



## Clinical trial results:

### A Phase 3 Efficacy and Safety Study of Ataluren in Patients With Nonsense Mutation Distrophinopathy

#### Summary

|                          |                            |
|--------------------------|----------------------------|
| EudraCT number           | 2012-004527-20             |
| Trial protocol           | BE CZ SE GB DE IT ES PL FR |
| Global end of trial date | 20 August 2015             |

#### Results information

|                                |                |
|--------------------------------|----------------|
| Result version number          | v1 (current)   |
| This version publication date  | 02 August 2020 |
| First version publication date | 02 August 2020 |

#### Trial information

##### Trial identification

|                       |                   |
|-----------------------|-------------------|
| Sponsor protocol code | PTC124-GD-020-DMD |
|-----------------------|-------------------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT01826487 |
| 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-PIP01-07 |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? |                     |
| 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                       | 23 September 2015 |
| Is this the analysis of the primary completion data? | No                |
| Global end of trial reached?                         | Yes               |
| Global end of trial date                             | 20 August 2015    |
| Was the trial ended prematurely?                     | No                |

Notes:

## General information about the trial

Main objective of the trial:

The primary objective of the study was to determine the ability of ataluren to slow disease progression as assessed by ambulatory decline (decrease in 6-minute walk distance [6MWD]).

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

|   |               |
|---|---------------|
| Actual start date of recruitment                          | 26 March 2013 |
| Long term follow-up planned                               | Yes           |
| Long term follow-up rationale                             | Safety        |
| Long term follow-up duration                              | 35 Months     |
| Independent data monitoring committee (IDMC) involvement? | Yes           |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                       |
|--------------------------------------|-----------------------|
| Country: Number of subjects enrolled | United States: 68     |
| Country: Number of subjects enrolled | Spain: 22             |
| Country: Number of subjects enrolled | France: 17            |
| Country: Number of subjects enrolled | Turkey: 16            |
| Country: Number of subjects enrolled | Chile: 14             |
| Country: Number of subjects enrolled | Germany: 13           |
| Country: Number of subjects enrolled | United Kingdom: 13    |
| Country: Number of subjects enrolled | Italy: 11             |
| Country: Number of subjects enrolled | Australia: 10         |
| Country: Number of subjects enrolled | Poland: 8             |
| Country: Number of subjects enrolled | Canada: 7             |
| Country: Number of subjects enrolled | Sweden: 7             |
| Country: Number of subjects enrolled | Belgium: 6            |
| Country: Number of subjects enrolled | Brazil: 5             |
| Country: Number of subjects enrolled | Korea, Republic of: 4 |
| Country: Number of subjects enrolled | Switzerland: 3        |
| Country: Number of subjects enrolled | Czech Republic: 3     |
| Country: Number of subjects enrolled | Israel: 3             |

|                                    |     |
|------------------------------------|-----|
| Worldwide total number of subjects | 230 |
| EEA total number of subjects       | 100 |

Notes:

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**Subjects enrolled per age group**

|   |     |
|---|-----|
| In utero                                  | 0   |
| Preterm newborn - gestational age < 37 wk | 0   |
| Newborns (0-27 days)                      | 0   |
| Infants and toddlers (28 days-23 months)  | 0   |
| Children (2-11 years)                     | 209 |
| Adolescents (12-17 years)                 | 21  |
| Adults (18-64 years)                      | 0   |
| From 65 to 84 years                       | 0   |
| 85 years and over                         | 0   |

## Subject disposition

### Recruitment

Recruitment details:

A total of 291 participants were screened for eligibility, of which 61 participants did not meet entry criteria.

### Pre-assignment

Screening details:

A total of 230 eligible participants were randomized in 1:1 ratio to receive either placebo or ataluren. 2 participants, 1 in each treatment arm, were excluded from intent-to-treat (ITT) population; as they did not have at least 1 valid post-baseline 6MWD value, a requirement for inclusion in ITT population.

### Period 1

|                              |  |
|------------------------------|--|
| Period 1 title               | Overall Study (overall period)         |
| Is this the baseline period? | Yes                                    |
| Allocation method            | Randomised - controlled                |
| Blinding used                | Double blind                           |
| Roles blinded                | Subject, Investigator, Carer, Assessor |

### Arms

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

Arm description:

Participants received placebo matched to ataluren orally 3 times a day (TID) at morning, midday, and evening for 48 weeks.

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

Dosage and administration details:

Placebo matched to ataluren will be administered as per the schedule specified in the arm.

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

Arm description:

Participants received ataluren suspension orally TID, 10 milligrams/kilogram (mg/kg) at morning, 10 mg/kg at midday, and 20 mg/kg at evening (total daily dose 40 mg/kg) for 48 weeks.

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

Dosage and administration details:

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

| <b>Number of subjects in period 1</b> | Placebo | Ataluren |
|---------------------------------------|---------|----------|
| Started                               | 115     | 115      |
| As-treated Population                 | 115     | 115      |
| ITT Population                        | 114     | 114      |
| Completed                             | 111     | 110      |
| Not completed                         | 4       | 5        |
| Consent withdrawn by subject          | 1       | 3        |
| Adverse event, non-fatal              | 1       | 1        |
| Lost to follow-up                     | 1       | -        |
| Protocol deviation                    | 1       | 1        |

## Baseline characteristics

### Reporting groups

|  |          |
|--|----------|
| Reporting group title  | Placebo  |
| Reporting group description:   |          |
| Participants received placebo matched to ataluren orally 3 times a day (TID) at morning, midday, and evening for 48 weeks.   |          |
| Reporting group title  | Ataluren |
| Reporting group description:   |          |
| Participants received ataluren suspension orally TID, 10 milligrams/kilogram (mg/kg) at morning, 10 mg/kg at midday, and 20 mg/kg at evening (total daily dose 40 mg/kg) for 48 weeks. |          |

| Reporting group values   | Placebo  | Ataluren | Total |
|--|----------|----------|-------|
| Number of subjects   | 115      | 115      | 230   |
| Age categorical  |          |          |       |
| Units: Subjects  |          |          |       |
| Age Continuous   |          |          |       |
| Units: years   |          |          |       |
| arithmetic mean  | 9.0      | 8.9      |       |
| standard deviation   | ± 1.65   | ± 1.79   | -     |
| Sex: Female, Male  |          |          |       |
| Units: Subjects  |          |          |       |
| Female   | 0        | 0        | 0     |
| Male   | 115      | 115      | 230   |
| Baseline 6MWD  |          |          |       |
| The 6MWD test is a non-encouraged test performed in a 30 meters long flat corridor, where the participant is instructed to walk as far as possible, back and forth around two cones, with the permission to slow down, rest, or stop if needed. Ambulation was assessed via the 6MWD test following standardized procedures by measuring the 6MWD in meters. Participants were not permitted to use assistive devices (walker, long leg braces, or short leg braces) during the 6MWD test. |          |          |       |
| Units: Subjects  |          |          |       |
| <300 meters  | 22       | 25       | 47    |
| >=300 to <400 meters   | 52       | 47       | 99    |
| >=400 meters   | 41       | 43       | 84    |
| 6MWD   |          |          |       |
| 6MWD test is a non-encouraged test performed in a 30 meters long flat corridor, where the participant is instructed to walk as far as possible, back and forth around two cones, with the permission to slow down, rest, or stop if needed. Ambulation was assessed via the 6MWD test following standardized procedures by measuring the 6MWD in meters. Participants were not permitted to use assistive devices (walker, long leg braces, or short leg braces) during the 6MWD test.     |          |          |       |
| Units: meters  |          |          |       |
| arithmetic mean  | 362.69   | 364.04   |       |
| standard deviation   | ± 81.424 | ± 73.342 | -     |
| Time to Walk/Run 10 Meters   |          |          |       |
| Units: seconds   |          |          |       |
| arithmetic mean  | 6.83     | 6.66     |       |
| standard deviation   | ± 2.924  | ± 3.078  | -     |
| Time to Climb 4 Stairs   |          |          |       |
| Number of participants analyzed were 112 for each arm.   |          |          |       |
| Units: seconds   |          |          |       |
| arithmetic mean  | 6.76     | 5.99     |       |

|   |         |         |   |
|---|---------|---------|---|
| standard deviation  | ± 7.287 | ± 5.347 | - |
| Time to Descend 4 Stairs  |         |         |   |
| Number of participants analyzed were 109 and 112 for Placebo and Ataluren arm respectively.   |         |         |   |
| Units: seconds  |         |         |   |
| arithmetic mean   | 5.05    | 5.07    |   |
| standard deviation  | ± 5.362 | ± 5.157 | - |
| Physical Function Total Score as Measured by North Star Ambulatory Assessment (NSAA)  |         |         |   |
| Number of participants analyzed were 114 for each arm.  |         |         |   |
| Units: units on a scale   |         |         |   |
| arithmetic mean   | 60.2    | 60.9    |   |
| standard deviation  | ± 18.37 | ± 17.97 | - |
| Pediatric Outcomes Data Collection Instrument (PODCI) Transfers/Basic Mobility Score  |         |         |   |
| PODCI includes a Global Functioning Scale and 5 core scales: Upper Extremity & Physical Function, Transfer/Basic Mobility, Sports/Physical Functioning, Pain/Comfort, and Happiness. Transfers/Basic Mobility domain assesses difficulty experienced in performing routine motor activities in daily life. Each domain was scored from 0 (poor outcome/worse health) to 100 (the highest level of functioning & least pain). Number of participants analyzed were 114 for each arm.       |         |         |   |
| Units: units on a scale   |         |         |   |
| arithmetic mean   | 81.4    | 83.9    |   |
| standard deviation  | ± 15.79 | ± 13.10 | - |
| Pediatric Outcomes Data Collection Instrument (PODCI) Sports/Physical Functioning Score   |         |         |   |
| PODCI includes a Global Functioning Scale and 5 core scales: Upper Extremity & Physical Function, Transfer/Basic Mobility, Sports/Physical Functioning, Pain/Comfort, and Happiness. Sports/Physical Functioning domain assesses difficulty encountered in participating in more active recreational activities. Each domain was scored from 0 (poor outcome/worse health) to 100 (the highest level of functioning & least pain). Number of participants analyzed were 114 for each arm. |         |         |   |
| Units: units on a scale   |         |         |   |
| arithmetic mean   | 56.0    | 56.2    |   |
| standard deviation  | ± 20.94 | ± 18.94 | - |

## End points

### End points reporting groups

|  |          |
|--|----------|
| Reporting group title  | Placebo  |
| Reporting group description:   |          |
| Participants received placebo matched to ataluren orally 3 times a day (TID) at morning, midday, and evening for 48 weeks.   |          |
| Reporting group title  | Ataluren |
| Reporting group description:   |          |
| Participants received ataluren suspension orally TID, 10 milligrams/kilogram (mg/kg) at morning, 10 mg/kg at midday, and 20 mg/kg at evening (total daily dose 40 mg/kg) for 48 weeks. |          |

### Primary: Change From Baseline in 6MWD at Week 48

|   |   |
|---|---|
| End point title   | Change From Baseline in 6MWD at Week 48 |
| End point description:  |   |
| The 6MWD test is a non-encouraged test performed in a 30 meters long flat corridor, where the participant is instructed to walk as far as possible, back and forth around two cones, with the permission to slow down, rest, or stop if needed. Ambulation was assessed via the 6MWD test following standardized procedures by measuring the 6MWD in meters. Participants were not permitted to use assistive devices (walker, long leg braces, or short leg braces) during the 6MWD test. Participants with confirmed loss of ambulation at a particular visit were assigned a 6MWD result of 0. Baseline and Week 48 6MWD values are each the average of two valid 6MWD values, or a single available value if one was missing. ITT population included all participants who were randomized and received any study treatment; and had a valid baseline, and at least one valid post-baseline 6MWD value. Multiple imputation was applied to impute missing values within the treatment groups. |   |
| End point type  | Primary                                 |
| End point timeframe:  |   |
| Baseline, Week 48   |   |

| End point values                    | Placebo               | Ataluren              |  |  |
|-------------------------------------|-----------------------|-----------------------|--|--|
| Subject group type                  | Reporting group       | Reporting group       |  |  |
| Number of subjects analysed         | 114                   | 114                   |  |  |
| Units: meters                       |                       |                       |  |  |
| least squares mean (standard error) | -60.67 ( $\pm$ 9.323) | -47.69 ( $\pm$ 9.247) |  |  |

### Statistical analyses

|   |                         |
|---|-------------------------|
| Statistical analysis title  | Placebo versus Ataluren |
| Statistical analysis description:   |                         |
| Analysis was performed using analysis of covariance (ANCOVA) method including stratification factors for age (less than [ $<$ ] 9 years versus [vs.] greater than or equal to [ $\geq$ ] 9 years), duration of use of corticosteroids at baseline (approx. $\geq 6$ to $< 12$ months vs. $\geq 12$ months), and baseline 6MWD category ( $\geq 350$ meters vs $< 350$ meters), as well as baseline 6MWD as covariate. |                         |
| Comparison groups   | Placebo v Ataluren      |



|   |                                |
|---|--------------------------------|
| Number of subjects included in analysis | 228                            |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | other                          |
| P-value                                 | = 0.213 <sup>[1]</sup>         |
| Method                                  | Mixed models analysis          |
| Parameter estimate                      | Mean difference (final values) |
| Point estimate                          | 12.98                          |
| Confidence interval                     |                                |
| level                                   | 95 %                           |
| sides                                   | 2-sided                        |
| lower limit                             | -7.44                          |
| upper limit                             | 33.39                          |
| Variability estimate                    | Standard error of the mean     |
| Dispersion value                        | 10.415                         |

Notes:

[1] - Threshold for significance at 0.05. Secondary endpoints were tested for significance, only if the primary endpoint was statistically significant.

### Secondary: Time to 10 Percent (%) Persistent Worsening in 6MWD

|  |   |
|--|---|
| End point title  | Time to 10 Percent (%) Persistent Worsening in 6MWD |
| End point description:   |   |
| <p>6MWD test was performed in a 30 meters long flat corridor, where participant was instructed to walk as far as possible, back and forth around two cones, with permission to slow down, rest, or stop. Participants were not permitted to use assistive devices (walker, long leg braces, or short leg braces) during test. Time to 10% persistent worsening in 6MWD: last time that 6MWD was not 10% worse than baseline. For participants who did not have 10% 6MWD worsening or who were removed from study, time to 10% 6MWD worsening was censored at the time of last 6MWD test. Participants who became non-ambulatory were considered to have 10% worsening. ITT population: all participants who were randomized and received any study treatment; and had a valid baseline, and at least one valid post-baseline 6MWD value. Multiple imputation was applied to impute missing value. 'n'=participants evaluable for specified categories. '99999'=data not calculated due to smaller number of participant with an event.</p> |   |
| End point type   | Secondary   |
| End point timeframe:   |   |
| Baseline to Week 48  |   |

| End point values                 | Placebo                | Ataluren               |  |  |
|----------------------------------|------------------------|------------------------|--|--|
| Subject group type               | Reporting group        | Reporting group        |  |  |
| Number of subjects analysed      | 114                    | 114                    |  |  |
| Units: days                      |                        |                        |  |  |
| median (confidence interval 95%) |                        |                        |  |  |
| <300 meters (n=21,24)            | 56 (1.0 to 111.0)      | 164 (1.0 to 225.0)     |  |  |
| >=300 to <400 meters (n=52,47)   | 280 (169.0 to 99999)   | 99999 (280.0 to 99999) |  |  |
| >=400 meters (n=41,43)           | 99999 (99999 to 99999) | 99999 (99999 to 99999) |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change From Baseline in Time to Walk/Run 10 Meters at Week 48

|                 |   |
|-----------------|---|
| End point title | Change From Baseline in Time to Walk/Run 10 Meters at Week 48 |
|-----------------|---|

End point description:

The method of walk/run used by participant was categorized as follows: 1. Unable to walk independently; 2. Unable to walk independently but can walk with support; 3. Highly adapted gait, wide-based lordotic gait, cannot increase walking speed; 4. Moderately adapted gait, can pick up speed but cannot run; 5. Able to pick up speed but runs with a double stance phase (that is, cannot achieve both feet off the ground); 6. Runs and gets both feet off the ground (with no double stance phase). If time taken to perform a test exceeded 30 seconds or if a participant could not perform test due to disease progression, a value of 30 seconds was used. A cumulative change from baseline data has been reported. ITT population included all participants who were randomized and received any study treatment; and had a valid baseline, and at least one valid post-baseline 6MWD value. Here, 'Overall number of participants analyzed' signifies participants evaluable for this outcome measure.

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

End point timeframe:

Baseline, Week 48

| End point values                     | Placebo         | Ataluren        |  |  |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type                   | Reporting group | Reporting group |  |  |
| Number of subjects analysed          | 110             | 109             |  |  |
| Units: seconds                       |                 |                 |  |  |
| arithmetic mean (standard deviation) | 3.47 (± 6.393)  | 2.27 (± 5.216)  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change From Baseline in Time to Climb 4 Stairs at Week 48

|                 |   |
|-----------------|---|
| End point title | Change From Baseline in Time to Climb 4 Stairs at Week 48 |
|-----------------|---|

End point description:

The method of climbing used by participant was categorized as follows: 1. Unable to up climb 4 standard stairs; 2. Climbs 4 standard stairs "marking time" (climbs one foot at a time, with both feet on a step before moving to next step), using both arms on one or both handrails; 3. Climbs 4 standard stairs "marking time" (climbs one foot at a time, with both feet on a step before moving to next step), using one arm on one handrail; 4. Climbs 4 standard stairs "marking time", not needing handrail; 5. Climbs 4 standard stairs alternating feet, needs handrail for support; 6. Climbs 4 standard stairs alternating feet, not needing handrail support. A cumulative change from baseline data has been reported. ITT population included all participants who were randomized and received any study treatment; and had a valid baseline, and at least one valid post-baseline 6MWD value. Here, 'Overall number of participants analyzed' signifies participants evaluable for this outcome measure.

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

End point timeframe:

Baseline, Week 48

| End point values                     | Placebo             | Ataluren            |  |  |
|--------------------------------------|---------------------|---------------------|--|--|
| Subject group type                   | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed          | 103                 | 105                 |  |  |
| Units: seconds                       |                     |                     |  |  |
| arithmetic mean (standard deviation) | 4.46 ( $\pm$ 7.310) | 2.65 ( $\pm$ 5.297) |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change From Baseline in Time to Descend 4 Stairs at Week 48

|  |   |
|--|---|
| End point title  | Change From Baseline in Time to Descend 4 Stairs at Week 48 |
| End point description:   |   |
| The method of descending used by participant was categorized as follows: 1. Unable to descend 4 standard stairs; 2. Descends 4 standard stairs "marking time" (climbs one foot at a time, with both feet on a step before moving to next step), using both arms on one or both handrails; 3. Descends 4 standard stairs "marking time", using one arm on one handrail; 4. Descends 4 standard stairs "marking time" (climbs one foot at a time, with both feet on a step before moving to next step), not needing handrail; 5. Descends 4 standard stairs alternating feet, needs handrail for support; 6. Descends 4 standard stairs alternating feet, not needing handrail support. A cumulative change from baseline data has been reported. ITT population included all participants who were randomized and received any study treatment; and had a valid baseline, and at least one valid post-baseline 6MWD value. Here, 'Overall number of participants analyzed' signifies participants evaluable for this outcome measure. |   |
| End point type   | Secondary   |
| End point timeframe:   |   |
| Baseline, Week 48  |   |

| End point values                     | Placebo             | Ataluren            |  |  |
|--------------------------------------|---------------------|---------------------|--|--|
| Subject group type                   | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed          | 100                 | 106                 |  |  |
| Units: seconds                       |                     |                     |  |  |
| arithmetic mean (standard deviation) | 3.97 ( $\pm$ 7.854) | 2.15 ( $\pm$ 5.306) |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Participants With Treatment-Emergent Adverse Events (AEs)

|   |   |
|---|---|
| End point title   | Percentage of Participants With Treatment-Emergent Adverse Events (AEs) |
| End point description:  |   |
| An AE was any untoward medical occurrence in a participant who received study drug without regard to possibility of causal relationship. Serious adverse event (SAE) was an AE resulting in any of the following outcomes or deemed significant for any other reason: death; initial or prolonged inpatient hospitalization; life-threatening experience (immediate risk of dying); persistent or significant disability/incapacity; congenital anomaly. AEs included both SAEs and non-serious AEs. Treatment- |   |

emergent adverse event (TEAE) was defined as an adverse event that occurred or worsened in the period extending from first dose of study drug to 6 weeks after the last dose of study drug. A summary of other non-serious AEs and all SAEs, regardless of causality is located in the 'Reported AE section'. As-treated population included all randomized participants who actually received any study treatment.

|                        |           |
|------------------------|-----------|
| End point type         | Secondary |
| End point timeframe:   |           |
| Baseline up to Week 54 |           |

| End point values                  | Placebo         | Ataluren        |  |  |
|-----------------------------------|-----------------|-----------------|--|--|
| Subject group type                | Reporting group | Reporting group |  |  |
| Number of subjects analysed       | 115             | 115             |  |  |
| Units: percentage of participants |                 |                 |  |  |
| number (not applicable)           | 87.8            | 89.6            |  |  |

## Statistical analyses

No statistical analyses for this end point

## Other pre-specified: Number of Participants With Change From Baseline in Activities of Daily Living and Disease Status at Week 48, as Assessed by a Standardized Survey Administered by Site Personnel

|                 |   |
|-----------------|---|
| End point title | Number of Participants With Change From Baseline in Activities of Daily Living and Disease Status at Week 48, as Assessed by a Standardized Survey Administered by Site Personnel |
|-----------------|---|

End point description:

At screening or baseline, participant and/or parent/caregiver were asked to identify any activities of daily living (ambulation, balance, personal hygiene/grooming, dressing and undressing, self-feeding, using bathroom, handwriting, school performance, behavior or energy level) or symptoms that were affected by participant's DMD. At post-baseline (Week 48), same participant and/or parent/caregiver was asked to describe any changes from baseline in those activities of daily living/symptoms, within following categories: physical functioning(PF); general energy level(EL); cognition/school function(C/SF); emotional/social functioning(E/SocF); and sleep. Changes were reported on a 5-point Likert scale: 1=much worse, 2=slightly worse, 3=unchanged, 4=slightly better, or 5=much better. ITT population: all participants who were randomized and received any study treatment; and had a valid baseline, and at least one valid post-baseline 6MWD value. 'n'=participants evaluable for specified categories.

|                      |                     |
|----------------------|---------------------|
| End point type       | Other pre-specified |
| End point timeframe: |                     |
| Baseline, Week 48    |                     |

| End point values                                  | Placebo         | Ataluren        |  |  |
|---|-----------------|-----------------|--|--|
| Subject group type                                | Reporting group | Reporting group |  |  |
| Number of subjects analysed                       | 114             | 114             |  |  |
| Units: participants                               |                 |                 |  |  |
| PF:Upper Extremity Activity-Much better (n=82,88) | 1               | 4               |  |  |
| PF:Walking-Much better (n=112,108)                | 5               | 8               |  |  |

|  |    |    |  |  |
|--|----|----|--|--|
| PF:Climbing Stairs-Much better (n=105,110)         | 4  | 4  |  |  |
| PF:Other-Much better (n=65,68)                     | 4  | 5  |  |  |
| C/SF-Much better (n=92,104)                        | 6  | 5  |  |  |
| E/SocF-Much better (n=94,105)                      | 3  | 8  |  |  |
| General EL-Much better (n=83,89)                   | 3  | 8  |  |  |
| Sleep-Much better (n=85,91)                        | 3  | 3  |  |  |
| Other-Much better (n=23,23)                        | 0  | 1  |  |  |
| PF:Upper Extremity Activity-Slight better(n=82,88) | 7  | 7  |  |  |
| PF:Walking-Slightly better (n=112,108)             | 13 | 16 |  |  |
| PF:Climbing Stairs-Slightly better (n=105,110)     | 8  | 13 |  |  |
| PF:Other-Slightly better (n=65,68)                 | 9  | 10 |  |  |
| C/SF-Slightly better (n=92,104)                    | 12 | 20 |  |  |
| E/SocF-Slightly better (n=94,105)                  | 9  | 21 |  |  |
| General EL-Slightly better (n=83,89)               | 12 | 12 |  |  |
| Sleep-Slightly better (n=85,91)                    | 4  | 8  |  |  |
| Other-Slightly better (n=23,23)                    | 5  | 6  |  |  |
| PF:Upper Extremity Activity-Unchanged (n=82,88)    | 67 | 73 |  |  |
| PF:Walking-Unchanged (n=112,108)                   | 57 | 60 |  |  |
| PF:Climbing Stairs-Unchanged (n=105,110)           | 61 | 65 |  |  |
| PF:Other-Unchanged (n=65,68)                       | 38 | 44 |  |  |
| C/SF-Unchanged (n=92,104)                          | 71 | 74 |  |  |
| E/SocF-Unchanged (n=94,105)                        | 75 | 68 |  |  |
| General EL-Unchanged (n=83,89)                     | 54 | 63 |  |  |
| Sleep-Unchanged (n=85,91)                          | 73 | 76 |  |  |
| Other-Unchanged (n=23,23)                          | 15 | 13 |  |  |
| PF:Upper Extremity Activity-Slight worse (n=82,88) | 6  | 2  |  |  |
| PF:Walking-Slightly worse (n=112,108)              | 19 | 21 |  |  |
| PF:Climbing Stairs-Slightly worse (n=105,110)      | 17 | 15 |  |  |
| PF:Other-Slightly worse (n=65,68)                  | 7  | 8  |  |  |
| C/SF-Slightly worse (n=92,104)                     | 3  | 3  |  |  |
| E/SocF-Slightly worse (n=94,105)                   | 5  | 6  |  |  |
| General EL-Slightly worse (n=83,89)                | 11 | 5  |  |  |
| Sleep-Slightly worse (n=85,91)                     | 5  | 2  |  |  |
| Other-Slightly worse (n=23,23)                     | 2  | 3  |  |  |
| PF:Upper Extremity Activity-Much worse (n=82,88)   | 1  | 2  |  |  |
| PF:Walking-Much worse (n=112,108)                  | 18 | 3  |  |  |
| PF:Climbing Stairs-Much worse (n=105,110)          | 15 | 13 |  |  |
| PF:Other-Much worse (n=65,68)                      | 7  | 1  |  |  |
| C/SF-Much worse (n=92,104)                         | 0  | 2  |  |  |
| E/SocF-Much worse (n=94,105)                       | 2  | 2  |  |  |
| General EL-Much worse (n=83,89)                    | 3  | 1  |  |  |
| Sleep-Much worse (n=85,91)                         | 0  | 2  |  |  |
| Other-Much worse (n=23,23)                         | 1  | 0  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Other pre-specified: Ataluren Plasma Concentration

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

End point description:

Plasma samples for the determination of ataluren concentrations were analyzed using a validated high performance liquid chromatography with tandem mass spectrometry (HPLC/MS-MS) method with a lower limit of quantitation of 0.5 micrograms/milliliter (mcg/mL). As-treated population included all randomized participants who actually received any study treatment. Here, 'n' signifies participants evaluable at specified timepoint.

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

End point timeframe:

Weeks 8, 16, 24, 32, 40, and 48

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The endpoint is reporting statistics for Ataluren arm only.

| End point values                     | Ataluren         |  |  |  |
|--------------------------------------|------------------|--|--|--|
| Subject group type                   | Reporting group  |  |  |  |
| Number of subjects analysed          | 115              |  |  |  |
| Units: mcg/mL                        |                  |  |  |  |
| arithmetic mean (standard deviation) |                  |  |  |  |
| Week 08 (n=113)                      | 4.230 (± 5.3913) |  |  |  |
| Week 16 (n=113)                      | 3.429 (± 3.9275) |  |  |  |
| Week 24 (n=112)                      | 3.323 (± 3.6135) |  |  |  |
| Week 32 (n=113)                      | 3.480 (± 3.1053) |  |  |  |
| Week 40 (n=111)                      | 3.997 (± 4.7615) |  |  |  |
| Week 48 (n=110)                      | 3.544 (± 3.8082) |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Other pre-specified: Study Drug Compliance

|                 |                       |
|-----------------|-----------------------|
| End point title | Study Drug Compliance |
|-----------------|-----------------------|

End point description:

Study drug compliance was assessed by quantification of used and unused study drug. Compliance was

assessed in terms of the percentage of drug actually taken relative to the amount that should have been taken during the study. As-treated population included all randomized participants who actually received any study treatment.

|                      |                     |
|----------------------|---------------------|
| End point type       | Other pre-specified |
| End point timeframe: |                     |
| Baseline to Week 48  |                     |

| End point values                     | Placebo            | Ataluren           |  |  |
|--------------------------------------|--------------------|--------------------|--|--|
| Subject group type                   | Reporting group    | Reporting group    |  |  |
| Number of subjects analysed          | 115                | 115                |  |  |
| Units: percentage of drug            |                    |                    |  |  |
| arithmetic mean (standard deviation) | 95.1 ( $\pm$ 9.43) | 95.7 ( $\pm$ 7.57) |  |  |

## Statistical analyses

No statistical analyses for this end point

## Other pre-specified: Change From Baseline in Physical Function Total Score as Measured by NSAA at Week 48

|                 |  |
|-----------------|--|
| End point title | Change From Baseline in Physical Function Total Score as Measured by NSAA at Week 48 |
|-----------------|--|

End point description:

NSAA is a functional scale specifically designed for ambulant Duchenne muscular dystrophy (DMD) participants. It comprised tests for 17 abilities: ability to stand, rise from floor, get from lying to sitting, get from sitting to standing, raise one's head, stand on one's heels, hop, jump, and run. For each activity, a score of 0,1, or 2 was recorded, with 0=unable to achieve independently,1=modified method but achieves goal independently, or 2 =normal- achieves goal independently. Sum of these scores(except for 'raise one's head' activity) was reported as ordinal total score, which was transformed to a linear total score ranging from 0(worst) to 100(best). Participants with confirmed loss of ambulation at a particular visit were assigned a score of 0. ITT population:all participants who were randomized and received any study treatment; and had a valid baseline, and at least one valid post-baseline 6MWD value. 'Number of participants analyzed'=participants evaluable for this endpoint.

|                      |                     |
|----------------------|---------------------|
| End point type       | Other pre-specified |
| End point timeframe: |                     |
| Baseline, Week 48    |                     |

| End point values                     | Placebo             | Ataluren            |  |  |
|--------------------------------------|---------------------|---------------------|--|--|
| Subject group type                   | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed          | 108                 | 106                 |  |  |
| Units: units on a scale              |                     |                     |  |  |
| arithmetic mean (standard deviation) | -8.4 ( $\pm$ 10.65) | -6.3 ( $\pm$ 10.64) |  |  |

## Statistical analyses

No statistical analyses for this end point

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**Other pre-specified: Change From Baseline in PODCI Transfers/Basic Mobility and Sports/Physical Functioning Scores at Week 48**

---

|                 |  |
|-----------------|--|
| End point title | Change From Baseline in PODCI Transfers/Basic Mobility and Sports/Physical Functioning Scores at Week 48 |
|-----------------|--|

End point description:

Changes in health-related quality of life (HRQL) were measured via PODCI questionnaire. PODCI includes a Global Functioning Scale and 5 core scales: Upper Extremity and Physical Function, Transfer/Basic Mobility, Sports/Physical Functioning, Pain/Comfort, and Happiness. Following PODCI domains were prespecified in protocol for analysis: Transfers/Basic Mobility domain assesses difficulty experienced in performing routine motor activities in daily life. Sports/Physical Functioning domain assesses difficulty encountered in participating in more active recreational activities. Each domain was scored from 0 to 100, with 0=poor outcome/worse health, while 100=the highest level of functioning and least pain. ITT population: all participants who were randomized and received any study treatment; and had a valid baseline, and at least one valid post-baseline 6MWD value. 'Number of participants analyzed'=participants evaluable for this endpoint.

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

End point timeframe:

Baseline, Week 48

---

| End point values                     | Placebo         | Ataluren        |  |  |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type                   | Reporting group | Reporting group |  |  |
| Number of subjects analysed          | 110             | 109             |  |  |
| Units: units on a scale              |                 |                 |  |  |
| arithmetic mean (standard deviation) |                 |                 |  |  |
| Transfers/Basic Mobility Score       | -8.8 (± 15.80)  | -6.6 (± 14.76)  |  |  |
| Sports/Physical Functioning Score    | -7.3 (± 15.87)  | -5.6 (± 15.91)  |  |  |

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**Statistical analyses**

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No statistical analyses for this end point



## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Baseline up to 6 weeks after the last dose of study drug (Week 54)

Adverse event reporting additional description:

As-treated population included all randomized participants who actually received any study treatment.

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 15.1 |
|--------------------|------|

### Reporting groups

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

Reporting group description:

Participants received placebo matched to ataluren orally TID at morning, midday, and evening for 48 weeks.

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

Reporting group description:

Participants received ataluren suspension orally TID, 10 mg/kg at morning, 10 mg/kg at midday, and 20 mg/kg at evening (total daily dose 40 mg/kg) for 48 weeks.

| Serious adverse events                            | Placebo         | Ataluren        |  |
|---|-----------------|-----------------|--|
| Total subjects affected by serious adverse events |                 |                 |  |
| subjects affected / exposed                       | 4 / 115 (3.48%) | 4 / 115 (3.48%) |  |
| number of deaths (all causes)                     | 0               | 0               |  |
| number of deaths resulting from adverse events    |                 |                 |  |
| Injury, poisoning and procedural complications    |                 |                 |  |
| Post-traumatic pain                               |                 |                 |  |
| subjects affected / exposed                       | 1 / 115 (0.87%) | 0 / 115 (0.00%) |  |
| occurrences causally related to treatment / all   | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all        | 0 / 0           | 0 / 0           |  |
| Femur fracture                                    |                 |                 |  |
| subjects affected / exposed                       | 0 / 115 (0.00%) | 1 / 115 (0.87%) |  |
| occurrences causally related to treatment / all   | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all        | 0 / 0           | 0 / 0           |  |
| Lower limb fracture                               |                 |                 |  |
| subjects affected / exposed                       | 0 / 115 (0.00%) | 1 / 115 (0.87%) |  |
| occurrences causally related to treatment / all   | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all        | 0 / 0           | 0 / 0           |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| Cardiac disorders                               |                 |                 |  |
| Myocarditis                                     |                 |                 |  |
| subjects affected / exposed                     | 0 / 115 (0.00%) | 1 / 115 (0.87%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Respiratory, thoracic and mediastinal disorders |                 |                 |  |
| Adenoidal hypertrophy                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 115 (0.87%) | 0 / 115 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Nasal turbinate hypertrophy                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 115 (0.87%) | 0 / 115 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hepatobiliary disorders                         |                 |                 |  |
| Hepatic function abnormal                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 115 (0.00%) | 1 / 115 (0.87%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Musculoskeletal and connective tissue disorders |                 |                 |  |
| Tendon disorder                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 115 (0.87%) | 0 / 115 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Infections and infestations                     |                 |                 |  |
| Pneumonia                                       |                 |                 |  |
| subjects affected / exposed                     | 2 / 115 (1.74%) | 0 / 115 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Bronchiolitis                                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 115 (0.87%) | 0 / 115 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastroenteritis                                 |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 115 (0.00%) | 1 / 115 (0.87%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

Frequency threshold for reporting non-serious adverse events: 0 %

| <b>Non-serious adverse events</b>                                   | Placebo           | Ataluren           |  |
|---|-------------------|--------------------|--|
| Total subjects affected by non-serious adverse events               |                   |                    |  |
| subjects affected / exposed   | 99 / 115 (86.09%) | 103 / 115 (89.57%) |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                   |                    |  |
| Skin papilloma  |                   |                    |  |
| subjects affected / exposed   | 2 / 115 (1.74%)   | 1 / 115 (0.87%)    |  |
| occurrences (all)   | 2                 | 1                  |  |
| Vascular disorders  |                   |                    |  |
| Hypertension  |                   |                    |  |
| subjects affected / exposed   | 2 / 115 (1.74%)   | 1 / 115 (0.87%)    |  |
| occurrences (all)   | 2                 | 1                  |  |
| Hypotension   |                   |                    |  |
| subjects affected / exposed   | 0 / 115 (0.00%)   | 1 / 115 (0.87%)    |  |
| occurrences (all)   | 0                 | 1                  |  |
| Aortic dilatation   |                   |                    |  |
| subjects affected / exposed   | 1 / 115 (0.87%)   | 0 / 115 (0.00%)    |  |
| occurrences (all)   | 1                 | 0                  |  |
| Flushing  |                   |                    |  |
| subjects affected / exposed   | 3 / 115 (2.61%)   | 0 / 115 (0.00%)    |  |
| occurrences (all)   | 3                 | 0                  |  |
| Haematoma   |                   |                    |  |
| subjects affected / exposed   | 1 / 115 (0.87%)   | 0 / 115 (0.00%)    |  |
| occurrences (all)   | 1                 | 0                  |  |
| General disorders and administration site conditions                |                   |                    |  |
| Pyrexia   |                   |                    |  |
| subjects affected / exposed   | 12 / 115 (10.43%) | 16 / 115 (13.91%)  |  |
| occurrences (all)   | 17                | 20                 |  |
| Disease progression   |                   |                    |  |

|                             |                   |                 |  |
|-----------------------------|-------------------|-----------------|--|
| subjects affected / exposed | 14 / 115 (12.17%) | 9 / 115 (7.83%) |  |
| occurrences (all)           | 15                | 9               |  |
| Abasia                      |                   |                 |  |
| subjects affected / exposed | 0 / 115 (0.00%)   | 3 / 115 (2.61%) |  |
| occurrences (all)           | 0                 | 3               |  |
| Oedema peripheral           |                   |                 |  |
| subjects affected / exposed | 0 / 115 (0.00%)   | 3 / 115 (2.61%) |  |
| occurrences (all)           | 0                 | 3               |  |
| Fatigue                     |                   |                 |  |
| subjects affected / exposed | 3 / 115 (2.61%)   | 1 / 115 (0.87%) |  |
| occurrences (all)           | 3                 | 1               |  |
| Non-cardiac chest pain      |                   |                 |  |
| subjects affected / exposed | 1 / 115 (0.87%)   | 1 / 115 (0.87%) |  |
| occurrences (all)           | 1                 | 1               |  |
| Influenza like illness      |                   |                 |  |
| subjects affected / exposed | 2 / 115 (1.74%)   | 1 / 115 (0.87%) |  |
| occurrences (all)           | 2                 | 1               |  |
| Gait disturbance            |                   |                 |  |
| subjects affected / exposed | 1 / 115 (0.87%)   | 0 / 115 (0.00%) |  |
| occurrences (all)           | 1                 | 0               |  |
| Malaise                     |                   |                 |  |
| subjects affected / exposed | 3 / 115 (2.61%)   | 0 / 115 (0.00%) |  |
| occurrences (all)           | 3                 | 0               |  |
| Thirst                      |                   |                 |  |
| subjects affected / exposed | 1 / 115 (0.87%)   | 0 / 115 (0.00%) |  |
| occurrences (all)           | 1                 | 0               |  |
| Immune system disorders     |                   |                 |  |
| Allergy to chemicals        |                   |                 |  |
| subjects affected / exposed | 0 / 115 (0.00%)   | 1 / 115 (0.87%) |  |
| occurrences (all)           | 0                 | 1               |  |
| Seasonal allergy            |                   |                 |  |
| subjects affected / exposed | 2 / 115 (1.74%)   | 2 / 115 (1.74%) |  |
| occurrences (all)           | 2                 | 2               |  |
| Rhinitis allergic           |                   |                 |  |
| subjects affected / exposed | 0 / 115 (0.00%)   | 1 / 115 (0.87%) |  |
| occurrences (all)           | 0                 | 1               |  |

|  |                         |                         |  |
|--|-------------------------|-------------------------|--|
| Allergy to vaccine<br>subjects affected / exposed<br>occurrences (all)   | 1 / 115 (0.87%)<br>1    | 0 / 115 (0.00%)<br>0    |  |
| Drug hypersensitivity<br>subjects affected / exposed<br>occurrences (all)  | 2 / 115 (1.74%)<br>2    | 0 / 115 (0.00%)<br>0    |  |
| Reproductive system and breast disorders<br>Genital discomfort<br>subjects affected / exposed<br>occurrences (all) | 0 / 115 (0.00%)<br>0    | 1 / 115 (0.87%)<br>1    |  |
| Respiratory, thoracic and mediastinal disorders<br>Cough<br>subjects affected / exposed<br>occurrences (all)       | 13 / 115 (11.30%)<br>17 | 19 / 115 (16.52%)<br>23 |  |
| Oropharyngeal pain<br>subjects affected / exposed<br>occurrences (all)   | 6 / 115 (5.22%)<br>9    | 7 / 115 (6.09%)<br>7    |  |
| Epistaxis<br>subjects affected / exposed<br>occurrences (all)  | 4 / 115 (3.48%)<br>11   | 7 / 115 (6.09%)<br>10   |  |
| Nasal congestion<br>subjects affected / exposed<br>occurrences (all)   | 2 / 115 (1.74%)<br>3    | 3 / 115 (2.61%)<br>5    |  |
| Rhinorrhoea<br>subjects affected / exposed<br>occurrences (all)  | 3 / 115 (2.61%)<br>3    | 3 / 115 (2.61%)<br>4    |  |
| Wheezing<br>subjects affected / exposed<br>occurrences (all)   | 0 / 115 (0.00%)<br>0    | 3 / 115 (2.61%)<br>3    |  |
| Asthmatic crisis<br>subjects affected / exposed<br>occurrences (all)   | 0 / 115 (0.00%)<br>0    | 1 / 115 (0.87%)<br>1    |  |
| Productive cough<br>subjects affected / exposed<br>occurrences (all)   | 0 / 115 (0.00%)<br>0    | 1 / 115 (0.87%)<br>1    |  |
| Sneezing   |                         |                         |  |

|  |                 |                 |  |
|--|-----------------|-----------------|--|
| subjects affected / exposed              | 0 / 115 (0.00%) | 1 / 115 (0.87%) |  |
| occurrences (all)                        | 0               | 1               |  |
| Dyspnoea                                 |                 |                 |  |
| subjects affected / exposed              | 1 / 115 (0.87%) | 0 / 115 (0.00%) |  |
| occurrences (all)                        | 1               | 0               |  |
| Sinus congestion                         |                 |                 |  |
| subjects affected / exposed              | 2 / 115 (1.74%) | 0 / 115 (0.00%) |  |
| occurrences (all)                        | 3               | 0               |  |
| Sleep apnoea syndrome                    |                 |                 |  |
| subjects affected / exposed              | 2 / 115 (1.74%) | 0 / 115 (0.00%) |  |
| occurrences (all)                        | 2               | 0               |  |
| Throat irritation                        |                 |                 |  |
| subjects affected / exposed              | 1 / 115 (0.87%) | 0 / 115 (0.00%) |  |
| occurrences (all)                        | 1               | 0               |  |
| Psychiatric disorders                    |                 |                 |  |
| Attention deficit/hyperactivity disorder |                 |                 |  |
| subjects affected / exposed              | 1 / 115 (0.87%) | 3 / 115 (2.61%) |  |
| occurrences (all)                        | 1               | 3               |  |
| Aggression                               |                 |                 |  |
| subjects affected / exposed              | 0 / 115 (0.00%) | 2 / 115 (1.74%) |  |
| occurrences (all)                        | 0               | 2               |  |
| Sleep disorder                           |                 |                 |  |
| subjects affected / exposed              | 0 / 115 (0.00%) | 2 / 115 (1.74%) |  |
| occurrences (all)                        | 0               | 3               |  |
| Abnormal behaviour                       |                 |                 |  |
| subjects affected / exposed              | 0 / 115 (0.00%) | 1 / 115 (0.87%) |  |
| occurrences (all)                        | 0               | 1               |  |
| Negativism                               |                 |                 |  |
| subjects affected / exposed              | 0 / 115 (0.00%) | 1 / 115 (0.87%) |  |
| occurrences (all)                        | 0               | 1               |  |
| Obsessive-compulsive disorder            |                 |                 |  |
| subjects affected / exposed              | 1 / 115 (0.87%) | 1 / 115 (0.87%) |  |
| occurrences (all)                        | 1               | 1               |  |
| Anxiety                                  |                 |                 |  |

|  |                         |                         |  |
|--|-------------------------|-------------------------|--|
| subjects affected / exposed<br>occurrences (all)   | 2 / 115 (1.74%)<br>2    | 0 / 115 (0.00%)<br>0    |  |
| Dysphemia<br>subjects affected / exposed<br>occurrences (all)  | 1 / 115 (0.87%)<br>1    | 0 / 115 (0.00%)<br>0    |  |
| Middle insomnia<br>subjects affected / exposed<br>occurrences (all)  | 1 / 115 (0.87%)<br>1    | 0 / 115 (0.00%)<br>0    |  |
| Mood swings<br>subjects affected / exposed<br>occurrences (all)  | 2 / 115 (1.74%)<br>2    | 0 / 115 (0.00%)<br>0    |  |
| Investigations<br>Renin increased<br>subjects affected / exposed<br>occurrences (all)                                | 3 / 115 (2.61%)<br>3    | 1 / 115 (0.87%)<br>1    |  |
| Injury, poisoning and procedural complications<br>Arthropod bite<br>subjects affected / exposed<br>occurrences (all) | 0 / 115 (0.00%)<br>0    | 2 / 115 (1.74%)<br>2    |  |
| Arthropod sting<br>subjects affected / exposed<br>occurrences (all)  | 1 / 115 (0.87%)<br>1    | 1 / 115 (0.87%)<br>1    |  |
| Concussion<br>subjects affected / exposed<br>occurrences (all)   | 1 / 115 (0.87%)<br>1    | 0 / 115 (0.00%)<br>0    |  |
| Fall<br>subjects affected / exposed<br>occurrences (all)   | 20 / 115 (17.39%)<br>31 | 21 / 115 (18.26%)<br>35 |  |
| Contusion<br>subjects affected / exposed<br>occurrences (all)  | 4 / 115 (3.48%)<br>4    | 3 / 115 (2.61%)<br>3    |  |
| Ligament sprain<br>subjects affected / exposed<br>occurrences (all)  | 7 / 115 (6.09%)<br>7    | 3 / 115 (2.61%)<br>3    |  |
| Laceration   |                         |                         |  |

|                             |                 |                 |
|-----------------------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 115 (0.87%) | 2 / 115 (1.74%) |
| occurrences (all)           | 1               | 3               |
| Post-traumatic pain         |                 |                 |
| subjects affected / exposed | 4 / 115 (3.48%) | 2 / 115 (1.74%) |
| occurrences (all)           | 5               | 2               |
| Spinal compression fracture |                 |                 |
| subjects affected / exposed | 1 / 115 (0.87%) | 2 / 115 (1.74%) |
| occurrences (all)           | 1               | 2               |
| Electrical burn             |                 |                 |
| subjects affected / exposed | 0 / 115 (0.00%) | 1 / 115 (0.87%) |
| occurrences (all)           | 0               | 1               |
| Excoriation                 |                 |                 |
| subjects affected / exposed | 1 / 115 (0.87%) | 1 / 115 (0.87%) |
| occurrences (all)           | 1               | 1               |
| Fibula fracture             |                 |                 |
| subjects affected / exposed | 0 / 115 (0.00%) | 1 / 115 (0.87%) |
| occurrences (all)           | 0               | 1               |
| Foot fracture               |                 |                 |
| subjects affected / exposed | 1 / 115 (0.87%) | 1 / 115 (0.87%) |
| occurrences (all)           | 1               | 1               |
| Hand fracture               |                 |                 |
| subjects affected / exposed | 1 / 115 (0.87%) | 1 / 115 (0.87%) |
| occurrences (all)           | 1               | 1               |
| Joint injury                |                 |                 |
| subjects affected / exposed | 1 / 115 (0.87%) | 1 / 115 (0.87%) |
| occurrences (all)           | 1               | 1               |
| Muscle injury               |                 |                 |
| subjects affected / exposed | 0 / 115 (0.00%) | 1 / 115 (0.87%) |
| occurrences (all)           | 0               | 1               |
| Muscle strain               |                 |                 |
| subjects affected / exposed | 0 / 115 (0.00%) | 1 / 115 (0.87%) |
| occurrences (all)           | 0               | 1               |
| Scratch                     |                 |                 |
| subjects affected / exposed | 0 / 115 (0.00%) | 1 / 115 (0.87%) |
| occurrences (all)           | 0               | 2               |
| Tibia fracture              |                 |                 |



|                               |                 |                 |  |
|-------------------------------|-----------------|-----------------|--|
| subjects affected / exposed   | 0 / 115 (0.00%) | 1 / 115 (0.87%) |  |
| occurrences (all)             | 0               | 1               |  |
| Tooth injury                  |                 |                 |  |
| subjects affected / exposed   | 0 / 115 (0.00%) | 1 / 115 (0.87%) |  |
| occurrences (all)             | 0               | 1               |  |
| Ulna fracture                 |                 |                 |  |
| subjects affected / exposed   | 0 / 115 (0.00%) | 1 / 115 (0.87%) |  |
| occurrences (all)             | 0               | 1               |  |
| Upper limb fracture           |                 |                 |  |
| subjects affected / exposed   | 0 / 115 (0.00%) | 1 / 115 (0.87%) |  |
| occurrences (all)             | 0               | 1               |  |
| Head injury                   |                 |                 |  |
| subjects affected / exposed   | 1 / 115 (0.87%) | 0 / 115 (0.00%) |  |
| occurrences (all)             | 1               | 0               |  |
| Limb injury                   |                 |                 |  |
| subjects affected / exposed   | 1 / 115 (0.87%) | 0 / 115 (0.00%) |  |
| occurrences (all)             | 1               | 0               |  |
| Lip injury                    |                 |                 |  |
| subjects affected / exposed   | 1 / 115 (0.87%) | 0 / 115 (0.00%) |  |
| occurrences (all)             | 1               | 0               |  |
| Thermal burn                  |                 |                 |  |
| subjects affected / exposed   | 2 / 115 (1.74%) | 0 / 115 (0.00%) |  |
| occurrences (all)             | 2               | 0               |  |
| Cardiac disorders             |                 |                 |  |
| Right ventricular hypertrophy |                 |                 |  |
| subjects affected / exposed   | 0 / 115 (0.00%) | 2 / 115 (1.74%) |  |
| occurrences (all)             | 0               | 2               |  |
| Left ventricular dysfunction  |                 |                 |  |
| subjects affected / exposed   | 0 / 115 (0.00%) | 1 / 115 (0.87%) |  |
| occurrences (all)             | 0               | 2               |  |
| Left ventricular hypertrophy  |                 |                 |  |
| subjects affected / exposed   | 0 / 115 (0.00%) | 1 / 115 (0.87%) |  |
| occurrences (all)             | 0               | 1               |  |
| Myocardial fibrosis           |                 |                 |  |
| subjects affected / exposed   | 0 / 115 (0.00%) | 1 / 115 (0.87%) |  |
| occurrences (all)             | 0               | 1               |  |

|                                |                   |                   |  |
|--------------------------------|-------------------|-------------------|--|
| Palpitations                   |                   |                   |  |
| subjects affected / exposed    | 2 / 115 (1.74%)   | 1 / 115 (0.87%)   |  |
| occurrences (all)              | 2                 | 1                 |  |
| Cardiomyopathy                 |                   |                   |  |
| subjects affected / exposed    | 1 / 115 (0.87%)   | 0 / 115 (0.00%)   |  |
| occurrences (all)              | 1                 | 0                 |  |
| Wolff-Parkinson-White syndrome |                   |                   |  |
| subjects affected / exposed    | 1 / 115 (0.87%)   | 0 / 115 (0.00%)   |  |
| occurrences (all)              | 1                 | 0                 |  |
| Nervous system disorders       |                   |                   |  |
| Headache                       |                   |                   |  |
| subjects affected / exposed    | 21 / 115 (18.26%) | 21 / 115 (18.26%) |  |
| occurrences (all)              | 29                | 55                |  |
| Autism                         |                   |                   |  |
| subjects affected / exposed    | 0 / 115 (0.00%)   | 1 / 115 (0.87%)   |  |
| occurrences (all)              | 0                 | 1                 |  |
| Coordination abnormal          |                   |                   |  |
| subjects affected / exposed    | 0 / 115 (0.00%)   | 1 / 115 (0.87%)   |  |
| occurrences (all)              | 0                 | 1                 |  |
| Epilepsy                       |                   |                   |  |
| subjects affected / exposed    | 0 / 115 (0.00%)   | 1 / 115 (0.87%)   |  |
| occurrences (all)              | 0                 | 1                 |  |
| Migraine                       |                   |                   |  |
| subjects affected / exposed    | 1 / 115 (0.87%)   | 1 / 115 (0.87%)   |  |
| occurrences (all)              | 1                 | 2                 |  |
| Dizziness                      |                   |                   |  |
| subjects affected / exposed    | 1 / 115 (0.87%)   | 0 / 115 (0.00%)   |  |
| occurrences (all)              | 1                 | 0                 |  |
| Hypotonia                      |                   |                   |  |
| subjects affected / exposed    | 1 / 115 (0.87%)   | 0 / 115 (0.00%)   |  |
| occurrences (all)              | 1                 | 0                 |  |
| Sinus headache                 |                   |                   |  |
| subjects affected / exposed    | 0 / 115 (0.00%)   | 2 / 115 (1.74%)   |  |
| occurrences (all)              | 0                 | 2                 |  |
| Petit mal epilepsy             |                   |                   |  |

|  |                      |                      |  |
|--|----------------------|----------------------|--|
| subjects affected / exposed<br>occurrences (all)                               | 0 / 115 (0.00%)<br>0 | 1 / 115 (0.87%)<br>1 |  |
| Psychomotor hyperactivity<br>subjects affected / exposed<br>occurrences (all)  | 1 / 115 (0.87%)<br>1 | 1 / 115 (0.87%)<br>1 |  |
| Restless legs syndrome<br>subjects affected / exposed<br>occurrences (all)     | 0 / 115 (0.00%)<br>0 | 1 / 115 (0.87%)<br>1 |  |
| Tremor<br>subjects affected / exposed<br>occurrences (all)                     | 0 / 115 (0.00%)<br>0 | 1 / 115 (0.87%)<br>2 |  |
| Blood and lymphatic system disorders   |                      |                      |  |
| Neutropenia<br>subjects affected / exposed<br>occurrences (all)                | 0 / 115 (0.00%)<br>0 | 1 / 115 (0.87%)<br>1 |  |
| Splenomegaly<br>subjects affected / exposed<br>occurrences (all)               | 0 / 115 (0.00%)<br>0 | 1 / 115 (0.87%)<br>1 |  |
| Leukocytosis<br>subjects affected / exposed<br>occurrences (all)               | 1 / 115 (0.87%)<br>1 | 0 / 115 (0.00%)<br>0 |  |
| Lymphadenopathy<br>subjects affected / exposed<br>occurrences (all)            | 1 / 115 (0.87%)<br>1 | 0 / 115 (0.00%)<br>0 |  |
| Ear and labyrinth disorders  |                      |                      |  |
| Ear pain<br>subjects affected / exposed<br>occurrences (all)                   | 4 / 115 (3.48%)<br>4 | 0 / 115 (0.00%)<br>0 |  |
| Middle ear effusion<br>subjects affected / exposed<br>occurrences (all)        | 1 / 115 (0.87%)<br>1 | 0 / 115 (0.00%)<br>0 |  |
| Tympanic membrane disorder<br>subjects affected / exposed<br>occurrences (all) | 1 / 115 (0.87%)<br>1 | 0 / 115 (0.00%)<br>0 |  |
| Eye disorders  |                      |                      |  |

|                             |                   |                   |  |
|-----------------------------|-------------------|-------------------|--|
| Astigmatism                 |                   |                   |  |
| subjects affected / exposed | 0 / 115 (0.00%)   | 1 / 115 (0.87%)   |  |
| occurrences (all)           | 0                 | 1                 |  |
| Cataract                    |                   |                   |  |
| subjects affected / exposed | 1 / 115 (0.87%)   | 1 / 115 (0.87%)   |  |
| occurrences (all)           | 1                 | 1                 |  |
| Conjunctivitis              |                   |                   |  |
| subjects affected / exposed | 2 / 115 (1.74%)   | 0 / 115 (0.00%)   |  |
| occurrences (all)           | 2                 | 0                 |  |
| Eye allergy                 |                   |                   |  |
| subjects affected / exposed | 0 / 115 (0.00%)   | 1 / 115 (0.87%)   |  |
| occurrences (all)           | 0                 | 1                 |  |
| Conjunctivitis allergic     |                   |                   |  |
| subjects affected / exposed | 1 / 115 (0.87%)   | 0 / 115 (0.00%)   |  |
| occurrences (all)           | 1                 | 0                 |  |
| Eye movement disorder       |                   |                   |  |
| subjects affected / exposed | 1 / 115 (0.87%)   | 0 / 115 (0.00%)   |  |
| occurrences (all)           | 1                 | 0                 |  |
| Eyelid oedema               |                   |                   |  |
| subjects affected / exposed | 1 / 115 (0.87%)   | 0 / 115 (0.00%)   |  |
| occurrences (all)           | 1                 | 0                 |  |
| Myopia                      |                   |                   |  |
| subjects affected / exposed | 1 / 115 (0.87%)   | 0 / 115 (0.00%)   |  |
| occurrences (all)           | 1                 | 0                 |  |
| Gastrointestinal disorders  |                   |                   |  |
| Diarrhoea                   |                   |                   |  |
| subjects affected / exposed | 10 / 115 (8.70%)  | 20 / 115 (17.39%) |  |
| occurrences (all)           | 13                | 33                |  |
| Abdominal pain upper        |                   |                   |  |
| subjects affected / exposed | 13 / 115 (11.30%) | 9 / 115 (7.83%)   |  |
| occurrences (all)           | 17                | 9                 |  |
| Abdominal pain              |                   |                   |  |
| subjects affected / exposed | 5 / 115 (4.35%)   | 7 / 115 (6.09%)   |  |
| occurrences (all)           | 10                | 8                 |  |
| Abdominal discomfort        |                   |                   |  |

|                                  |                  |                 |
|----------------------------------|------------------|-----------------|
| subjects affected / exposed      | 0 / 115 (0.00%)  | 3 / 115 (2.61%) |
| occurrences (all)                | 0                | 4               |
| Constipation                     |                  |                 |
| subjects affected / exposed      | 10 / 115 (8.70%) | 3 / 115 (2.61%) |
| occurrences (all)                | 12               | 4               |
| Flatulence                       |                  |                 |
| subjects affected / exposed      | 1 / 115 (0.87%)  | 2 / 115 (1.74%) |
| occurrences (all)                | 1                | 2               |
| Abnormal faeces                  |                  |                 |
| subjects affected / exposed      | 0 / 115 (0.00%)  | 1 / 115 (0.87%) |
| occurrences (all)                | 0                | 1               |
| Breath odour                     |                  |                 |
| subjects affected / exposed      | 0 / 115 (0.00%)  | 1 / 115 (0.87%) |
| occurrences (all)                | 0                | 1               |
| Dental caries                    |                  |                 |
| subjects affected / exposed      | 0 / 115 (0.00%)  | 1 / 115 (0.87%) |
| occurrences (all)                | 0                | 2               |
| Dry mouth                        |                  |                 |
| subjects affected / exposed      | 1 / 115 (0.87%)  | 1 / 115 (0.87%) |
| occurrences (all)                | 1                | 2               |
| Dyspepsia                        |                  |                 |
| subjects affected / exposed      | 3 / 115 (2.61%)  | 1 / 115 (0.87%) |
| occurrences (all)                | 3                | 1               |
| Gastritis                        |                  |                 |
| subjects affected / exposed      | 1 / 115 (0.87%)  | 1 / 115 (0.87%) |
| occurrences (all)                | 1                | 1               |
| Gastrooesophageal reflux disease |                  |                 |
| subjects affected / exposed      | 2 / 115 (1.74%)  | 1 / 115 (0.87%) |
| occurrences (all)                | 2                | 1               |
| Haemorrhoids                     |                  |                 |
| subjects affected / exposed      | 1 / 115 (0.87%)  | 1 / 115 (0.87%) |
| occurrences (all)                | 1                | 1               |
| Anal fissure                     |                  |                 |
| subjects affected / exposed      | 1 / 115 (0.87%)  | 0 / 115 (0.00%) |
| occurrences (all)                | 1                | 0               |
| Food poisoning                   |                  |                 |

|                             |                   |                   |
|-----------------------------|-------------------|-------------------|
| subjects affected / exposed | 1 / 115 (0.87%)   | 0 / 115 (0.00%)   |
| occurrences (all)           | 1                 | 0                 |
| Haematochezia               |                   |                   |
| subjects affected / exposed | 1 / 115 (0.87%)   | 0 / 115 (0.00%)   |
| occurrences (all)           | 1                 | 0                 |
| Inguinal hernia             |                   |                   |
| subjects affected / exposed | 1 / 115 (0.87%)   | 0 / 115 (0.00%)   |
| occurrences (all)           | 1                 | 0                 |
| Irritable bowel syndrome    |                   |                   |
| subjects affected / exposed | 1 / 115 (0.87%)   | 0 / 115 (0.00%)   |
| occurrences (all)           | 1                 | 0                 |
| Vomiting                    |                   |                   |
| subjects affected / exposed | 21 / 115 (18.26%) | 26 / 115 (22.61%) |
| occurrences (all)           | 26                | 44                |
| Nausea                      |                   |                   |
| subjects affected / exposed | 7 / 115 (6.09%)   | 7 / 115 (6.09%)   |
| occurrences (all)           | 8                 | 7                 |
| Tooth crowding              |                   |                   |
| subjects affected / exposed | 0 / 115 (0.00%)   | 2 / 115 (1.74%)   |
| occurrences (all)           | 0                 | 2                 |
| Malocclusion                |                   |                   |
| subjects affected / exposed | 0 / 115 (0.00%)   | 1 / 115 (0.87%)   |
| occurrences (all)           | 0                 | 1                 |
| Odynophagia                 |                   |                   |
| subjects affected / exposed | 0 / 115 (0.00%)   | 1 / 115 (0.87%)   |
| occurrences (all)           | 0                 | 2                 |
| Oral pain                   |                   |                   |
| subjects affected / exposed | 0 / 115 (0.00%)   | 1 / 115 (0.87%)   |
| occurrences (all)           | 0                 | 1                 |
| Rectal haemorrhage          |                   |                   |
| subjects affected / exposed | 2 / 115 (1.74%)   | 0 / 115 (0.00%)   |
| occurrences (all)           | 2                 | 0                 |
| Swollen tongue              |                   |                   |
| subjects affected / exposed | 1 / 115 (0.87%)   | 0 / 115 (0.00%)   |
| occurrences (all)           | 1                 | 0                 |
| Toothache                   |                   |                   |

|   |                      |                      |  |
|---|----------------------|----------------------|--|
| subjects affected / exposed<br>occurrences (all)                              | 1 / 115 (0.87%)<br>1 | 0 / 115 (0.00%)<br>0 |  |
| Hepatobiliary disorders   |                      |                      |  |
| Hepatic function abnormal<br>subjects affected / exposed<br>occurrences (all) | 1 / 115 (0.87%)<br>1 | 0 / 115 (0.00%)<br>0 |  |
| Hepatic steatosis<br>subjects affected / exposed<br>occurrences (all)         | 1 / 115 (0.87%)<br>1 | 0 / 115 (0.00%)<br>0 |  |
| Skin and subcutaneous tissue disorders  |                      |                      |  |
| Blister<br>subjects affected / exposed<br>occurrences (all)                   | 0 / 115 (0.00%)<br>0 | 1 / 115 (0.87%)<br>1 |  |
| Acne<br>subjects affected / exposed<br>occurrences (all)                      | 1 / 115 (0.87%)<br>1 | 0 / 115 (0.00%)<br>0 |  |
| Dermatitis allergic<br>subjects affected / exposed<br>occurrences (all)       | 1 / 115 (0.87%)<br>1 | 0 / 115 (0.00%)<br>0 |  |
| Rash<br>subjects affected / exposed<br>occurrences (all)                      | 4 / 115 (3.48%)<br>5 | 4 / 115 (3.48%)<br>6 |  |
| Ingrowing nail<br>subjects affected / exposed<br>occurrences (all)            | 0 / 115 (0.00%)<br>0 | 2 / 115 (1.74%)<br>2 |  |
| Pruritus<br>subjects affected / exposed<br>occurrences (all)                  | 2 / 115 (1.74%)<br>2 | 2 / 115 (1.74%)<br>2 |  |
| Rash erythematous<br>subjects affected / exposed<br>occurrences (all)         | 1 / 115 (0.87%)<br>1 | 2 / 115 (1.74%)<br>2 |  |
| Dry skin<br>subjects affected / exposed<br>occurrences (all)                  | 0 / 115 (0.00%)<br>0 | 1 / 115 (0.87%)<br>1 |  |
| Ecchymosis  |                      |                      |  |

|                             |                 |                 |  |
|-----------------------------|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 115 (0.00%) | 1 / 115 (0.87%) |  |
| occurrences (all)           | 0               | 1               |  |
| Hair texture abnormal       |                 |                 |  |
| subjects affected / exposed | 0 / 115 (0.00%) | 1 / 115 (0.87%) |  |
| occurrences (all)           | 0               | 1               |  |
| Hirsutism                   |                 |                 |  |
| subjects affected / exposed | 0 / 115 (0.00%) | 1 / 115 (0.87%) |  |
| occurrences (all)           | 0               | 1               |  |
| Seborrhoeic dermatitis      |                 |                 |  |
| subjects affected / exposed | 0 / 115 (0.00%) | 1 / 115 (0.87%) |  |
| occurrences (all)           | 0               | 1               |  |
| Skin burning sensation      |                 |                 |  |
| subjects affected / exposed | 0 / 115 (0.00%) | 1 / 115 (0.87%) |  |
| occurrences (all)           | 0               | 1               |  |
| Skin lesion                 |                 |                 |  |
| subjects affected / exposed | 0 / 115 (0.00%) | 1 / 115 (0.87%) |  |
| occurrences (all)           | 0               | 1               |  |
| Skin mass                   |                 |                 |  |
| subjects affected / exposed | 0 / 115 (0.00%) | 1 / 115 (0.87%) |  |
| occurrences (all)           | 0               | 1               |  |
| Erythema                    |                 |                 |  |
| subjects affected / exposed | 1 / 115 (0.87%) | 0 / 115 (0.00%) |  |
| occurrences (all)           | 1               | 0               |  |
| Skin exfoliation            |                 |                 |  |
| subjects affected / exposed | 1 / 115 (0.87%) | 0 / 115 (0.00%) |  |
| occurrences (all)           | 1               | 0               |  |
| Skin hyperpigmentation      |                 |                 |  |
| subjects affected / exposed | 1 / 115 (0.87%) | 0 / 115 (0.00%) |  |
| occurrences (all)           | 1               | 0               |  |
| Renal and urinary disorders |                 |                 |  |
| Haematuria                  |                 |                 |  |
| subjects affected / exposed | 1 / 115 (0.87%) | 7 / 115 (6.09%) |  |
| occurrences (all)           | 1               | 7               |  |
| Dysuria                     |                 |                 |  |
| subjects affected / exposed | 3 / 115 (2.61%) | 2 / 115 (1.74%) |  |
| occurrences (all)           | 3               | 4               |  |



|                             |                 |                 |  |
|-----------------------------|-----------------|-----------------|--|
| Bladder trabeculation       |                 |                 |  |
| subjects affected / exposed | 0 / 115 (0.00%) | 1 / 115 (0.87%) |  |
| occurrences (all)           | 0               | 1               |  |
| Enuresis                    |                 |                 |  |
| subjects affected / exposed | 1 / 115 (0.87%) | 2 / 115 (1.74%) |  |
| occurrences (all)           | 1               | 4               |  |
| Flank pain                  |                 |                 |  |
| subjects affected / exposed | 0 / 115 (0.00%) | 1 / 115 (0.87%) |  |
| occurrences (all)           | 0               | 1               |  |
| Hypercalciuria              |                 |                 |  |
| subjects affected / exposed | 1 / 115 (0.87%) | 0 / 115 (0.00%) |  |
| occurrences (all)           | 1               | 0               |  |
| Myoglobinuria               |                 |                 |  |
| subjects affected / exposed | 1 / 115 (0.87%) | 0 / 115 (0.00%) |  |
| occurrences (all)           | 1               | 0               |  |
| Nephrolithiasis             |                 |                 |  |
| subjects affected / exposed | 2 / 115 (1.74%) | 0 / 115 (0.00%) |  |
| occurrences (all)           | 2               | 0               |  |
| Urinary incontinence        |                 |                 |  |
| subjects affected / exposed | 1 / 115 (0.87%) | 2 / 115 (1.74%) |  |
| occurrences (all)           | 1               | 2               |  |
| Polyuria                    |                 |                 |  |
| subjects affected / exposed | 0 / 115 (0.00%) | 1 / 115 (0.87%) |  |
| occurrences (all)           | 0               | 1               |  |
| Urine abnormality           |                 |                 |  |
| subjects affected / exposed | 2 / 115 (1.74%) | 1 / 115 (0.87%) |  |
| occurrences (all)           | 5               | 2               |  |
| Renal cyst                  |                 |                 |  |
| subjects affected / exposed | 0 / 115 (0.00%) | 1 / 115 (0.87%) |  |
| occurrences (all)           | 0               | 1               |  |
| Pollakiuria                 |                 |                 |  |
| subjects affected / exposed | 1 / 115 (0.87%) | 0 / 115 (0.00%) |  |
| occurrences (all)           | 1               | 0               |  |
| Endocrine disorders         |                 |                 |  |
| Hypothyroidism              |                 |                 |  |

|   |                   |                  |  |
|---|-------------------|------------------|--|
| subjects affected / exposed                     | 0 / 115 (0.00%)   | 1 / 115 (0.87%)  |  |
| occurrences (all)                               | 0                 | 1                |  |
| Hyperaldosteronism                              |                   |                  |  |
| subjects affected / exposed                     | 1 / 115 (0.87%)   | 0 / 115 (0.00%)  |  |
| occurrences (all)                               | 1                 | 0                |  |
| Musculoskeletal and connective tissue disorders |                   |                  |  |
| Back pain                                       |                   |                  |  |
| subjects affected / exposed                     | 8 / 115 (6.96%)   | 11 / 115 (9.57%) |  |
| occurrences (all)                               | 8                 | 15               |  |
| Arthralgia                                      |                   |                  |  |
| subjects affected / exposed                     | 5 / 115 (4.35%)   | 6 / 115 (5.22%)  |  |
| occurrences (all)                               | 5                 | 7                |  |
| Foot deformity                                  |                   |                  |  |
| subjects affected / exposed                     | 2 / 115 (1.74%)   | 3 / 115 (2.61%)  |  |
| occurrences (all)                               | 3                 | 3                |  |
| Growing pains                                   |                   |                  |  |
| subjects affected / exposed                     | 0 / 115 (0.00%)   | 1 / 115 (0.87%)  |  |
| occurrences (all)                               | 0                 | 1                |  |
| Bone pain                                       |                   |                  |  |
| subjects affected / exposed                     | 2 / 115 (1.74%)   | 0 / 115 (0.00%)  |  |
| occurrences (all)                               | 2                 | 0                |  |
| Pain in extremity                               |                   |                  |  |
| subjects affected / exposed                     | 14 / 115 (12.17%) | 10 / 115 (8.70%) |  |
| occurrences (all)                               | 17                | 12               |  |
| Myalgia   |                   |                  |  |
| subjects affected / exposed                     | 0 / 115 (0.00%)   | 3 / 115 (2.61%)  |  |
| occurrences (all)                               | 0                 | 4                |  |
| Musculoskeletal chest pain                      |                   |                  |  |
| subjects affected / exposed                     | 2 / 115 (1.74%)   | 2 / 115 (1.74%)  |  |
| occurrences (all)                               | 2                 | 3                |  |
| Musculoskeletal pain                            |                   |                  |  |
| subjects affected / exposed                     | 2 / 115 (1.74%)   | 2 / 115 (1.74%)  |  |
| occurrences (all)                               | 2                 | 2                |  |
| Joint contracture                               |                   |                  |  |

|                             |                 |                 |  |
|-----------------------------|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 115 (0.00%) | 1 / 115 (0.87%) |  |
| occurrences (all)           | 0               | 1               |  |
| Muscle atrophy              |                 |                 |  |
| subjects affected / exposed | 0 / 115 (0.00%) | 1 / 115 (0.87%) |  |
| occurrences (all)           | 0               | 1               |  |
| Muscle tightness            |                 |                 |  |
| subjects affected / exposed | 0 / 115 (0.00%) | 1 / 115 (0.87%) |  |
| occurrences (all)           | 0               | 1               |  |
| Muscular weakness           |                 |                 |  |
| subjects affected / exposed | 1 / 115 (0.87%) | 1 / 115 (0.87%) |  |
| occurrences (all)           | 1               | 1               |  |
| Osteoporosis                |                 |                 |  |
| subjects affected / exposed | 0 / 115 (0.00%) | 1 / 115 (0.87%) |  |
| occurrences (all)           | 0               | 1               |  |
| Scoliosis                   |                 |                 |  |
| subjects affected / exposed | 2 / 115 (1.74%) | 1 / 115 (0.87%) |  |
| occurrences (all)           | 2               | 1               |  |
| Tendinous contracture       |                 |                 |  |
| subjects affected / exposed | 0 / 115 (0.00%) | 1 / 115 (0.87%) |  |
| occurrences (all)           | 0               | 1               |  |
| Joint crepitation           |                 |                 |  |
| subjects affected / exposed | 1 / 115 (0.87%) | 0 / 115 (0.00%) |  |
| occurrences (all)           | 1               | 0               |  |
| Lordosis                    |                 |                 |  |
| subjects affected / exposed | 1 / 115 (0.87%) | 0 / 115 (0.00%) |  |
| occurrences (all)           | 1               | 0               |  |
| Muscle spasms               |                 |                 |  |
| subjects affected / exposed | 1 / 115 (0.87%) | 0 / 115 (0.00%) |  |
| occurrences (all)           | 1               | 0               |  |
| Osteopenia                  |                 |                 |  |
| subjects affected / exposed | 2 / 115 (1.74%) | 0 / 115 (0.00%) |  |
| occurrences (all)           | 2               | 0               |  |
| Infections and infestations |                 |                 |  |
| Ear infection               |                 |                 |  |
| subjects affected / exposed | 1 / 115 (0.87%) | 6 / 115 (5.22%) |  |
| occurrences (all)           | 1               | 8               |  |

|                                   |                 |                 |
|-----------------------------------|-----------------|-----------------|
| Gastroenteritis                   |                 |                 |
| subjects affected / exposed       | 4 / 115 (3.48%) | 5 / 115 (4.35%) |
| occurrences (all)                 | 4               | 7               |
| Influenza                         |                 |                 |
| subjects affected / exposed       | 5 / 115 (4.35%) | 3 / 115 (2.61%) |
| occurrences (all)                 | 8               | 4               |
| Bronchitis                        |                 |                 |
| subjects affected / exposed       | 3 / 115 (2.61%) | 2 / 115 (1.74%) |
| occurrences (all)                 | 3               | 2               |
| Conjunctivitis infective          |                 |                 |
| subjects affected / exposed       | 0 / 115 (0.00%) | 2 / 115 (1.74%) |
| occurrences (all)                 | 0               | 2               |
| Fungal skin infection             |                 |                 |
| subjects affected / exposed       | 1 / 115 (0.87%) | 2 / 115 (1.74%) |
| occurrences (all)                 | 1               | 4               |
| Gastroenteritis viral             |                 |                 |
| subjects affected / exposed       | 0 / 115 (0.00%) | 2 / 115 (1.74%) |
| occurrences (all)                 | 0               | 2               |
| Gastrointestinal viral infection  |                 |                 |
| subjects affected / exposed       | 0 / 115 (0.00%) | 2 / 115 (1.74%) |
| occurrences (all)                 | 0               | 3               |
| Hordeolum                         |                 |                 |
| subjects affected / exposed       | 3 / 115 (2.61%) | 2 / 115 (1.74%) |
| occurrences (all)                 | 3               | 3               |
| Eye infection                     |                 |                 |
| subjects affected / exposed       | 1 / 115 (0.87%) | 1 / 115 (0.87%) |
| occurrences (all)                 | 1               | 1               |
| Gingivitis                        |                 |                 |
| subjects affected / exposed       | 0 / 115 (0.00%) | 1 / 115 (0.87%) |
| occurrences (all)                 | 0               | 2               |
| Herpes simplex                    |                 |                 |
| subjects affected / exposed       | 0 / 115 (0.00%) | 1 / 115 (0.87%) |
| occurrences (all)                 | 0               | 2               |
| Lower respiratory tract infection |                 |                 |
| subjects affected / exposed       | 4 / 115 (3.48%) | 1 / 115 (0.87%) |
| occurrences (all)                 | 4               | 2               |

|                                   |                   |                   |
|-----------------------------------|-------------------|-------------------|
| Lung infection                    |                   |                   |
| subjects affected / exposed       | 0 / 115 (0.00%)   | 1 / 115 (0.87%)   |
| occurrences (all)                 | 0                 | 1                 |
| Acute tonsillitis                 |                   |                   |
| subjects affected / exposed       | 1 / 115 (0.87%)   | 0 / 115 (0.00%)   |
| occurrences (all)                 | 1                 | 0                 |
| Adenoiditis                       |                   |                   |
| subjects affected / exposed       | 1 / 115 (0.87%)   | 0 / 115 (0.00%)   |
| occurrences (all)                 | 1                 | 0                 |
| Gastrointestinal infection        |                   |                   |
| subjects affected / exposed       | 2 / 115 (1.74%)   | 0 / 115 (0.00%)   |
| occurrences (all)                 | 2                 | 0                 |
| Gingival infection                |                   |                   |
| subjects affected / exposed       | 1 / 115 (0.87%)   | 0 / 115 (0.00%)   |
| occurrences (all)                 | 1                 | 0                 |
| Helminthic infection              |                   |                   |
| subjects affected / exposed       | 1 / 115 (0.87%)   | 0 / 115 (0.00%)   |
| occurrences (all)                 | 1                 | 0                 |
| Infected bites                    |                   |                   |
| subjects affected / exposed       | 1 / 115 (0.87%)   | 0 / 115 (0.00%)   |
| occurrences (all)                 | 1                 | 0                 |
| Nasopharyngitis                   |                   |                   |
| subjects affected / exposed       | 22 / 115 (19.13%) | 24 / 115 (20.87%) |
| occurrences (all)                 | 33                | 43                |
| Upper respiratory tract infection |                   |                   |
| subjects affected / exposed       | 6 / 115 (5.22%)   | 11 / 115 (9.57%)  |
| occurrences (all)                 | 11                | 16                |
| Rhinitis                          |                   |                   |
| subjects affected / exposed       | 4 / 115 (3.48%)   | 8 / 115 (6.96%)   |
| occurrences (all)                 | 4                 | 13                |
| Pharyngitis                       |                   |                   |
| subjects affected / exposed       | 4 / 115 (3.48%)   | 4 / 115 (3.48%)   |
| occurrences (all)                 | 5                 | 4                 |
| Tonsillitis                       |                   |                   |
| subjects affected / exposed       | 2 / 115 (1.74%)   | 3 / 115 (2.61%)   |
| occurrences (all)                 | 3                 | 3                 |

|                             |                 |                 |
|-----------------------------|-----------------|-----------------|
| Sinusitis                   |                 |                 |
| subjects affected / exposed | 2 / 115 (1.74%) | 5 / 115 (4.35%) |
| occurrences (all)           | 2               | 6               |
| Viral infection             |                 |                 |
| subjects affected / exposed | 3 / 115 (2.61%) | 3 / 115 (2.61%) |
| occurrences (all)           | 3               | 3               |
| Nail infection              |                 |                 |
| subjects affected / exposed | 0 / 115 (0.00%) | 2 / 115 (1.74%) |
| occurrences (all)           | 0               | 3               |
| Respiratory tract infection |                 |                 |
| subjects affected / exposed | 1 / 115 (0.87%) | 2 / 115 (1.74%) |
| occurrences (all)           | 1               | 2               |
| Pneumonia                   |                 |                 |
| subjects affected / exposed | 0 / 115 (0.00%) | 2 / 115 (1.74%) |
| occurrences (all)           | 0               | 2               |
| Otitis externa              |                 |                 |
| subjects affected / exposed | 0 / 115 (0.00%) | 1 / 115 (0.87%) |
| occurrences (all)           | 0               | 1               |
| Otitis media                |                 |                 |
| subjects affected / exposed | 2 / 115 (1.74%) | 1 / 115 (0.87%) |
| occurrences (all)           | 3               | 1               |
| Parasitic gastroenteritis   |                 |                 |
| subjects affected / exposed | 0 / 115 (0.00%) | 1 / 115 (0.87%) |
| occurrences (all)           | 0               | 1               |
| Skin infection              |                 |                 |
| subjects affected / exposed | 1 / 115 (0.87%) | 1 / 115 (0.87%) |
| occurrences (all)           | 1               | 1               |
| Mycoplasma infection        |                 |                 |
| subjects affected / exposed | 1 / 115 (0.87%) | 0 / 115 (0.00%) |
| occurrences (all)           | 1               | 0               |
| Oral candidiasis            |                 |                 |
| subjects affected / exposed | 1 / 115 (0.87%) | 0 / 115 (0.00%) |
| occurrences (all)           | 1               | 0               |
| Oral herpes                 |                 |                 |
| subjects affected / exposed | 1 / 115 (0.87%) | 0 / 115 (0.00%) |
| occurrences (all)           | 1               | 0               |

|   |                      |                      |  |
|---|----------------------|----------------------|--|
| Pharyngitis streptococcal<br>subjects affected / exposed<br>occurrences (all) | 1 / 115 (0.87%)<br>1 | 0 / 115 (0.00%)<br>0 |  |
| Rubella<br>subjects affected / exposed<br>occurrences (all)                   | 1 / 115 (0.87%)<br>1 | 0 / 115 (0.00%)<br>0 |  |
| Tracheitis<br>subjects affected / exposed<br>occurrences (all)                | 1 / 115 (0.87%)<br>1 | 0 / 115 (0.00%)<br>0 |  |
| Urinary tract infection<br>subjects affected / exposed<br>occurrences (all)   | 2 / 115 (1.74%)<br>2 | 0 / 115 (0.00%)<br>0 |  |
| Metabolism and nutrition disorders  |                      |                      |  |
| Hypertriglyceridaemia<br>subjects affected / exposed<br>occurrences (all)     | 3 / 115 (2.61%)<br>3 | 5 / 115 (4.35%)<br>5 |  |
| Decreased appetite<br>subjects affected / exposed<br>occurrences (all)        | 2 / 115 (1.74%)<br>2 | 3 / 115 (2.61%)<br>3 |  |
| Electrolyte imbalance<br>subjects affected / exposed<br>occurrences (all)     | 1 / 115 (0.87%)<br>1 | 2 / 115 (1.74%)<br>2 |  |
| Vitamin D deficiency<br>subjects affected / exposed<br>occurrences (all)      | 0 / 115 (0.00%)<br>0 | 2 / 115 (1.74%)<br>2 |  |
| Abnormal weight gain<br>subjects affected / exposed<br>occurrences (all)      | 1 / 115 (0.87%)<br>1 | 1 / 115 (0.87%)<br>1 |  |
| Dyslipidaemia<br>subjects affected / exposed<br>occurrences (all)             | 0 / 115 (0.00%)<br>0 | 1 / 115 (0.87%)<br>1 |  |
| Fluid retention<br>subjects affected / exposed<br>occurrences (all)           | 0 / 115 (0.00%)<br>0 | 1 / 115 (0.87%)<br>3 |  |
| Hypercholesterolaemia   |                      |                      |  |

|                             |                 |                 |
|-----------------------------|-----------------|-----------------|
| subjects affected / exposed | 2 / 115 (1.74%) | 1 / 115 (0.87%) |
| occurrences (all)           | 2               | 1               |
| Hyperlipidaemia             |                 |                 |
| subjects affected / exposed | 1 / 115 (0.87%) | 1 / 115 (0.87%) |
| occurrences (all)           | 1               | 1               |
| Iron deficiency             |                 |                 |
| subjects affected / exposed | 0 / 115 (0.00%) | 1 / 115 (0.87%) |
| occurrences (all)           | 0               | 1               |
| Hyperglycaemia              |                 |                 |
| subjects affected / exposed | 1 / 115 (0.87%) | 0 / 115 (0.00%) |
| occurrences (all)           | 1               | 0               |
| Hyperkalaemia               |                 |                 |
| subjects affected / exposed | 1 / 115 (0.87%) | 0 / 115 (0.00%) |
| occurrences (all)           | 1               | 0               |
| Hyperuricaemia              |                 |                 |
| subjects affected / exposed | 2 / 115 (1.74%) | 0 / 115 (0.00%) |
| occurrences (all)           | 2               | 0               |
| Hypervitaminosis D          |                 |                 |
| subjects affected / exposed | 1 / 115 (0.87%) | 0 / 115 (0.00%) |
| occurrences (all)           | 1               | 0               |
| Hypoglycaemia               |                 |                 |
| subjects affected / exposed | 1 / 115 (0.87%) | 0 / 115 (0.00%) |
| occurrences (all)           | 1               | 0               |
| Hyponatraemia               |                 |                 |
| subjects affected / exposed | 1 / 115 (0.87%) | 0 / 115 (0.00%) |
| occurrences (all)           | 1               | 0               |
| Increased appetite          |                 |                 |
| subjects affected / exposed | 1 / 115 (0.87%) | 0 / 115 (0.00%) |
| occurrences (all)           | 1               | 0               |
| Metabolic acidosis          |                 |                 |
| subjects affected / exposed | 1 / 115 (0.87%) | 0 / 115 (0.00%) |
| occurrences (all)           | 1               | 0               |



## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date          | Amendment   |
|---------------|---|
| 13 June 2013  | The changes implemented with this amendment are: - Incorporated feedback from the European Medicines Agency (EMA) related to the non-allowance of protocol waivers; - Added the timed test of rising from supine to stand; - Amended the criteria for withdrawal of a participant from the study due to the participant's condition substantially worsening after initiating study drug to include worsening of cardiac events such as QTc interval limits, new evidence of symptomatic cardiomyopathy, and significant decrease in left ventricular ejection fraction; - Deleted any requirement that there be any discussion between the investigator and the PTC Therapeutics medical monitor before unblinding a participant; Added information regarding benefits and risks of study participation.  |
| 04 March 2014 | The changes implemented with this amendment are: - Updated information regarding ongoing ataluren studies; - Clarified inclusion criterion related to documentation of gene sequencing; - Clarified inclusion criterion related to no more than 20% change from screening to baseline 6MWD; - Updated the approximate number of investigator sites participating in study; - Updated the requirement for collection of date of birth for Screening; - Updated the actions to be taken in event of urine blood abnormalities; - Added information regarding renal abnormalities related to aminoglycosides; - Updated information regarding drugs metabolized by cytochrome P450 enzymes; - Updated information regarding potential drug interactions; - Updated schedule of events to clarify the timing of events such as randomization, study drug administration in clinic, study drug dispensing, and the Visit 2, Day 2 6MWT; - Updated the recommended sequence of study procedures at Visit 2 to 8, by updating sequence of events and timing of randomization; - Clarified the timing of randomization of a participant at Visit 2, Day 2; - Clarified End-of-Treatment Visit procedures for participants who discontinue prematurely; - Clarified Post-Treatment Visits procedures; - Added information regarding videotaping of the 6MWT, timed function tests, and NSAA; - Clarified the schedule for administration of Activities of Daily Living/Disease Symptom Survey at baseline; - Updated the blood volumes for the required blood draws; - Added information regarding blood pressure assessment; - Summarized information regarding tumor findings in rat studies as already included in the Ataluren Investigator Brochure; - Deleted any mention of forfeiture of participation in the open-label extension study for breaking the blind of the study; - Added information regarding benefits and risks of study participation. |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported