EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Translarna

International non-proprietary name: ataluren

Procedure No. EMEA/H/C/002720/II/0049

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Background information on the procedure

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, PTC Therapeutics International Limited submitted to the European Medicines Agency on 16 November 2018 an application for a variation.

The following changes were proposed:

Variation requested		Type	Annexes affected
C.I.13	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	Type II	None

Submission of the final CSR for study PTC124-GD-030-DMD (Study 030) listed as a category 3 study in the RMP. This is a phase 2 Study of the safety, pharmacokinetics, and pharmacodynamics of ataluren in patients aged ≥2 to <5 years with nonsense mutation dystrophinopathy (nmDMD).

This submission is also made in accordance with the requirements of the Article 46 of the Paediatric Regulation.

The requested variation proposed no amendments to the Product Information.

2. Overall conclusion and impact on the benefit/risk balance

The applicant proposes no amendments to the SmPC based on the results from Study 030.

The interim report for this study, Study 030, was submitted in support of the extension of the indication to include nmDMD patients ranging 2-5 years of age. This was during procedure EMEA/H/C/002720/II/0037. In brief the study was a 4 week PK study, with an extension to 52 weeks, and an interim analysis at 28 weeks. The efficacy data comprised 28 week and 52 week assessment of the TFT and NSAA. The safety data contained reported adverse events and measured laboratory findings during the course of the study. There was no control arm included in the study. For the 28 week interim report the applicant submitted comparison to the historical data set CINRG.

The 28 week data provided were considered not robust on their own, as there are too many factors which influence the interpretation and question the effect size and clinical relevance. However, the preliminary short term safety data seems in line with ≥5 years of age nmDMD patients. The reported adverse events in nmDMD patients 2-5 years of age were also in line with the patients aged ≥5 years of age and childhood illnesses. Moreover, from a treatment perspective, treatment should be initiated as early as possible. As the plasma concentration levels between the two groups, i.e. patients ≥2 to <5 years of age and those ≥5 years of age, were comparable, a similar efficacy and safety profile could be assumed. This was already incorporated in the SmPC.

For the 52 week assessment, no comparative data to historical data set is provided. Therefore, the previous conclusion remains, e.g. no conclusion can be drawn on the submitted data. However, based on comparable plasma levels and safety profile, also a comparable efficacy is anticipated. Thus, the benefit-risk balance of ataluren, remains positive.

Ataluren is currently approved under conditional MA. The applicant is conducting a confirmatory safety and efficacy study in nmDMD patients aged >5 years of age, study 041. To confirm the long term efficacy and safety in nmDMD patients aged 2-5 years of age, data will be collected in study 025o, an open label long term safety study.

3. Recommendations

Based on the review of the submitted data, this application regarding the following change:

Variation accepted		Type	Annexes affected
C.I.13	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	Type II	None

Submission of the final CSR for study PTC124-GD-030-DMD (Study 030) listed as a category 3 study in the RMP. This is a phase 2 Study of the safety, pharmacokinetics, and pharmacodynamics of ataluren in patients aged ≥2 to <5 years with nonsense mutation dystrophinopathy (nmDMD).

This submission is also made in accordance with the requirements of the Article 46 of the Paediatric Regulation.

☒ is recommended for approval.

Amendments to the marketing authorisation

The variation leads to no amendments to the terms of the Community Marketing Authorisation. The MAH already committed to include patients aged ≥2 to <5 years of age in the long term observation study, Study 025o. This study includes both long term safety and long term efficacy assessments.

4. Introduction

Ataluren (Translarna™) is indicated for the treatment of Duchenne muscular dystrophy (DMD) resulting from a nonsense mutation in the dystrophin gene (nmDMD), in ambulatory patients aged ≥2 years.

Ataluren was granted a conditional market authorization in 2014 for ambulatory nmDMD patients aged ≥ 5 years of age.

In July 2018 the CHMP approved the extension to include patients aged ≥2 to <5 years of age during the procedure EMEA/H/C/002720/II/037. The data package included up to 28 week data of the current, study 030.

The MAH has now completed study 030 and in line with the PIP requirements has submitted the study results of a 52-week treatment period.

5. Clinical Pharmacology aspects

No new PK data was submitted by the applicant.

The PK data was assessed during the request for extension to include patients aged ≥2 to <5 years of age during the procedure EMEA/H/C/002720/II/037.

