Medicinrådet

Baggrund for Medicinrådets anbefaling vedrørende ataluren som mulig standardbehandling til Duchennes muskeldystrofi

Handelsnavn	Translarna
Generisk navn	Ataluren
Firma	PTC Therapeutics
ATC-kode	M09AX03
Virkningsmekanisme	Ataluren promoverer ribosomal gennemlæsning af mRNA indeholdende præmature stopkodons, hvilket faciliterer produktionen af fuldlængdeprotein
Administration/dosis	Administreres som granulat til oral suspension hver dag i 3 doser. Total daglig dosis på 40 mg/kg legemsvægt
EMA-indikation	Behandling af Duchennes muskeldystrofi, der er forårsaget af en nonsensmutation i dystrofingenet hos gående patienter i alderen 5 år og derover
Godkendelsesdato Offentliggørelsesdato Dokumentnummer Versionsnummer	12. december 2018 12. december 2018 34633 1.0
Fagudvalgets sammensætning og sekretariatets arbejdsgruppe	Se afsnit 7

Om Medicinrådet:

Medicinrådet er et uafhængigt råd, som udarbejder anbefalinger og vejledninger om lægemidler til de fem regioner.

Medicinrådet vurderer, om nye lægemidler og nye indikationer kan anbefales som standardbehandling og udarbejder fælles regionale behandlingsvejledninger.

Nye lægemidler vurderes i forhold til effekt, eksisterende behandling og pris. Det skal give lavere priser og lægemidler, der er til størst mulig gavn for patienterne.

De fælles regionale behandlingsvejledninger er vurderinger af, hvilke lægemidler der er mest hensigtsmæssige til behandling af patienter inden for et terapiområde og dermed grundlag for ensartet høj kvalitet for patienterne på tværs af sygehuse og regioner.

Indhold

1 Medicinrådets anbefaling

Medicinrådet **anbefaler ikke** ataluren som mulig standardbehandling til gående patienter i alderen 5 år og derover med Duchennes muskeldystrofi forårsaget af en nonsensmutation i dystrofingenet.

Medicinrådet har vurderet, at ataluren har **ingen klinisk merværdi** sammenlignet med placebo. Medicinrådet kan derfor ikke anbefale ataluren som mulig standardbehandling uanset pris. Det kliniske spørgsmål, som ligger til grund for anbefalingen, er som følger:

Hvad er den kliniske merværdi af ataluren til gående patienter i alderen 5 år eller derover med Duchennes muskeldystrofi forårsaget af nonsensmutation?

2 Introduktion

2.1 Om indikationen

Duchennes muskeldystrofi er en af de hyppigste muskelsvindssygdomme hos børn. Duchennes muskeldystrofi er en gradvis tiltagende sygdom, hvor der sker en svækkelse i alle kroppens muskler, fordi muskelfibrene gradvist ødelægges. Hos en mindre andel af patienterne (10-15 %) skyldes sygdommen en nonsensmutation i dystrofingenet. Ataluren er målrettet patienter, der har nonsensmutationer i dystrofingenet. Det anslås, at der i Danmark er 9 patienter med Duchennes muskeldystrofi forårsaget af en nonsensmutation, og der forventes på landsplan 1-2 nye tilfælde om året.

Yderligere baggrundsinformation findes i "Medicinrådets vurdering af klinisk merværdi af ataluren til Duchennes muskeldystrofi", bilag 3.

2.2 Sagsbehandlingstid og proces for Medicinrådets vurdering

Medicinrådet modtog den endelige ansøgning fra PTC-Therapeutics den 14. marts 2018. Under sagsbehandlingen har ansøger den 3. oktober 2018 valgt at trække sin endelige ansøgning tilbage. Medicinrådet besluttede på sit møde den 10. oktober 2018 at tage vurderingen op af egen drift.

