pulmonary function test decreased                     |                   |                  |                    |
| subjects affected / exposed                           | 9 / 95 (9.47%)    | 3 / 96 (3.13%)   | 12 / 191 (6.28%)   |
| occurrences (all)                                     | 10                | 3                | 13                 |
| Nervous system disorders                              |                   |                  |                    |
| Headache                                              |                   |                  |                    |
| subjects affected / exposed                           | 12 / 95 (12.63%)  | 14 / 96 (14.58%) | 26 / 191 (13.61%)  |
| occurrences (all)                                     | 27                | 34               | 61                 |
| General disorders and administration site conditions  |                   |                  |                    |
| Pyrexia                                               |                   |                  |                    |
| subjects affected / exposed                           | 19 / 95 (20.00%)  | 19 / 96 (19.79%) | 38 / 191 (19.90%)  |
| occurrences (all)                                     | 30                | 54               | 84                 |
| Fatigue                                               |                   |                  |                    |
| subjects affected / exposed                           | 4 / 95 (4.21%)    | 13 / 96 (13.54%) | 17 / 191 (8.90%)   |
| occurrences (all)                                     | 5                 | 19               | 24                 |
| Immune system disorders                               |                   |                  |                    |

|                                                                           |                         |                         |                           |
|---------------------------------------------------------------------------|-------------------------|-------------------------|---------------------------|
| Drug hypersensitivity<br>subjects affected / exposed<br>occurrences (all) | 2 / 95 (2.11%)<br>2     | 7 / 96 (7.29%)<br>7     | 9 / 191 (4.71%)<br>9      |
| Gastrointestinal disorders                                                |                         |                         |                           |
| Diarrhoea<br>subjects affected / exposed<br>occurrences (all)             | 13 / 95 (13.68%)<br>19  | 16 / 96 (16.67%)<br>31  | 29 / 191 (15.18%)<br>50   |
| Abdominal pain<br>subjects affected / exposed<br>occurrences (all)        | 14 / 95 (14.74%)<br>35  | 13 / 96 (13.54%)<br>31  | 27 / 191 (14.14%)<br>66   |
| Constipation<br>subjects affected / exposed<br>occurrences (all)          | 12 / 95 (12.63%)<br>16  | 15 / 96 (15.63%)<br>22  | 27 / 191 (14.14%)<br>38   |
| Vomiting<br>subjects affected / exposed<br>occurrences (all)              | 9 / 95 (9.47%)<br>11    | 13 / 96 (13.54%)<br>15  | 22 / 191 (11.52%)<br>26   |
| Abdominal pain upper<br>subjects affected / exposed<br>occurrences (all)  | 8 / 95 (8.42%)<br>11    | 13 / 96 (13.54%)<br>18  | 21 / 191 (10.99%)<br>29   |
| Nausea<br>subjects affected / exposed<br>occurrences (all)                | 5 / 95 (5.26%)<br>8     | 16 / 96 (16.67%)<br>24  | 21 / 191 (10.99%)<br>32   |
| Abdominal distension<br>subjects affected / exposed<br>occurrences (all)  | 5 / 95 (5.26%)<br>5     | 4 / 96 (4.17%)<br>4     | 9 / 191 (4.71%)<br>9      |
| Respiratory, thoracic and mediastinal disorders                           |                         |                         |                           |
| Cystic fibrosis lung<br>subjects affected / exposed<br>occurrences (all)  | 66 / 95 (69.47%)<br>186 | 69 / 96 (71.88%)<br>194 | 135 / 191 (70.68%)<br>380 |
| Cough<br>subjects affected / exposed<br>occurrences (all)                 | 29 / 95 (30.53%)<br>45  | 28 / 96 (29.17%)<br>68  | 57 / 191 (29.84%)<br>113  |
| Haemoptysis<br>subjects affected / exposed<br>occurrences (all)           | 13 / 95 (13.68%)<br>19  | 18 / 96 (18.75%)<br>29  | 31 / 191 (16.23%)<br>48   |
| Productive cough                                                          |                         |                         |                           |

|                                        |                  |                  |                  |
|----------------------------------------|------------------|------------------|------------------|
| subjects affected / exposed            | 8 / 95 (8.42%)   | 11 / 96 (11.46%) | 19 / 191 (9.95%) |
| occurrences (all)                      | 10               | 16               | 26               |
| Rales                                  |                  |                  |                  |
| subjects affected / exposed            | 10 / 95 (10.53%) | 9 / 96 (9.38%)   | 19 / 191 (9.95%) |
| occurrences (all)                      | 13               | 9                | 22               |
| Oropharyngeal pain                     |                  |                  |                  |
| subjects affected / exposed            | 5 / 95 (5.26%)   | 11 / 96 (11.46%) | 16 / 191 (8.38%) |
| occurrences (all)                      | 5                | 15               | 20               |
| Nasal congestion                       |                  |                  |                  |
| subjects affected / exposed            | 4 / 95 (4.21%)   | 6 / 96 (6.25%)   | 10 / 191 (5.24%) |
| occurrences (all)                      | 4                | 6                | 10               |
| Nasal polyps                           |                  |                  |                  |
| subjects affected / exposed            | 5 / 95 (5.26%)   | 1 / 96 (1.04%)   | 6 / 191 (3.14%)  |
| occurrences (all)                      | 5                | 1                | 6                |
| Respiratory tract congestion           |                  |                  |                  |
| subjects affected / exposed            | 0 / 95 (0.00%)   | 6 / 96 (6.25%)   | 6 / 191 (3.14%)  |
| occurrences (all)                      | 0                | 7                | 7                |
| Rhinitis allergic                      |                  |                  |                  |
| subjects affected / exposed            | 0 / 95 (0.00%)   | 5 / 96 (5.21%)   | 5 / 191 (2.62%)  |
| occurrences (all)                      | 0                | 7                | 7                |
| Rhinorrhoea                            |                  |                  |                  |
| subjects affected / exposed            | 0 / 95 (0.00%)   | 5 / 96 (5.21%)   | 5 / 191 (2.62%)  |
| occurrences (all)                      | 0                | 5                | 5                |
| Wheezing                               |                  |                  |                  |
| subjects affected / exposed            | 0 / 95 (0.00%)   | 5 / 96 (5.21%)   | 5 / 191 (2.62%)  |
| occurrences (all)                      | 0                | 5                | 5                |
| Skin and subcutaneous tissue disorders |                  |                  |                  |
| Rash                                   |                  |                  |                  |
| subjects affected / exposed            | 3 / 95 (3.16%)   | 8 / 96 (8.33%)   | 11 / 191 (5.76%) |
| occurrences (all)                      | 3                | 8                | 11               |
| Pruritus                               |                  |                  |                  |
| subjects affected / exposed            | 3 / 95 (3.16%)   | 7 / 96 (7.29%)   | 10 / 191 (5.24%) |
| occurrences (all)                      | 3                | 8                | 11               |
| Psychiatric disorders                  |                  |                  |                  |
| Insomnia                               |                  |                  |                  |

|                                                                                                                            |                        |                        |                          |
|----------------------------------------------------------------------------------------------------------------------------|------------------------|------------------------|--------------------------|
| subjects affected / exposed<br>occurrences (all)                                                                           | 1 / 95 (1.05%)<br>1    | 6 / 96 (6.25%)<br>7    | 7 / 191 (3.66%)<br>8     |
| Anxiety<br>subjects affected / exposed<br>occurrences (all)                                                                | 1 / 95 (1.05%)<br>1    | 5 / 96 (5.21%)<br>6    | 6 / 191 (3.14%)<br>7     |
| Renal and urinary disorders<br>Hypercreatininaemia<br>subjects affected / exposed<br>occurrences (all)                     | 7 / 95 (7.37%)<br>9    | 9 / 96 (9.38%)<br>14   | 16 / 191 (8.38%)<br>23   |
| Dysuria<br>subjects affected / exposed<br>occurrences (all)                                                                | 4 / 95 (4.21%)<br>4    | 9 / 96 (9.38%)<br>10   | 13 / 191 (6.81%)<br>14   |
| Musculoskeletal and connective tissue disorders<br>Back pain<br>subjects affected / exposed<br>occurrences (all)           | 5 / 95 (5.26%)<br>6    | 10 / 96 (10.42%)<br>17 | 15 / 191 (7.85%)<br>23   |
| Arthralgia<br>subjects affected / exposed<br>occurrences (all)                                                             | 6 / 95 (6.32%)<br>13   | 8 / 96 (8.33%)<br>10   | 14 / 191 (7.33%)<br>23   |
| Infections and infestations<br>Viral upper respiratory tract infection<br>subjects affected / exposed<br>occurrences (all) | 26 / 95 (27.37%)<br>39 | 32 / 96 (33.33%)<br>66 | 58 / 191 (30.37%)<br>105 |
| Rhinitis<br>subjects affected / exposed<br>occurrences (all)                                                               | 13 / 95 (13.68%)<br>16 | 15 / 96 (15.63%)<br>19 | 28 / 191 (14.66%)<br>35  |
| Nasopharyngitis<br>subjects affected / exposed<br>occurrences (all)                                                        | 13 / 95 (13.68%)<br>21 | 14 / 96 (14.58%)<br>21 | 27 / 191 (14.14%)<br>42  |
| Sinusitis<br>subjects affected / exposed<br>occurrences (all)                                                              | 11 / 95 (11.58%)<br>18 | 13 / 96 (13.54%)<br>20 | 24 / 191 (12.57%)<br>38  |
| Respiratory tract infection bacterial<br>subjects affected / exposed<br>occurrences (all)                                  | 9 / 95 (9.47%)<br>24   | 10 / 96 (10.42%)<br>18 | 19 / 191 (9.95%)<br>42   |
| Lung infection pseudomonal                                                                                                 |                        |                        |                          |

|                                            |                  |                  |                  |
|--------------------------------------------|------------------|------------------|------------------|
| subjects affected / exposed                | 11 / 95 (11.58%) | 7 / 96 (7.29%)   | 18 / 191 (9.42%) |