6. Clinical Efficacy aspects

6.1. Study design / method

Study 030 was a Phase 2, multiple-dose, open-label study evaluating the safety, PK, and pharmacodynamics (PD) of ataluren in subjects aged ≥2 to <5 years old with nmDMD. This study included a 4-week screening period, a 52-week treatment period (the first 4 weeks of which included PK parameters), and a 4-week follow-up period for subjects who completed the treatment period (60 weeks total duration) (see Table 1). The objective of the extension period (treatment period after PK parameters have been completed) was to assess the long-term safety of chronic administration of ataluren in this patient population. The study report contains all efficacy, safety, and PK data.

Dosing based on body weight was employed. Such dosing is common in pediatrics and reduces potential variability in exposure by accommodating differences in patient size across the span of ages of the patients who participated in the clinical study.

Table 1: Schedule of Events

	Screening	Ataluren Treatment						4-Week Follow-Up
Day (±2)	**-28**	**1[a]**	**28**	**112**	**196**	**280**	**364**	**392**
Weeks	**-4**	**0**	**4**	**16**	**28**	**40**	**52/ET[b]**	**56**
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Informed consent	X							
Clinical and medication history	X							
Vital signs	X	X	X	X	X	X	X	X
Height	X	X	X	X	X	X	X	X
Weight	X	X	X	X	X	X	X	X
Physical examination	X	As clinically indicated						X
Hematology	X	X	X	X	X	X	X	X
Blood sample for gene sequencing[c]	X							
Biochemistry[d]	X	X	X	X	X	X	X	X
Urinalysis	X	X	X	X	X	X	X	X
12-lead ECG	X		X				X	X
Timed function tests		X			X		X	
North Star Ambulatory Assessment		X			X		X	
Blood for ataluren PK[e]		X	X					
Palatability questionnaire			X					
Drug administration		X----------X						
Adverse events		X----------X						
Concomitant medications	X----------X							
Non-DMD-related adverse events								X

a All study and laboratory assessments on the first day of treatment were done prior to ataluren dosing.
b Subjects who terminated the study early were to complete all assessments required for Week 52/ET (Visit 7) and were required to return 4 weeks from the final dose of study medication for the 4-Week Follow-up Visit.
c Verification that a blood sample had been drawn for sequencing of the dystrophin gene. A subject who had written documentation of a nonsense mutation as the cause of DMD needed not wait for confirmatory results to start study drug as long as the confirmatory blood sample for gene sequencing was drawn.
d Biochemistry laboratory assessments included hepatic transaminases and additional parameters (Appendix 16.2.8.5)
e On Days 1 and 28, blood samples for PK assessment were drawn pre-dose and 1 (±15 min), 2 (±15 min), 4 (±30 min), 6 (±30 min), 8 (±30 min), and 10 (±30 min) hours post-dose.
Abbreviations: ECG = electrocardiogram, ET = early termination, PK = pharmacokinetic

6.2. Results

6.2.1. Demographics

All subjects who received at least 1 dose of ataluren were included in the analyses of safety.
The results from this study are presented using 4 populations (Table 2):
Enrolled Subjects: All subjects who were successfully screened and enrolled into the study.
Safety Population: All subjects who received at least 1 dose of ataluren. The safety population was used for the safety summary.
PK Population: All subjects who received at least 1 dose of ataluren and had at least 1 PK concentration datum. The PK population was used for PK analyses.
Evaluable Population: All subjects who received at least 1 dose of ataluren and had baseline and at least 1 post-baseline measurement for TFTs, NSAA, or response to the *palatability of ataluren* questions. The evaluable population was used for the efficacy analyses.

Table 2: Subject disposition

Characteristic Category	All Subjects [1]
Subjects Screened	14
Screen Failures	0
Enrolled Subjects	14
Safety Population	14 (100.0%)
PK Population	14 (100.0%)
Evaluable Population	14 (100.0%)
Final Study Disposition by Study Phase	
Completed the PK Phase	14 (100.0%)
Completed the Extension Phase	14 (100.0%)
Completed the Study	14 (100.0%)
Discontinued from the Study	0 (0.0%)

A summary of demographic data is provided in Table 3. The mean age of subjects was 3.4 years, ranging from 2 to 4. All of the subjects were male. Six (42.9%) of the subjects were taking corticosteroids at baseline.

All of the subjects reported taking concomitant medication during the study. Overall, the most common concomitant medications were taken for the alimentary tract and metabolism (12 subjects [85.7%]), including vitamins and supplements, ondansetron, simethicone, and macrogol. Nine (64.3%) subjects took ibuprofen and 7 (50%) took paracetamol at some point during the study. Systemic antiinfectives were taken by 8 subjects (57.1%) and systemic corticosteroids were taken by 7 (50%) subjects. Drugs for the respiratory system were used by 7 (50%) subjects and included salbutamol, brompheniramine, cetirizine hydrochloride, cyproheptadine, fluticasone propionate, and montelukast sodium. In addition, 1 subject was given IV heparin for prophylaxis and another subject was given batroxobin for a pre-existing indication.

Table 3: Demographics and Baseline Characteristics (Safety Analysis population*)

Characteristic Statistic / Category	All Subjects (N=14)
Gender	
Male	14 (100.0%)
Age (years)	
n	14
Mean	3.4
Standard Deviation	0.76
Median	4.0
Minimum, Maximum	2, 4
Race/Ethnicity	
Asian	3 (21.4%)
White	11 (78.6%)
Hispanic or Latino	3 (21.4%)
Not Hispanic or Latino	11 (78.6%)
Baseline Height (cm)	
n	14
Mean	99.43
Standard Deviation	5.28
Median	98.55
Minimum, Maximum	88.8, 108.0
Baseline Weight (kg)	
n	14
Mean	16.99
Standard Deviation	3.26
Median	16.40
Minimum, Maximum	13.2, 25.2
Baseline BMI (kg/m^2)	
n	14
Mean	17.09
Standard deviation	2.22
Median	16.64
Minimum, Maximum	14.78, 22.94
Corticosteroids	
Subjects on Corticosteroids at Baseline	6 (42.9%)
Deflazacort	3 (21.4%)
Prednisone	2 (14.3%)
Prednisolone Sodium Phosphate	1 (7.1%)

Source: Appendix 16.2.4.1 and Section 14.1 Table 14.1.3

6.2.2. Palatability characteristics

Table 11-7 provides a summary of the palatability characteristics of ataluren. Ten (71.5%) of the respondents either agreed or strongly agreed that the medication was pleasant based on the child's reaction, while 2 (14.3%) disagreed. Only 2 (14.3%) respondents reported having problems giving the medication to the child. The question regarding the taste of the medicine was designed to be answered by the subject or the caregiver (if the subject was not able to assess or formalize a response).

Table 4: Summary of Palatability Characteristics at Visit 3 (Evaluable population)

Question Response	All Subjects (N=14)
How did the medicine taste?	
No Response	12 (85.7%)
Neither Agree nor Disagree	2 (14.3%)
On the basis of reaction / facial expression of your child, do you think that the medication is pleasant?	
Disagree	2 (14.3%)
Neither Agree nor Disagree	2 (14.3%)
Agree	6 (42.9%)
Strongly Agree	4 (28.6%)
You sometimes have problems in giving the medication to your child because he/she refuses to take it or throws it up.	
Strongly Disagree	5 (35.7%)
Disagree	7 (50.0%)
Agree	2 (14.3%)

Source: Appendix 16.2.6.3 and Section 14.2 Table 14.2.3

CHMP Comments

Generally, the patients agreed with the flavour of ataluren. Two patients (14.3%) did not agree with the flavour, which hampered the administration of ataluren as can be anticipated.

6.2.3. Time function test

A summary of Timed Function Test results by visit is provided in Table 5,Table 6,Table 7 and

Table 8, for each parameter assessed. Individual results are provided. All assessments showed overall improvements from baseline. The mean (SD) time taken to descend 4 standard stairs decreased by 7.17 (26.433) percent and 24.22 (28.322) percent at Week 28 (Visit 5) and Week 52 (Visit 7), respectively. A similar trend was seen for the stair climbing test, which demonstrated mean (SD) improvements of 9.10 (29.630) percent and 23.36 (26.249) percent at Week 28 and Week 52, respectively. Improvements in the stand from supine position assessment were similar at Week 28 and Week 52. The ten meter run/walk assessment showed mean (SD) improvements of 8.35 (22.778) percent at Week 28 and 14.54 (14.862) percent at Week 52.

Table 5: Summary of Timed Function Test by Visit (Evaluable Population) - Descend four standard stairs (sec)

Parameter (unit) Time Point Statistic	All Subjects (N=14) Baseline	Post-Baseline Time Point	Change from Baseline	Percent Change from Baseline
DESCEND FOUR STANDARD STAIRS (SEC)				
BASELINE				
n	13			
Mean	7.5			
Standard Deviation	3.95			
Median	6.0			
Minimum, Maximum	3, 16			
95% Confidence Interval	(5.1, 9.8)			
WEEK 28 (VISIT 5)				
n	12	12	12	12
Mean	7.1	6.5	-0.6	-7.17
Standard Deviation	3.87	3.85	1.93	26.433
Median	6.0	5.0	-1.0	-16.25
Minimum, Maximum	3, 16	3, 14	-3, 4	-40.0, 44.4
95% Confidence Interval	(4.6, 9.5)	(4.1, 8.9)	(-1.8, 0.6)	(-23.96, 9.63)
WEEK 52 (VISIT 7/ET)				
n	13	13	13	13
Mean	7.5	5.3	-2.2	-24.22
Standard Deviation	3.95	3.40	2.58	28.322
Median	6.0	4.0	-2.0	-28.57
Minimum, Maximum	3, 16	3, 15	-7, 1	-66.7, 33.3
95% Confidence Interval	(5.1, 9.8)	(3.3, 7.4)	(-3.7, -0.6)	(-41.33, -7.10)

Table 6: Summary of Timed Function Test by Visit (Evaluable Population) - Star climbing test (sec)

Parameter (unit) Time Point Statistic	All Subjects (N=14) Baseline	Post-Baseline Time Point	Change from Baseline	Percent Change from Baseline
STAIR CLIMBING TEST (SEC)				
BASELINE				
n	14			
Mean	7.1			
Standard Deviation	6.95			
Median	5.5			
Minimum, Maximum	2, 30			
95% Confidence Interval	(3.1, 11.2)			
WEEK 28 (VISIT 5)				
n	13	13	13	13
Mean	7.2	5.3	-1.8	-9.10
Standard Deviation	7.23	3.07	4.85	29.630
Median	5.0	4.0	0.0	0.00
Minimum, Maximum	2, 30	3, 13	-17, 1	-56.7, 50.0
95% Confidence Interval	(2.8, 11.5)	(3.5, 7.2)	(-4.8, 1.1)	(-27.01, 8.80)
WEEK 52 (VISIT 7/ET)				
n	14	14	14	14
Mean	7.1	4.5	-2.6	-23.36
Standard Deviation	6.95	2.41	5.00	26.249
Median	5.5	4.0	-1.0	-19.44
Minimum, Maximum	2, 30	2, 11	-19, 1	-63.3, 20.0
95% Confidence Interval	(3.1, 11.2)	(3.1, 5.9)	(-5.5, 0.2)	(-38.52, -8.21)

Table 7: Summary of Timed Function Test by Visit (Evaluable Population) – Standing from Supine position (sec)

Parameter (unit) Time Point Statistic	All Subjects (N=14) Baseline	Post-Baseline Time Point	Change from Baseline	Percent Change from Baseline
STAND FROM SUPINE POSITION (SEC)				
BASELINE				
n	14			
Mean	7.2			
Standard Deviation	7.21			
Median	4.5			
Minimum, Maximum	3, 26			
95% Confidence Interval	(3.0, 11.4)			
WEEK 28 (VISIT 5)				
n	13	13	13	13
Mean	7.4	4.3	-3.1	-19.35
Standard Deviation	7.48	1.60	6.47	30.499
Median	4.0	4.0	-1.0	-20.00
Minimum, Maximum	3, 26	3, 8	-18, 2	-77.3, 40.0
95% Confidence Interval	(2.9, 11.9)	(3.3, 5.3)	(-7.0, 0.8)	(-37.78, -0.92)
WEEK 52 (VISIT 7/ET)				
n	14	14	14	14
Mean	7.2	4.1	-3.1	-21.40
Standard Deviation	7.21	1.61	6.50	34.565
Median	4.5	4.0	-1.0	-22.50
Minimum, Maximum	3, 26	2, 8	-20, 3	-76.9, 60.0
95% Confidence Interval	(3.0, 11.4)	(3.2, 5.1)	(-6.8, 0.7)	(-41.36, -1.45)

Table 8: Summary of Timed Function Test by Visit (Evaluable Population) - 10m Run/Walk(sec)

Parameter (unit) Time Point Statistic	All Subjects (N=14) Baseline	Post-Baseline Time Point	Change from Baseline	Percent Change from Baseline
TEN METER RUN/WALK (SEC)				
BASELINE				
n	14			
Mean	6.6			
Standard Deviation	2.37			
Median	6.0			
Minimum, Maximum	4, 12			
95% Confidence Interval	(5.3, 8.0)			
WEEK 28 (VISIT 5)				
n	13	13	13	13
Mean	6.7	5.9	-0.8	-8.35
Standard Deviation	2.46	2.22	1.54	22.778
Median	6.0	5.0	-1.0	-8.33
Minimum, Maximum	4, 12	4, 11	-3, 2	-33.3, 25.0
95% Confidence Interval	(5.2, 8.2)	(4.6, 7.3)	(-1.7, 0.2)	(-22.12, 5.41)
WEEK 52 (VISIT 7/ET)				
n	14	14	14	14
Mean	6.6	5.5	-1.1	-14.54
Standard Deviation	2.37	1.65	1.35	14.862
Median	6.0	5.0	-1.0	-16.67
Minimum, Maximum	4, 12	4, 9	-4, 1	-33.3, 12.5
95% Confidence Interval	(5.3, 8.0)	(4.5, 6.5)	(-1.9, -0.4)	(-23.12, -5.96)

Source: Appendix 16.2.6.1 and Section 14.2 Table 14.2.1

CHMP Comments

The current 28 week data presented differs slightly from the previous presented data submitted in the interim report. This difference cannot be explained solely on the differences in number of subjects included in the analysis. However, as these are minor differences and do not impact the outcome, this issue will not be pursued.

CHMP Comments

No conclusion can be drawn from this data, as no comparative data are provided. The patients in this population still develop and improve on the assessment scales used. The marginal improvement seen, could be due to the general development of this population. Moreover, the clinical relevance of the effect size is questionable.

6.2.4. North Star Ambulatory Assessment

16-Item Scale

A summary of the 16-Item North Star Ambulatory Assessment total score by visit is provided in

Table 9. Improvements were seen in mean (SD) NSAA total score over the baseline value of 16.0 (4.66). The mean (SD) value for NSAA total score at Week 28 was 19.8 (6.17), an improvement of 24.88 (27.203) percent. The mean (SD) value for NSAA total score at Week 52 was 21.5 (6.48), an improvement of 36.63 (29.956) percent.

Table 9: Summary of the 16-item North Star Ambulatory Assessment Total Score by Visit (Evaluable Population)

Parameter (unit) Time Point Statistic	All Subjects (N=14) Baseline	Post-Baseline Time Point	Change from Baseline	Percent Change from Baseline
NSAA TOTAL SCORE - 16				
BASELINE				
n	14			
Mean	16.0			
Standard Deviation	4.66			
Median	17.5			
Minimum, Maximum	7, 22			
95% Confidence Interval	(13.3, 18.7)			
WEEK 28 (VISIT 5)				
n	13	13	13	13
Mean	16.2	19.8	3.5	24.88
Standard Deviation	4.76	6.17	3.43	27.203
Median	19.0	20.0	4.0	21.05
Minimum, Maximum	7, 22	10, 29	-3, 9	-23.1, 71.4
95% Confidence Interval	(13.4, 19.1)	(16.0, 23.5)	(1.5, 5.6)	(8.44, 41.31)
WEEK 52 (VISIT 7/ET)				
n	14	14	14	14
Mean	16.0	21.5	5.5	36.63
Standard Deviation	4.66	6.48	4.43	29.956
Median	17.5	22.5	4.5	35.66
Minimum, Maximum	7, 22	8, 29	-1, 14	-5.3, 100.0
95% Confidence Interval	(13.3, 18.7)	(17.8, 25.2)	(2.9, 8.1)	(19.33, 53.92)

Source: Appendix 16.2.6.2 and Section 14.2 Table 14.2.2.1

8-Item Subscale

A summary of the 8-Item North Star Ambulatory Assessment total score by visit is provided in Table 10 and in Section 14 Table 14.2.2.1.2. Improvements were seen in mean (SD) NSAA total score over the baseline value of 10.5 (2.56). The mean (SD) value for NSAA total score at Week 28 was 12.1 (3.12), an improvement of 15.14 (14.742) percent. The mean (SD) value for NSAA total score at Week 52 was 12.8 (3.12), an improvement of 23.31 (22.916) percent.

Table 10: Summary of the 8-item North Star Ambulatory Assessment Subscale by Visit (Evaluable Population)

Parameter (unit) Time Point Statistic	All Subjects (N=14) Baseline	Post-Baseline Time Point	Change from Baseline	Percent Change from Baseline
NSAA TOTAL SCORE - 8				
BASELINE				
n	14			
Mean	10.5			
Standard Deviation	2.56			
Median	10.5			
Minimum, Maximum	6, 15			
95% Confidence Interval	(9.0, 12.0)			
WEEK 28 (VISIT 5)				
n	13	13	13	13
Mean	10.5	12.1	1.5	15.14
Standard Deviation	2.67	3.12	1.39	14.742
Median	11.0	13.0	2.0	16.67
Minimum, Maximum	6, 15	7, 16	-1, 3	-12.5, 37.5
95% Confidence Interval	(8.9, 12.1)	(10.2, 14.0)	(0.7, 2.4)	(6.24, 24.05)
WEEK 52 (VISIT 7/ET)				
n	14	14	14	14
Mean	10.5	12.8	2.3	23.31
Standard Deviation	2.56	3.12	2.13	22.916
Median	10.5	14.0	1.5	16.67
Minimum, Maximum	6, 15	7, 16	0, 6	0.0, 75.0
95% Confidence Interval	(9.0, 12.0)	(11.0, 14.6)	(1.1, 3.5)	(10.07, 36.54)

Source: Appendix 16.2.6.2 and Section 14.2 Table 14.2.2.1.2

3-Item Subscale

A summary of the 3-Item North Star Ambulatory Assessment total score by visit is provided in

Table 11. Improvements were seen in mean (SD) NSAA total score over the baseline value of 5.4 (0.63). The mean (SD) value for NSAA total score at Week 28 was 5.8 (0.38), an improvement of 10.26 (16.858) percent. The mean (SD) value for NSAA total score at Week 52 was 5.6 (0.63), an improvement of 6.31 (14.532) percent.

Table 11: Summary of the 3-item North Star Ambulatory Assessment Subscale by Visit (Evaluable Population)

Parameter (unit) Time Point Statistic	All Subjects (N=14) Baseline	Post-Baseline Time Point	Change from Baseline	Percent Change from Baseline
NSAA TOTAL SCORE - 3				
BASELINE				
n	14			
Mean	5.4			
Standard Deviation	0.63			
Median	5.0			
Minimum, Maximum	4, 6			
95% Confidence Interval	(5.0, 5.7)			
WEEK 28 (VISIT 5)				
n [1]	13	13	13	13
Mean	5.4	5.8	0.5	10.26
Standard Deviation	0.65	0.38	0.78	16.858
Median	5.0	6.0	0.0	0.00
Minimum, Maximum	4, 6	5, 6	-1, 2	-16.7, 50.0
95% Confidence Interval	(5.0, 5.8)	(5.6, 6.1)	(-0.0, 0.9)	(0.07, 20.44)
WEEK 52 (VISIT 7/ET)				
n [1]	14	14	14	14
Mean	5.4	5.6	0.3	6.31
Standard Deviation	0.63	0.63	0.73	14.532
Median	5.0	6.0	0.0	0.00
Minimum, Maximum	4, 6	4, 6	-1, 1	-20.0, 25.0
95% Confidence Interval	(5.0, 5.7)	(5.3, 6.0)	(-0.1, 0.7)	(-2.08, 14.70)

Source: Appendix 16.2.6.1 and Section 14.2 Table 14.2.2.1.3

CHMP Comments:

There appear to be minor changes in the assessment scores. However, no conclusions can be drawn from the data provided, see previous comments for the TFT.

6.3. Discussion

Generally the data presented are in line with the previous submitted data, however minor differences in either the baseline mean values or treatment visit value at week 28 are observed between the interim report and current report for both TFT and NSAA. However, as these do not affect the outcome, this issue is not pursued.

On the data itself no conclusions can be drawn, as there is no comparator arm included. Generally, a slight improvement from baseline is observed for both TFT and NSAA, however, as these patients are developing, this could reflect the general development of the patient population.

The previous comments that the data are not considered robust on their own, as there are too many factors which influence the interpretation and question the effect size and clinical relevance, remain, thus no amendments to the SmPC are required.

7. Clinical Safety aspects

7.1. Treatment exposure

A summary of study drug administration is provided in

Table 12. The mean (SD) treatment duration was 366.1 (4.12) days. Seven (50.0%) subjects completed between 281 and 364 days of treatment, while 7 (50.0%) subjects completed more than 364 days of treatment.

Table 12: Summary of Administration of Study Drug (Safety Population)

Parameter Statistic / Category	All Subjects (N=14)
TREATMENT DURATION (DAYS)	
n	14
Mean	366.1
Standard Deviation	4.12
Median	364.5
Minimum, Maximum	361, 374
CATEGORY OF DURATION	
281-364 Days	7 (50.0%)
>364 Days	7 (50.0%)

Source: Appendix 16.2.5.1 and Section 14.1 Table 14.1.6

7.2. Adverse events

All 14 subjects in the study experienced at least 1 TEAE and 5 of these subjects had TEAEs classified as possibly related to the study medication (table 13). No subject experienced an SAE or prematurely discontinued study drug due to an AE. Table 14 lists TEAE by incidence in the PK and extension phases. The most common TEAE was pyrexia, affecting 6 (42.9%) subjects at some point during the study. The next most common TEAEs were ear infection affecting 5 (35.7%) subjects, nasopharyngitis affecting 4 (28.6%) subjects, vomiting occurring in 4 (28.6%) subjects, rash affecting 3 (21.4%) subjects, and cough affecting 3 (21.4%) subjects. The TEAEs classified as possibly related to ataluren were rash, flatulence, nausea, and vomiting. All TEAEs possibly related to ataluren were classified as mild, except for 2 occurrences of vomiting which were classified as moderate. There was one case of constipation classified as severe; this was not related to ataluren treatment. The dose of the drug was not changed as a result of any TEAE.

Table 13: Overall Summary of Treatment-Emergent Adverse Events (Safety Population)

Category	PK Phase (N=14)	Extension Phase (N=14)	Overall (N=14)
Number of TEAE	33	57	90
Number (%) of subjects with at least one TEAE	13 (92.9%)	10 (71.4%)	14 (100%)
Relationship to study medication			
Not Related	8 (57.1%)	10 (71.4%)	9 (64.3%)
Related	5 (35.7%)	0 (0.0%)	5 (35.7%)
Number (%) of subjects who discontinued due to TEAE	0 (0.0%)	0 (0.0%)	0 (0.0%)
Number (%) of subjects with serious TEAE	0 (0.0%)	0 (0.0%)	0 (0.0%)
Number (%) of subjects with TEAE by maximum CTCAE grade			
CTCAE Grade 1 Mild	8 (57.1%)	3 (21.4%)	5 (35.7%)
CTCAE Grade 2 Moderate	5 (35.7%)	6 (42.9%)	8 (57.1%)
CTCAE Grade 3 Severe	0 (0.0%)	1 (7.1%)	1 (7.1%)

Source: Appendix 16.2.7.1. and Section 14.3 Table 14.3.1.1

Table 14: Summary of Treatment-Emergent Adverse Events by Descending Incidence of Preferred Term (Safety Population)

Preferred Term	PK Phase (N=14)	Extension Phase (N=14)	Overall (N=14)
Number (%) Of Subjects Reporting Any Treatment-Emergent Adverse Events	13 (92.9%)	10 (71.4%)	14 (100%)
Pyrexia	5 (35.7%)	3 (21.4%)	6 (42.9%)
Rash	3 (21.4%)	0 (0.0%)	3 (21.4%)
Cough	2 (14.3%)	1 (7.1%)	3 (21.4%)
Flatulence	2 (14.3%)	0 (0.0%)	2 (14.3%)
Abdominal Pain Upper	1 (7.1%)	1 (7.1%)	2 (14.3%)
Constipation	1 (7.1%)	1 (7.1%)	2 (14.3%)
Contusion	1 (7.1%)	0 (0.0%)	1 (7.1%)
Decreased Appetite	1 (7.1%)	0 (0.0%)	1 (7.1%)
Ear Infection	1 (7.1%)	4 (28.6%)	5 (35.7%)
Enuresis	1 (7.1%)	0 (0.0%)	1 (7.1%)
Epistaxis	1 (7.1%)	0 (0.0%)	1 (7.1%)
Gingival Abscess	1 (7.1%)	0 (0.0%)	1 (7.1%)
Headache	1 (7.1%)	0 (0.0%)	1 (7.1%)
Hyperlipidaemia	1 (7.1%)	0 (0.0%)	1 (7.1%)
Hypertrichosis	1 (7.1%)	0 (0.0%)	1 (7.1%)
Nasopharyngitis	1 (7.1%)	3 (21.4%)	4 (28.6%)
Nausea	1 (7.1%)	0 (0.0%)	1 (7.1%)
Respiratory Tract Infection	1 (7.1%)	0 (0.0%)	1 (7.1%)
Rhinitis	1 (7.1%)	0 (0.0%)	1 (7.1%)
Rhinorrhoea	1 (7.1%)	0 (0.0%)	1 (7.1%)
Upper Respiratory Tract Infection	1 (7.1%)	1 (7.1%)	2 (14.3%)
Viral Rash	1 (7.1%)	0 (0.0%)	1 (7.1%)
Vomiting	1 (7.1%)	3 (21.4%)	4 (28.6%)
Abnormal Behaviour	0 (0.0%)	1 (7.1%)	1 (7.1%)
Arthralgia	0 (0.0%)	1 (7.1%)	1 (7.1%)
Arthropod Bite	0 (0.0%)	2 (14.3%)	2 (14.3%)
Bronchitis Viral	0 (0.0%)	1 (7.1%)	1 (7.1%)
Chromaturia	0 (0.0%)	1 (7.1%)	1 (7.1%)
Conjunctivitis	0 (0.0%)	1 (7.1%)	1 (7.1%)
Croup Infectious	0 (0.0%)	1 (7.1%)	1 (7.1%)
Fall	0 (0.0%)	1 (7.1%)	1 (7.1%)
Fatigue	0 (0.0%)	1 (7.1%)	1 (7.1%)
Gait Disturbance	0 (0.0%)	1 (7.1%)	1 (7.1%)
Gastroenteritis	0 (0.0%)	1 (7.1%)	1 (7.1%)
Gastroenteritis Norovirus	0 (0.0%)	1 (7.1%)	1 (7.1%)
Hepatic Enzyme Increased	0 (0.0%)	1 (7.1%)	1 (7.1%)
Hordeolum	0 (0.0%)	1 (7.1%)	1 (7.1%)
Influenza	0 (0.0%)	2 (14.3%)	2 (14.3%)
Insomnia	0 (0.0%)	1 (7.1%)	1 (7.1%)
Metabolic Acidosis	0 (0.0%)	1 (7.1%)	1 (7.1%)
Pain In Extremity	0 (0.0%)	1 (7.1%)	1 (7.1%)
Pharyngitis Streptococcal	0 (0.0%)	1 (7.1%)	1 (7.1%)
Rash Generalised	0 (0.0%)	1 (7.1%)	1 (7.1%)
Stomatitis	0 (0.0%)	1 (7.1%)	1 (7.1%)
Tibia Fracture	0 (0.0%)	1 (7.1%)	1 (7.1%)
Tonsillar Hypertrophy	0 (0.0%)	1 (7.1%)	1 (7.1%)
Urticaria	0 (0.0%)	1 (7.1%)	1 (7.1%)

Source: Appendix 16.2.7.1 and Section 14.3 Table 14.3.1.4

No subject experienced an SAE or a TEAE leading to discontinuation of the study drug. There were no hepatic or renal toxicities reported.

CHMP Comments:

As mentioned during the analysis of the interim report, the reported adverse events are either in line with the adverse events known for the patients aged ≥5years of age or common childhood illnesses. There was no difference between the events reported in the interim report at 28 weeks and the current report at 52 weeks.

7.3. Clinical Laboratory Evaluation

Hematology: There were no clinically significant changes in any of the tests.

Biochemistry: No clinically significant changes were observed in biochemistry values after administration of ataluren. All 14 of the subjects showed abnormally high levels of ALT, AST, CK, and/or lactate dehydrogenase, which were observed before the first dose of ataluren. These were considered likely related to the pathophysiology of nmDMD and associated muscle loss observed in this patient population.

Urinalysis: Seven of the subjects showed abnormal urinalysis results at different timepoints during the study. These included ketones in the urine for 2 subjects at screening and occult blood, glucose, protein, nitrite, and leukocyte esterase in the urine for 6 subjects at scheduled study visits. Given the sporadic nature of these findings, often observed before treatment exposure, the abnormal findings are of no clinical relevance.

CHMP Comments

The biochemistry and urinalysis data presented showed abnormalities generally before treatment exposure. It is therefore agreed with the MAH that these are likely related to the pathophysiology of nmDMD.

7.4. Vital signs and Electrocardiogram

No clinically significant mean change from screening was observed in any vital sign parameter.

No clinically significant abnormal results were found.

CHMP Comments

These findings correspond with the known effects of ataluren in DMD patients aged ≥5 years of age.

7.5. Discussion

No unexpected safety issues were encountered. The adverse events reported are in line with the adverse events known for the patients aged ≥5years of age and some are common childhood illnesses.