3 Medicinrådets vurdering af samlet klinisk merværdi

Medicinrådet har vurderet, at ataluren til Duchennes muskeldystrofi forårsaget af nonsensmutation giver **ingen klinisk merværdi** for den samlede population af gående patienter i alderen 5 år og derover, sammenlignet med placebo. Evidensens kvalitet er samlet vurderet som værende lav.

4 Høring

Medicinrådet har foretaget vurderingen af ataluren af egen drift, og derfor er der ikke udført høring af PTC-Therapeutics (indehaver af markedsføringstilladelsen for ataluren), da de ikke længere anses som part i sagen. PTC-Therapeutics er dog blevet anmodet om at kommentere på vurderingsrapporten. De indsendte kommentarer har ikke givet anledning til ændringer i Medicinrådets vurdering af ataluren.

5 Resumé af økonomisk beslutningsgrundlag

Der er ikke foretaget en sundhedsøkonomisk analyse af ataluren. En simpel beregning af lægemiddelomkostningerne viser, at det koster ca. 3 mio. kr. årligt at behandle en patient på 35 kg med ataluren (AIP-priser pr. 30. november 2018).

6 Overvejelser omkring alvorlighed/forsigtighed

Medicinrådet har ikke fundet anledning til at inddrage forhold vedrørende alvorlighed eller forsigtighed i anbefalingen.

7 Sammensætning af fagudvalg og kontaktinformation til Medicinrådet

Medicinrådets fagudvalg vedrørende Duchennes muskeldystrofi

Formand	**Indstillet af**
Charlotte Olesen Overlæge, ph.d.	Lægevidenskabelige Selskaber
Medlemmer	**Udpeget af**
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Søren Ulrich Patient/patientrepræsentant	Danske Patienter
En patient/patientrepræsentant	Danske Patienter

Medicinrådets sekretariat

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Annemette Anker Nielsen (teamleder)

8 Bilag

Bilagsliste:

1) Amgros' beslutningsgrundlag
2a) Kommentarer til vurderingsrapporten fra PTC-Therapeutics (indehaver af markedsføringstilladelsen for ataluren)
2b) Annex til kommentarer til vurderingsrapporten fra PTC-Therapeutics (indehaver af markedsføringstilladelsen for ataluren)
3) Medicinrådets vurdering af klinisk merværdi af ataluren til Duchennes muskeldystrofi – vers. 1.0
4) Protokol for vurdering af den kliniske merværdi af ataluren til behandling af Duchennes muskeldystrofi – vers. 1.0

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Beslutningsgrundlag til Medicinrådet

Dette dokument er Amgros' vurdering af ataluren (Translarna) som mulig standardbehandling til duchennes muskeldystrofi, der er forårsaget af en nonsens-mutation i dystrofin-genet hos ambulante patienter i alderen 5 år og derover.

Dato for Medicinrådsbeslutning	12-12-2018
Firma	PTC (ansøger)
Lægemiddel	Ataluren (Translarna)
Indikation	Duchennes muskeldystrofi

Amgros' vurdering

- Amgros kan ikke vurdere, om der er et rimeligt forhold mellem meromkostningerne og den kliniske merværdi for ataluren (Translarna) til duchennes muskeldystrofi, da der ikke foreligger en sundhedsøkonomisk analyse som Amgros kan træffe en beslutning på baggrund af.

Overordnet konklusion

Medicinrådet har vurderet, at ataluren (Translarna) giver **ingen klinisk merværdi** sammenlignet med standardbehandling.

Ansøger har trukket deres ansøgning og Amgros har derfor ikke noget grundlag for at vurdere meromkostningerne ved ataluren (Translarna).

En simpel beregning af lægemiddelomkostningerne for en patient i behandling med Ataluren (og med en gennemsnitsvægt på 35 kg) ligger på ca. 3 mio. kr. årligt.

Kontraktforhold

Der er foreligger ingen kontrakt med ansøger. De nuværende AIP-priser (30.11.2018) er listet i nedenstående tabel.