| occurrences (all)                          | 14               | 9                | 23               |
| Pharyngitis                                |                  |                  |                  |
| subjects affected / exposed                | 6 / 95 (6.32%)   | 10 / 96 (10.42%) | 16 / 191 (8.38%) |
| occurrences (all)                          | 8                | 10               | 18               |
| Bronchopulmonary aspergillosis<br>allergic |                  |                  |                  |
| subjects affected / exposed                | 6 / 95 (6.32%)   | 6 / 96 (6.25%)   | 12 / 191 (6.28%) |
| occurrences (all)                          | 6                | 8                | 14               |
| Bronchitis                                 |                  |                  |                  |
| subjects affected / exposed                | 6 / 95 (6.32%)   | 5 / 96 (5.21%)   | 11 / 191 (5.76%) |
| occurrences (all)                          | 7                | 6                | 13               |
| Bronchopulmonary aspergillosis             |                  |                  |                  |
| subjects affected / exposed                | 6 / 95 (6.32%)   | 5 / 96 (5.21%)   | 11 / 191 (5.76%) |
| occurrences (all)                          | 11               | 7                | 18               |
| Respiratory tract infection fungal         |                  |                  |                  |
| subjects affected / exposed                | 6 / 95 (6.32%)   | 3 / 96 (3.13%)   | 9 / 191 (4.71%)  |
| occurrences (all)                          | 6                | 4                | 10               |
| Upper respiratory tract infection          |                  |                  |                  |
| subjects affected / exposed                | 3 / 95 (3.16%)   | 6 / 96 (6.25%)   | 9 / 191 (4.71%)  |
| occurrences (all)                          | 7                | 9                | 16               |
| Oral fungal infection                      |                  |                  |                  |
| subjects affected / exposed                | 2 / 95 (2.11%)   | 5 / 96 (5.21%)   | 7 / 191 (3.66%)  |
| occurrences (all)                          | 2                | 5                | 7                |
| Metabolism and nutrition disorders         |                  |                  |                  |
| Abnormal loss of weight                    |                  |                  |                  |
| subjects affected / exposed                | 2 / 95 (2.11%)   | 9 / 96 (9.38%)   | 11 / 191 (5.76%) |
| occurrences (all)                          | 2                | 9                | 11               |
| Hypokalaemia                               |                  |                  |                  |
| subjects affected / exposed                | 0 / 95 (0.00%)   | 5 / 96 (5.21%)   | 5 / 191 (2.62%)  |
| occurrences (all)                          | 0                | 5                | 5                |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 07 February 2011 | This amendment introduced the following changes: <ul style="list-style-type: none"><li>* Increased the length of the study from 48 weeks to 96 weeks and added additional clinic visits and assessments as a result of the longer study duration.</li><li>* Corrected the definition for a <math>\geq</math>Grade 2 elevation in serum creatinine to correctly reflect the Common Terminology Criteria for Adverse Events definition of a Grade 2 serum creatinine elevation (from <math>\geq 1.5 \times \text{ULN}</math> for age to <math>&gt; 1.5 \times \text{ULN}</math> for age).</li><li>* Revised the text to allow more flexibility in the transition from Study 009 to Study 009e.</li><li>* Provided more detail regarding the collection of pharmacokinetic samples.</li></ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| 06 March 2013    | This amendment introduced the following changes: <ul style="list-style-type: none"><li>* Removed TEPD, sweat chloride, and CT scans as secondary study endpoints.</li><li>* Added a summary of TEPD, sweat chloride, and CT scan results from Study 009 to provide the rationale for removal of these parameters as secondary study endpoints.</li><li>* Revised information on renal abnormalities to reflect the final data from Study 009.</li><li>* Clarified that study drug must be interrupted if intravenous aminoglycosides or other nephrotoxic antibiotics (for example, vancomycin) were administered and clarified that appropriate laboratory procedures for monitoring therapy for CF pulmonary exacerbations or other CF complications pertained to the administration of non-nephrotoxic systemic antibiotics.</li><li>* Clarified the assessments that should be performed for participants who prematurely discontinued from the study (that is, before Week 96) and whose last dose of ataluren was taken <math>&gt;4</math> weeks before discontinuation.</li><li>* Changed the name of the vendor name for safety reporting from Kendle International to INC Research.</li><li>* Clarified that nephrolithiasis should be reported as an AE of special interest and that laboratory abnormalities as a result of analysis by the central laboratory did not need to be reported to the INC Research Safety and Pharmacovigilance Unit.</li><li>* Added an acceptable window (<math>\pm 30</math> days) for the collection of long-term safety data.</li><li>* Revised the total amount of blood that would be drawn over the 96-week study from 181.5 mL to 202.5 mL to correct an administrative error.</li></ul> |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported