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Human Medicines Evaluation Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Translarna

ataluren

Procedure no: EMEA/H/C/002720/P46/025

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

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1. Introduction

On 7 August 2019, the MAH submitted a completed paediatric study 020e "A Phase 3 Extension Study of Ataluren (PTC124) in Patients with Nonsense Mutation Dystrophinopathy", in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.
A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that Study 020e "A Phase 3 Extension Study of Ataluren (PTC124) in Patients with Nonsense Mutation Dystrophinopathy" is a stand-alone study.

2.2. Information on the pharmaceutical formulation used in the study

Ataluren used in Study 020e is the same drug as approved in EU. It is a white to off-white granules for oral suspension packaged in child-resistant sachets (packets) and supplied in dose strengths containing 125, 250, or 1000 mg of the active drug substance, which is 25% of the total formulation weight. The excipients were tested to pharmaceutical or food grade and are generally safe.

2.3. Clinical aspects

2.3.1. Introduction

DMD is a X-linked genetic disorder (Worton 2001, Khurana 2003) caused by defects in the gene for dystrophin (Lapidos 2004). The role of the dystrophin protein is to act as a shock absorber, bearing the mechanical stresses that occur during muscle contraction, stabilizing muscle cell membranes, and protecting muscles from injury (Petrof 1993). In the absence of dystrophin, the shear placed on the membranes during contractions causes them to tear, leading to membrane damage and muscle loss. Progressive muscle weakness is seen initially in the lower-extremity muscles and later in the upper extremity, respiratory, and cardiac muscles. Deterioration of ambulation occurs in the first decade of life, wheelchair dependency in the second decade, and eventual respiratory and cardiac failure with death by the third or fourth decade (Passamano 2012). Supportive care and off-label use of corticosteroids (usually prednisone or deflazacort) are currently the main treatment options. Mutation-specific therapies aimed at restoring dystrophin production, including ataluren and exon-skipping drugs, are being investigated, and ataluren is marketed for this indication in DMD. The goal of dystrophin restoration therapies is to slow the progression of DMD (Merlini 2015).

Ataluren is an orally bioavailable drug, has a Marketing Authorization in Europe, Chile, Israel, South Korea and Brazil and is investigational in other regions. Ataluren promotes ribosomal read through of premature stop codons, enabling production of full-length dystrophin (Welch 2007).

The MAH submitted a final report for:

- Study 020e "A Phase 3 Extension Study of Ataluren (PTC124) in Patients with Nonsense Mutation Dystrophinopathy"; Study 020e was a Phase 3 safety extension study following Study 020 of ataluren (PTC124) in patients with nonsense mutation DMD.

2.3.2. Clinical study

Study 020e "A Phase 3 Extension Study of Ataluren in Patients with Nonsense Mutation Dystrophinopathy"

Description

Study 020e was an international, open-label, single group, extension of the previous specific obligation study for conditional market authorization, Study 020. Study 020e included patients with nonsense mutation DMD who successfully completed the double-blind, placebo-controlled phase of study 020.

Note: a new specific obligation study to further confirm clinical efficacy in nmDMD patients is currently ongoing.

Methods

Objective(s)

The primary objective of the extension phase was to obtain long-term ataluren safety data to augment the ataluren safety. The secondary objectives were to augment the efficacy data collected in the double-blind study (Study 020).

Study design

Study 020e was a Phase 3, international, open-label, single group, extension safety and efficacy study.

Study population /Sample size

The study enrolled 218 patients with nonsense mutation DMD, aged ≥7 to ≤16 years of age, who had successfully completed the double-blind, placebo-controlled Study 020. A total of 68 patients completed 144 weeks of treatment. One patient discontinued due to an AE (anxiety of mild intensity). The high rate of study non-completion was due primarily to the commercial availability of ataluren.

Table 1: patient disposition

	Ambulatory at Study Entry		
	Yes N=198 n (%) [b]	**No N=20 n (%) [b]**	**Overall N=219* n (%) [b]**
Subjects enrolled, n	198	20	219
As Treated (AT) Population, n [a]	198	20	218
Completed Study, n (%)	56 (28.3)	12 (60.0)	68 (31.2)
Discontinued from study, n (%)	142 (71.7)	8 (40.0)	150 (68.8)
Primary reasons for study discontinuation			
Withdrew Consent, n (%)	10 (5.1)	0	10 (4.6)
Lost to follow up, n (%)	0	0	0
Adverse Event, n (%)	1 (0.5)	0	1 (0.5)
Investigator decision	2 (1.0)	0	2 (0.9)
Protocol noncompliance	0	0	0
Other, n (%)	129 (65.2)	8 (40.0)	137 (62.8)

Abbreviations: AT, as treated
*Subject 051-008 failed in screening and did not have ambulatory status at study entry.
[a] As Treated population consists of all subjects who had at least one dose of Ataluren.
[b] Percentages are calculated based on the total number of subjects in the As Treated Population
Source: Section 14.1, Table 14.1.1.1

CHMP comment

The main reason for drop out is the availability of commercial ataluren. It can be questioned whether this is a valid justification for study discontinuation considering that DMD patients are screened regularly and data could have been collected.

This issue will not be pursued as the MAH is currently conducting a long-term safety and efficacy study in patients on commercially available ataluren (study025o). In addition, the MAH is conducting a confirmative randomized placebo control study in nmDMD patients aged >5 years of age.

Treatments

All patients received ataluren administered three times a day (morning, noon, and evening at 10, 10, and 20 mg/kg, respectively).

Outcomes/endpoints

All AEs and laboratory abnormalities were assessed as the primary endpoints in this extension study.
The secondary endpoints of this study included physical assessment (6MWT, TFT, NSAA, and PUL), pulmonary assessments, patient-reported outcomes (PODCI and ADL), and exposure assessments.

Statistical Methods/ Handling of data

Several patients had early terminations or unscheduled visits during the study, thus the derived analysis visits were generated by visit window defined according to Section 6.1 of the SAP (Section 16.1.9). Imputation rules for missing/incomplete date information for AEs and for prior or concomitant medications are provided in Section 6.4 of the SAP.
No interim analyses were planned for this extension study.
Data from all sites were pooled for all analyses unless otherwise specified based on ITT.

Results

Recruitment/ Number analysed

Two-hundred-eighteen (218) patients, 198 ambulatory and 20 non-ambulatory were treated in Study 020e.

Baseline data

The mean age at baseline was 9.9 years with 80% of the patients between the ages of 6 and 11 years, inclusive. The majority (77.5%) of patients were white. Mean baseline 6-minute walk distance was 317.95 meters with little difference in the number of patients between baseline walk distance groups of <300 meters, ≥300 - <400 meters, and ≥400.

Safety results

The most frequently reported treatment-emergent adverse events (TEAEs) (≥ 15%) included nasopharyngitis (26.1%), disease progression (25.7%), fall (22%), headache (19.3%), and vomiting (17.0 %). Based on exposure-adjusted event rates, headache (23.2%), nasopharyngitis (19.8%), fall (15.2%) and vomiting (14.2%), were the most frequently reported TEAEs. The exposure-adjusted event rate for disease progression was 11.2%.

Loss of ambulation was recorded as disease progression on the AE case report form in this study.

There were no TEAEs leading to fatal outcomes; one TEAE (anxiety) of mild intensity led to study discontinuation. Forty-four serious TEAEs were reported in 24 patients (11%), none of which were considered related to study drug. Sixteen (7.3%) patients had serious TEAEs that were also severe (Grade 3) in intensity and 2 patients had life-threatening events, including hypoxia, femur fracture, hypotension, bradycardia, acute respiratory distress syndrome, and pneumonia aspiration, all of which resolved. Thirty-five patients had 51 adrenal, hepatic or renal TEAEs that were mild to moderate in intensity except for 1 event each of nephrolithiasis and hematuria, that were severe (Grade 3) in intensity. A total of 68 TEAEs in 44 (20.2%) patients were reported as being related to study medication. Hematuria (n = 11) was the only related preferred term occurring in ≥5% of patients. Narratives for these patients are in CSR 020e Section 12.3.2.

Mean high-density lipoprotein, low-density lipoprotein (LDL), total cholesterol, and triglycerides levels were in the upper range of normal/borderline high at baseline. Small mean increases in LDL, total cholesterol, and triglycerides levels were observed; but were not considered clinically relevant. There were no Grade 2, 3 or 4 TEAEs for hypercholesterolemia or for hypertriglyceridemia.

Laboratory monitoring of adrenal, renal and hepatic function revealed no evidence of injury to these organ systems. No clinically meaningful changes from baseline were observed in any other laboratory parameters at any post-baseline assessment.

There were no clinically significant differences from baseline in vital sign measurements. The proportion of patients who were prehypertensive or hypertensive during the study was relatively consistent with that observed at baseline. No clinically meaningful abnormalities were identified based on physical examinations.

Clinically significant electrocardiogram abnormalities were present in 2 (0.9%) patients at baseline and in 3 (1.4%) patients at Week 48.

CHMP comment

The adverse events reported are in line with the adverse events known for the patients aged ≥5years of age. Electrocardiogram abnormalities, which was reported in 1 more patient compared to baseline, could also be associated with the disease progression. Overall, no clinically significant mean changes were observed in vital sign parameters.

Efficacy results

Note to reader

Efficacy was assessed as a secondary outcome and a comparator arm is lacking.

The MAH's Critical Expert Overview focused on the outcomes in non-ambulatory patients, i.e. age at loss of ambulation, forced vital capacity and Performance of the Upper Limb (PUL). This focus may wrongfully suggest that the patients included in the study were non-ambulant. To correctly balance this report also the assessments in ambulatory patients (i.e. 6-MWD, TFT and NSAA,) which were the main group included is presented.

In the CSR-body submitted by the MAH focused on the 48-week results. However, this study lasted 144 weeks. To allow adequate representation of the efficacy data collected during the 144 weeks, the tables presented below were made by the assessor.

6-Minute Walk Distance

Mean (SD) baseline 6MWD was 352.28 (104.716) meters for ambulatory patients. At 48 weeks the mean change from baseline was -36.90 (54.924) meters.

Table 2: Summary of Six Minute Walk Distance (Meters) and Change from Baseline by Visit (As-Treated Population)

Visit	N	Baseline Observed Mean (SD)	Observed Mean (SD)	Change from baseline Mean (SD)
Baseline				
Overall*	214*	319.52 (142.821)*		
Ambulatory	194 [1]	352.28 (104.716)		
Week 12	181 [2]	358.93 (101.351)	344.58 (111.613)	-14.34 (36.517)
Week 24	179 [2]	361.82 (97.410)	337.41 (120.175)	-24.41 (47.503)
Week 36	165 [2]	369.99 (93.132)	337.85 (120.606)	-32.15 (50.688)
Week 48	142 [2]	381.76 (86.178)	344.86 (113.593)	-36.90 (54.924)
Week 60	133 [2]	387.16 (83.272)	339.52 (119.382)	-47.64 (65.221)
Week 72	121 [2]	391.60 (82.468)	334.67 (123.853)	-56.92 (68.892)
Week 84	109 [2]	399.18 (77.999)	338.24 (118.486)	-60.95 (73.025)
Week 96	95 [2]	402.67 (77.205)	332.24 (119.144)	-70.42 (76.676)
Week 108	78 [2]	409.71 (74.435)	342.36 (104.832)	-67.35 (68.051)
Week 120	61 [2]	413.22 (73.766)	336.31 (108.515)	-76.91 (77.785)
Week 132	43 [2]	427.81 (75.971)	337.08 (114.075)	-90.73 (82.011)
Week 144	26 [2]	428.31 (67.829)	330.13 (110.227)	-98.18 (86.604)

Source: PTC124-GD-020e-DMD-CSR-Body table 14.2.1.1
* only reported at baseline, includes both ambulatory and non-ambulatory patient data
[1] n= Number of subjects with a baseline value
[2] n=Number of subjects who had non-missing values for both baseline and post-baseline at the given visit.

CHMP comment

There appears to be a gradual decline in the performance of the 6-MWD. Patients with higher baseline values remained longer in the study.

Overall, no conclusions on efficacy can be drawn, due to lack of a comparator.

Timed function Tests

For the overall population, the mean (SD) time to walk/run 10 meters at baseline was 8.71 (6.592) seconds. At 48 weeks the time to walk/run 10 meters had increased by 1.66 (3.579) seconds.

At baseline, the mean (SD) time to ascend 4 stairs was 9.03 (8.939) seconds for the overall population; the mean (SD) time to descend 4 stairs was 7.52 (8.401) seconds. At 48 weeks, the mean (SD) time to ascend 4 stairs increased by 2.41 (4.329) seconds over baseline; the time to descend 4 stairs increased by 1.92 (4.827) seconds over baseline.

Table 3: Summary of Change from Baseline by Visit for the Time Function Test (sec) (As-Treated Population)

Visit	run/walk 10m [mean (SD)]	Climb 4 stairs [mean (SD)]	Descend 4 Stair	Stand from Supine
Baseline	8.71 (6.592)	9.03 (8.939)	7.52 (8.401)	12.45 (10.046)
CFB Week 12	0.68 (1.697)	1.42 (3.685)	1.05 (3.634)	1.17 (4.418)
CFB Week 24	1.17 (2.542)	2.36 (4.382)	1.76 (4.557)	1.52 (4.433)
CFB Week 36	1.40 (3.095)	2.15 (4.311)	2.13 (5.192)	2.05 (5.021)
CFB Week 48	1.66 (3.579)	2.41 (4.329)	1.92 (4.827)	3.18 (5.772)
CFB Week 60	1.89 (3.721)	2.46 (4.375)	2.35 (4.997)	3.93 (5.660)
CFB Week 72	2.33 (4.055)	3.29 (5.634)	2.56 (5.161)	3.87 (6.901)
CFB Week 84	2.14 (3.690)	3.78 (5.752)	2.87 (5.641)	4.47 (6.357)
CFB Week 96	2.65 (4.721)	3.92 (6.120)	2.88 (5.748)	4.27 (5.380)
CFB Week 108	2.53 (4.492)	4.32 (6.346)	2.70 (5.176)	5.79 (6.712)
CFB Week 120	2.74 (4.506)	3.72 (5.864)	3.10 (6.054)	5.29 (6.449)
CFB Week 132	2.49 (3.572)	4.09 (6.310)	2.84 (5.513)	5.53 (6.736)
CFB Week 144	2.29 (1.991)	4.01 (7.260)	2.45 (5.853)	5.22 (5.104)

Source: PTC124-GD-020e-DMD-CSR-Body Table 14.2.5.1, Table 14.2.5.7, Table 14.2.5.9 and Table 14.2.4.1. Only data from patients who had non-missing values for both baseline and post-baseline at the given visit were included.

North Star Ambulatory Assessment

The NSAA mean (SD) total score at baseline was 20.73 (8.513) for ambulatory patients. The change from baseline at 48 weeks was -3.41 (4.082). Of the 17 NSAA items the greatest loss of function at 48 weeks was noted for the ability to jump (28.4%), the ability to stand on heels (27%), the ability to hop on right and left legs (25.2% and 26.5%, respectively), and the ability to rise from the floor (25.0%).

Table 4: Summary of Total Score of North Star Ambulatory Assessment and Change from Baseline by Visit (As-Treated Population)

Visit	Ambulatory at study entry
Baseline	20.73 (8.513)
CFB Week 12	-0.84 (3.026)
CFB Week 24	-1.93 (3.204)
CFB Week 36	-2.50 (3.775)
CFB Week 48	-3.41 (4.082)
CFB Week 60	-3.95 (4.312)
CFB Week 72	-4.78 (4.957)

Visit	Ambulatory at study entry
CFB Week 84	-5.32 (4.974)
CFB Week 96	-5.77 (5.525)
CFB Week 108	-6.24 (5.383)
CFB Week 120	-6.66 (5.818)
CFB Week 132	-7.80 (6.120)
CFB Week 144	-8.32 (5.512)

Source: PTC124-GD-020e-DMD-CSR-Body Table 17.2.7.1 CFB= change from baseline

Table 5: North Star Ambulatory Assessment Loss of Function at Week 48 - By-item Analysis (As-Treated Population)

Item	(N=198) n/N1 (%) [1]	Item	(N=198) n/N1 (%) [1]
1 Stand	17/194 (8.8)	10 Gets to Sitting	11/192 (5.7)
2 Walk	18/193 (9.3)	11 Rise from Floor	35/143 (24.5)
3 Rise from Chair	36/172 (20.9)	12 Lift Head	8/175 (4.6)
4 Stand on R Leg	24/190 (12.6)	13 Stands on Heels	31/115 (27.0)
5 Stand on L Leg	21/189 (11.1)	14 Jump	42/148 (28.4)
6 Climb Box Step R	30/141 (21.3)	15 Hop R Leg	30/119 (25.2)
7 Climb Box Step L	36/145 (24.8)	16 Hop L Leg	31/117 (26.5)
8 Descend Box Step R	30/159 (18.9)	17 Run	31/156 (19.9)
9 Descend Box Step L	32/158 (20.3)		

Source: PTC124-GD-020e-DMD-CSR-Body Table 14.2.7.3. Note: Function loss defined as a shift from non-zero at baseline to zero at week 48, Missing data handled by LOCF.
[1] N1 is the number of subjects who had non-missing scores at both baseline and week 48. n is the number of subjects who lost function at week 48. The percentage is calculated by n/N1*100%.

CHMP comment

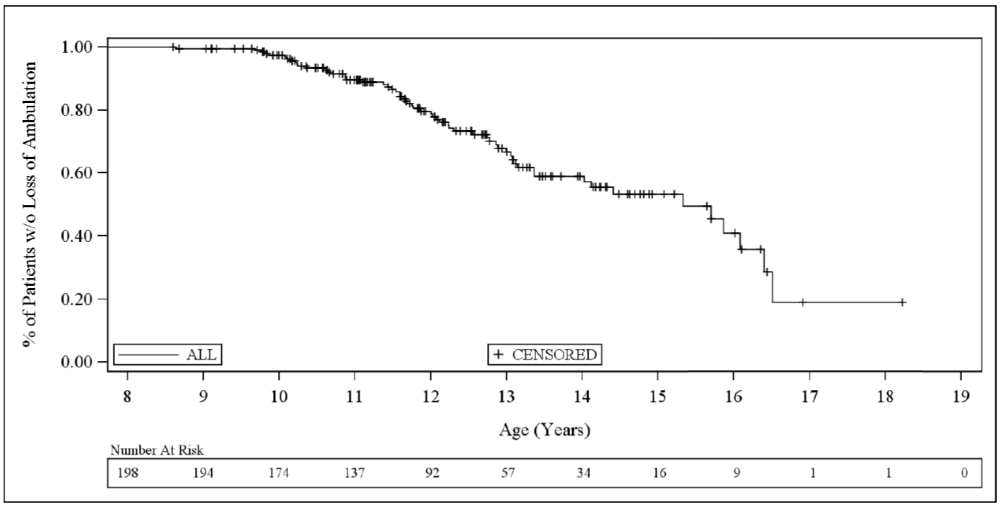
Not only the ability to jump, stand on heels, hop (right and left leg) and rise from floor change is lost in 25% of the patients. Also, the ability to rise from a chair (20.9%), climb box steps (21.3% R, 24.8 L) and descend box steps were reduced in approximately 20% of the patients. This is not unexpected as the average age of patients was 9.9 years at study entry. A decline in function is expected, however the actual decline in function may be higher than presented by the MAH as missing data is handled by last observation carried forward.

No conclusion on efficacy of ataluren can be drawn as the primary aim of the study was to assess the safety. The efficacy is considered only exploratory as a comparison is lacking.

Age at Loss of Ambulation

At study entry, 198 patients (90.8%) were ambulatory, 20 were not. During the study period,59/198 patients lost ambulation. Based on Kaplan-Meier analysis, the median age at loss of ambulation was 15.3 years (95% confidence interval 13.36, 16.40). Among patients who used deflazacort, the median age at loss of ambulation was 16.1 years and 14.0 years for patients who used prednisone/prednisolone. The median age at loss of ambulation was 13.4 years for patients with a cumulative corticosteroid use of <12 months at study entry, and 15.7 years for patients with ≥12 months of corticosteroid use prior to study entry.

Figure 1: KM Plot of Age at Loss of Ambulation for Study 020e



CHMP comment

No conclusions can be drawn on the data presented. It is unclear why the Applicant also performed KM analysis comparing deflazacort to prednisone/prednisolone and comparing corticosteroid use of <12 months to >12 months use. These are known factors that impact the outcome. However, the analysis performed do not allow any conclusion on whether ataluren lengthens the time to loss of ambulation as there is no comparator arm present in the study.

Percent Predicted Forced Vital Capacity

At 48 weeks the mean (SD) changes from baseline for percent predicted forced vital capacity (%pFVC) and percent predicted forced expiratory volume in 1 second (%pFEV1) were 9.82% (14.88) and 9.76% (16.743), respectively in patients (n = 17) who were non-ambulatory at baseline. Results for peak expiratory flow (PEF) and peak cough flow (PCF) were consistent with other spirometry outcomes.

Table 6: Summary of Spirometry Outcome and Change from Baseline by Visit (As-Treated Population)

Visit	%pFVC	%pFEV1	PEF (L/sec)	PCF (L/sec)
Baseline	68.12 (20.331)	62.41 (20.208)	3.89 (1.118)	3.82 (1.021)
CFB Week 24	13.69 (16.406)	15.31 (14.876)	0.02 (0.928)	0.12 (0.673)
CFB Week 48	9.82 (14.880)	9.76 (16.743)	-0.22 (0.816)	-0.02 (0.943)
CFB Week 72	9.00 (12.758)	8.79 (14.761)	0.08 (0.667)	0.33 (0.601)
CFB Week 84			0.70 (NA)*	1.00 (NA)*
CFB Week 96	-1.00 (21.699)	-2.31 (25.118)	-0.43 (1.088)	0.44 (1.236)
CFB Week 108	4.00 (NA)*	-2.00 (NA)*	-0.55 (0.212)	-0.25 (0.071)
CFB Week 120	0.33 (20.335)	-7.42 (23.865)	-0.22 (1.037)	0.65 (0.723)
CFB Week 144	2.20 (19.292)	-8.80 (22.914)	-0.18 (1.480)	0.64 (0.930)

Source: PTC124-GD-020e-DMD-CSR-Body Table 14.2.2.1, Table 14.2.3.1, Table 14.2.3.3, Table 14.2.3.2. *data obtained from 1 patient.

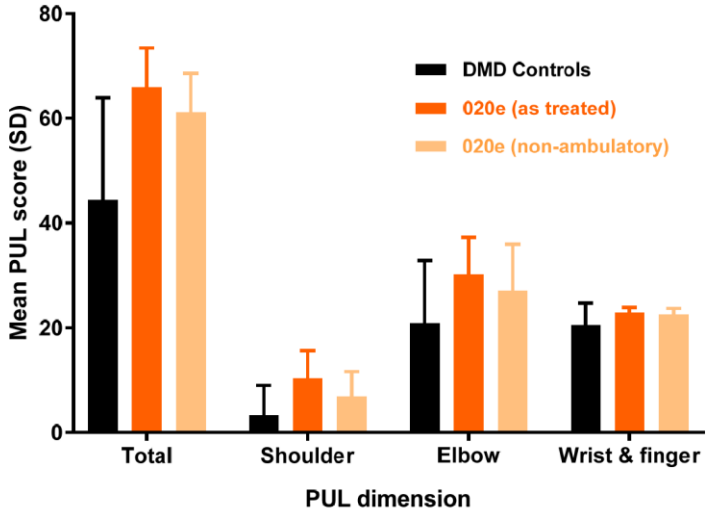
CHMP comment

There is a gradual decline in the spirometry performance, which is not unexpected, based on the population included in the study. Due to the lack of a comparator arm, no conclusions can be drawn

Performance of the Upper Limb (PUL)

The mean PUL total score for the last visit was 65.9 among ataluren-treated patients in the As-treated Population between the ages of 13 and 21.9. For the subset of patients in this age group who were non-ambulatory at their last visit, the mean total last visit PUL score was 61.1. Pull total score and per dimension are presented for the as-treated group, non-ambulatory group and natural history control in Figure 2.

Figure 2: Mean Performance of Upper Limb Score at Time of Last Assessment for study 20e Patients versus Duchenne Muscular Dystrophy Natural History Control



CHMP comment

The MAH present comparative PUL data to a historical control. However, no information is provided on how the control group was constructed. For further comments on the use of external controls in a safety study, see also the Type II variation, modification of the current therapeutic indication (EMEA/H/C/002720/II/0047). No conclusions can be drawn on the data presented above.

2.3.3. Discussion on clinical aspects

This study concerns the extension phase of the previous specific obligation study, i.e. Study 020, to establish efficacy in ambulatory patients aged >5 years of age. A new specific obligation study is currently ongoing.

The MAH submitted efficacy and safety data of 144 weeks ataluren treatment. A total of 219 patients were included, however only 68 completed the study. The MAH indicated that this is due to commercial availability. It is questioned if this is a valid justification for study discontinuation considering that DMD patients are screened regularly and data could have been collected. This issue will not be pursued as currently 2 trials are ongoing addressing the efficacy and safety.

The most frequently reported treatment-emergent adverse events (TEAEs) were nasopharyngitis (26.1%), disease progression (25.7%), fall (22%), headache (19.3%), and vomiting (17.0 %). The is in line with the already known safety profile of ataluren.

No conclusions on efficacy in ambulatory and non-ambulatory patients can be drawn due to the design of the study, i.e. powered on safety and lack of a comparator arm.

The MAH does not propose any changes to the SmPC, which is endorsed. As the applicant has provided the final study results as obligated, the requirements of the paediatric article 46 are considered fulfilled.

3. Rapporteur's overall conclusion and recommendation

No claims are made by the MAH in this procedure. No amendments to the SmPC are proposed by the MAH, which is endorsed. Therefore, the Paediatric Article 46 requirement is considered fulfilled with no regulatory action required.

☒ Fulfilled:

No regulatory action required.