Lægemiddel	Styrke	Pakning	AIP-pris (DKK)
Translarna (ataluren)	125 mg	30 stk. gran. til oral susp.	22.903
Translarna (ataluren)	250 mg	30 stk. gran. til oral susp.	45.806
Translarna (ataluren)	1000 mg	30 stk. gran. til oral susp.	183.224

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Date: November 12, 2018

Medicinrådet
Dampfærgevej 27-29, 3. th.
2100 København Ø
Denmark

Response to Danish Medicine Council drafted evaluation of clinical value for ataluren in Duchenne muscle dystrophy

Dear Danish medicine council,

PTC Therapeutics have now carefully reviewed the draft of the Danish medicine council (hereafter referred as DMC) evaluation of clinical value for ataluren in Duchenne muscle dystrophy (DMD).

Due to the concerning nature in the comments below, as well as the critical understanding of all scientific data, we ask the secretariat and expert group to re-assess the categorization of clinical value. For clarity we have organized our comments in 17 bullets below, ending with a conclusion. To fully support the understanding of the context of the data, as well as your transparent review of the scientific documentation, we have summarized the essence of evidence on hand in the Annex 1, a key document attached to this response.

1) **Absence of overall summary of the impact ataluren brings on the treatment paradigm**

In the treatment of boys over 5 years old suffering from nonsense mutation Duchenne muscular dystrophy (nmDMD), clinical trials including new data deriving from real world evidence indicate that ataluren (TRANSLARNA®) delays loss of ambulation significantly and in a clinically relevant manner. Historically, statistical limitations of 48 weeks trials and small sample sizes (phase II 007 and phase III 020) only allowed us to see trends with regards to 6MWT and NSAA. Long term clinical evidence (019 and 025 studies) and local clinical experience in expert centers now give us clear indication of the impact of TRANSLARNA in delaying loss of ambulation compared to natural history of the disease. Moreover, delaying loss of ambulation also postpones the detrimental impact of this event on patient and caregiver quality of life alongside onerous costs of complications to the healthcare system (Landfeldt publication 2014, NICE appraisal).

2) **Current treatment refers to corticosteroid therapy**

The description of the current medical treatment of nmDMD refers to corticosteroids. It seems inappropriate in the DMC report to mention treatments that do not have a marketing authorization in DMD. Indeed, corticosteroids fight inflammation but do not address the underlying cause of this rare genetic disease nor have been assessed by the CHMP for benefit/risk in DMD. Actually, there is no pharmacological comparator to TRANSLARNA®. TRANSLARNA® has been granted Orphan Drug Designation by the CHMP and is the only approved product in nmDMD for commercialization.

3) Expert group considers limitations to subgroup analyses in assessment of 020-study

A permutation test was used for evaluating the subgroup results in Study 020. The presence of highly correlated subgroups in Study 020 makes the use of traditional multiplicity adjustment methods (e.g., Bonferroni) not applicable; and hence the permutation test is appropriate (see Westfall 1993, Blakesley 2009).

For study 020, 9 different subgroups existed. These were:

- Baseline 6-minute walk distance (6MWD) stratification (≥350 meters and <350 meters)
- Baseline 6MWD groups (<300 meters, ≥300 to <400 meters, and ≥400 meters)
- Duration of prior corticosteroid use at baseline (approximately ≥6 months to <12 months and ≥12 months
- Baseline age group (<9 years and ≥9 years)

Among the 9 subgroups, 5 are different cuts of baseline 6MWD, 2 are different cuts of baseline corticosteroid usage, and 2 are different cuts of age groups. Since they are different cuts of the same variable, they are highly correlated within the same variables. For example, within each variable and particular cut (eg, ages <9 years and ≥9 years), the 2 subgroups are 100% negatively correlated, because the groups are mutually exclusive; a person in the <9-year-old group cannot be in the ≥9-year-old group. Similarly, for the different baseline 6MWD subgroups, the subgroups are either mutually exclusive (eg, subjects in the <350-meter group cannot be in the ≥350-meter group) or overlap (eg, a subject can be in both the <300 -meter subgroup and the <350-meter subgroup). In the cases of overlap, where there is a high likelihood that a patient may be in both groups, these subgroups will be highly correlated.

In addition, since age and prior steroid use are also important factors that influence the 6MWD performance, the variables are also correlated among themselves. Therefore, all 9 subgroups are highly correlated with each other.

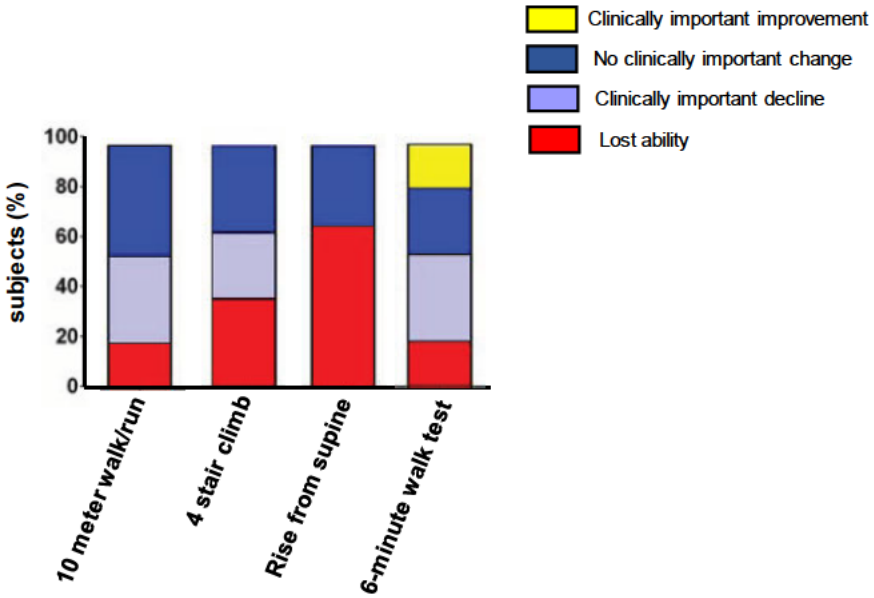
Growing insight into the natural history of DMD has resulted in a better understanding that DMD patients are a heterogenous population with regard to disease progression. As noted above, although TFTs and the 6MWT are highly correlated, the two tests evaluate different properties of muscle function; TFTs measure burst activity and functional aspects of proximal muscle strength, while 6MWT measures endurance and is more reflective of a patient's cardiopulmonary function and overall "well-being."

It has been shown that the 6MWT is less sensitive to changes in muscle performance in certain subgroups than TFTs, particularly in patients with a 6MWD <300 meters and those with 6MWD of ≥400 meters (Arora 2018). For example, recent results from a 4-year, longitudinal, observational study suggest that TFTs may be better predictors of changes in muscle function than the 6MWT in patients with DMD who have baseline 6MWD <300 meters (Arora 2018). The study included 92 patients with DMD, whose ages ranged from 5 to 12.3 years, and 45 age-matched unaffected controls. Consistent with characteristics of the rapid decline phase of the disease, the subgroup of DMD subjects with baseline 6MWD <300 meters was more likely to experience clinically important declines in performance for all TFTs (ie, time to walk/run 10 meters, time to climb 4 stairs, and time to rise from supine) over 1 year (see Figure below). In contrast, for the 6MWT, some patients showed clinical improvement. These findings suggest the 6MWT is limited in its ability to indicate change in motor function in patients with baseline 6MWD <300 meters, and that TFTs displayed higher sensitivity and responsiveness to change in this subgroup of patients (Arora 2018).

Consistent with these results, numerical benefit was observed with ataluren in the 4-stair climb, 4-stair descend, and 10-meter-walk/run tests but not in the 6MWT in subjects with baseline 6MWD <300 meters in Study 020.

Assessment of treatment effect in patients in the stable phase of the disease (i.e., 6MWD ≥400 meters) requires long-term studies as this phase of the disease is characterized by negligible changes or in 6MWD over the 1-year period of most DMD clinical trials.

Figure **Clinically Important Change in Functional Tests Over 1 Year for Subjects with Baseline 6MWD of <300 meters**



Abbreviations: 6MWD, 6-minute walk distance
Source: adapted from (Arora 2018)

References:

Arora, H, Willcocks, RJ, Lott, DJ, Harrington, AT, Senesac, CR, Zilke, KL, et al. Longitudinal timed function tests in Duchenne muscular dystrophy: Imaging dmd cohort natural history. Muscle Nerve 2018.

Blakesley, RE, Mazumdar, S, Dew, MA, Houck, PR, Tang, G, Reynolds, CF, et al. Comparisons of methods for multiple hypothesis testing in neuropsychological research. Neuropsychology 2009;23(2):255-264.

Westfall, PH and Young, SS (1993). The minp method for multiple comparison under heteroscedasticity. In Re-sampling-based multiple testing. Examples and methods for p-value adjustments; New York, Wiley:285-288.

4) For the efficacy target worsening of 10% from baseline

In the methodology section, DMC has found data on 6MWD worsening of >10% from baseline. PTC want to point out that IQWiG (The Institute for Quality and Efficiency in Healthcare, Germany) has published an analysis on this criterion and concluded to a minor benefit, as the expert committee in Denmark now conclude for study 007.

Morbidity					
Endpoint	**Placebo (N=57)**		**Ataluren[1] (N=57)**		**Placebo vs. Ataluren[1]** **Confidence interval [95% CI] p-value**
	Base line	**W. 48**	**Base line**	**W. 48**	
Walk distance 6MWT, min (m)	359,6	317,4	350,0	342,7	26,44 [-4,21; 57,09] p = 0,0905 (nominal) p = 0,1592 (Dunnett)[2]
	Ereignisse (Anteil)		**Ereignisse (Anteil)**		
6MWT at least 10 % deterioration	25 (43,9 %)		15 (26,3 %)		p = 0,0423
Time to at least 10 % deterioration					HR 0,52 [0,28; 0,966] p = 0,0386 (nominal) p = 0,078 (Dunnett)[2]
6MWT at least % improvement	6 (10,5 %)		12 (21,1 %)		p = 0,297

based on 007 phase II study

[1] Ataluren Dosierung 10/10/20 mg.

[2] Dunnett-t-Prozedur zur Berücksichtigung multipler Vergleiche

Moreover, based on 020 study ataluren SmPC states when analyzing the Time to 10% worsening in 6MWD defined as the last time that 6MWD was not 10% worse than baseline "In the ITT population, the hazard ratio for ataluren versus placebo was 0.75 (p=0.160), representing a 25% reduction in the risk of 10% 6MWD worsening."

5) In assessing quality of life, no adequate evaluation from 007 have been made.

Patient-reported HRQL - Study 007 - PedsQL

Patient-reported HRQL was assessed by the PedsQL, in study Study 007 which comprises physical functioning and psychosocial functioning (ie, emotional functioning, social functioning, and school functioning) scales. From baseline to Week 48, patients in the ataluren 10, 10, 20 mg/kg treatment group had a higher mean change in the PedsQL physical and school functioning score than placebo-dosed patients (see Table below).

Table: Patient-Reported Health Related Quality of Life (Study 007, ITT)

	Placebo		Ataluren 10, 10, 20 mg/kg		
Endpoint	**Baseline, mean**	**Δ at Wk 48, mean**	**Baseline, mean**	**Δ at Wk 48, mean**	**Difference, mean (95% CI)**
Physical	61.9	-1.0	59.3	2.4	3.4 (-5.5, 12.2)
Emotional	70.1	4.3	73.7	-1.8	-6.1 (-14.3, 2.1)
Social	63.4	7.8	65.1	3.9	-3.9 (-11.7, 4.0)
School	64.7	4.1	64.6	6.1	2.1 (-6.0, 10.1)

[a] Positive differences between ataluren and placebo represent better outcomes in ataluren-treated patients.
Abbreviation: ITT = intent-to-treat population
Source: Table 14.2.7.1, Table 14.2.7.5, Table 14.2.7.9, Table 14.2.7.13

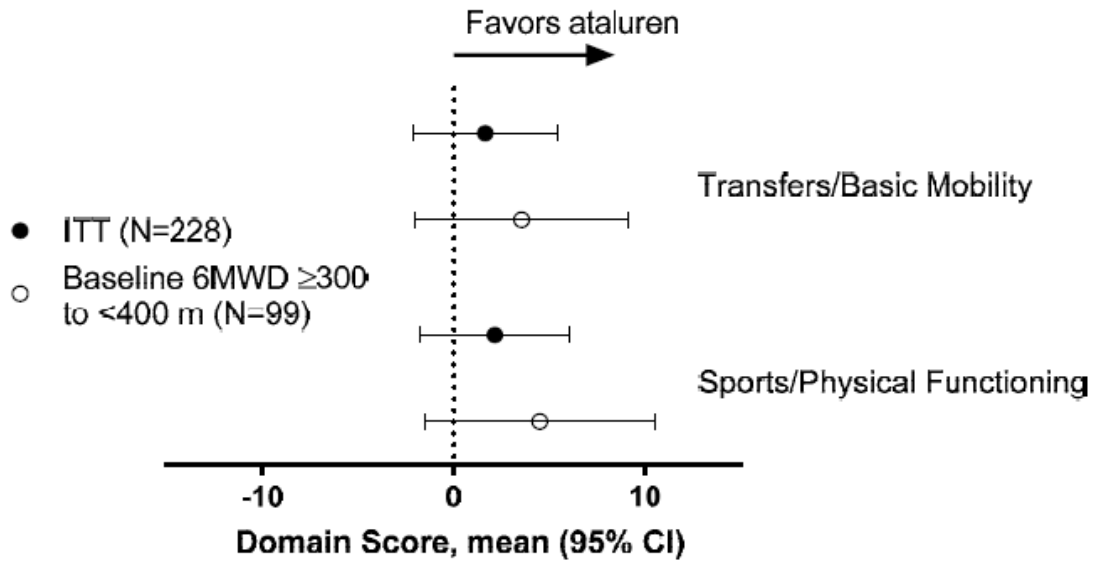
The interpreting patient-reported HRQL in Study 007 is complicated by the findings that patient/caregiver-reported HRQL often showed mean changes in the opposite direction from patient-reported HRQL for all 4 evaluated parameters in the PedQL, which has also been observed in other studies (Davis 2010)

Patient-reported HRQL - Study 020 - PODCI

In Study 020, two PODCI domains (transfers/mobility and sports/physical functioning) were evaluated. These 2 domains are significantly associated with disease progression in patients with DMD (McDonald 2010c); and consequently, were used in Study 020. The transfers/basic mobility domain assesses difficulty experienced in performing routine motor activities in daily life. The sports/physical functioning domain assesses difficulty encountered in participating in more active recreational activities. Each domain is scored from 0 to 100, with 100 representing the highest level of functioning and least pain.

Changes in parent/caregiver-reported HRQL, as assessed by the PODCI transfers/basic mobility and sports/physical functioning domain scores, favored ataluren over placebo in the ITT population and in patients with baseline 6MWD ≥300 to <400 meters (see Figure below).

Figure: PODCI Transfer/Basic Mobility and Sports/Physical Functioning Domain Scores



The plot displays model-estimated deltas and 95% confidence intervals for ataluren versus placebo at Week 48.
Abbreviations: 6MWD = 6-minute walk distance, CI = confidence interval, ITT = intent-to-treat, PODCI = Pediatric Outcomes Data Collection Instrument
Sources: Table 14.2.4.1.2, Table 14.2.4.2.2, Table 14.2.4.1.4, Table 14.2.4.2.4

REFERENCES

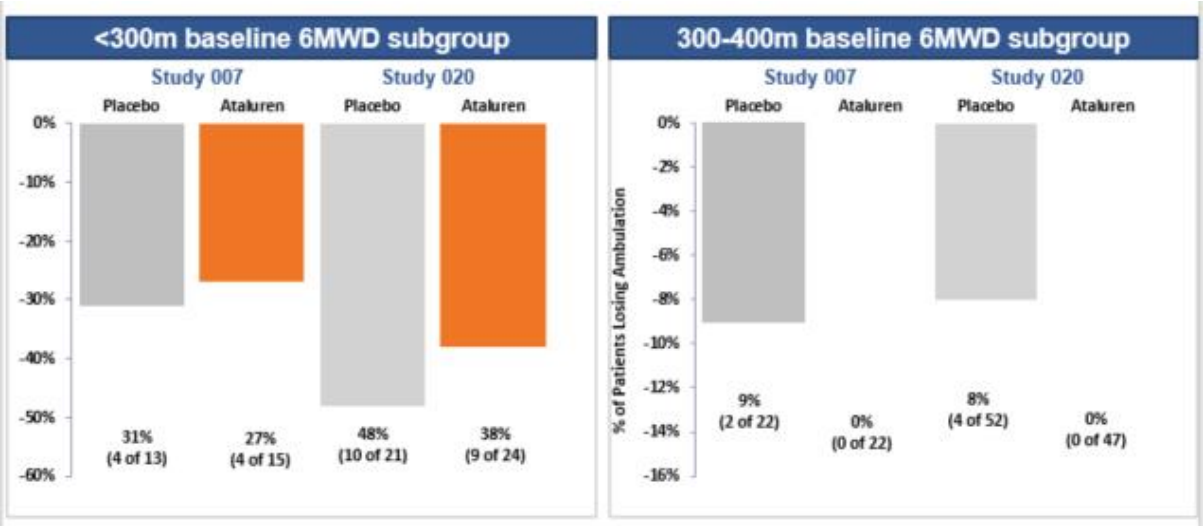
Davis, SE, Hynan, LS, Limbers, CA, Andersen, CM, Greene, MC, Varni, JW, et al. The pedsql in pediatric patients with duchenne muscular dystrophy: Feasibility, reliability, and validity of the pediatric quality of life inventory neuromuscular module and generic core scales. J Clin Neuromuscul Dis 2010;11(3):97-109.

McDonald, CM, McDonald, DA, Bagley, A, Sienko Thomas, S, Buckon, CE, Henricson, E, et al. Relationship between clinical outcome measures and parent proxy reports of health-related quality of life in ambulatory children with duchenne muscular dystrophy. J Child Neurol 2010c;25(9):1130-1144.

6) **The expert group were not able to find data for secondarily stratified subgroups in the analysis of the LoA**

Stratification of loss of ambulation to evaluate subjects with baseline 6MWD of <300 meters in Study 007 and Study 020 indicates a slightly greater percentage of subjects treated with ataluren who remained ambulatory over the 48-week treatment period than those receiving placebo (see Figure below). These findings are consistent with ataluren therapy slowing disease progression in patients who are rapidly losing muscle function at a highly variable rate.

Figure: Summary of Loss of Ambulation in Subjects with Baseline 6MWD of <300 meters or ≥300 to <400 meters.



7) **The statement No clinical added value for the overall population of patients over 5 years or older with nmDMD**

DMC expert committee estimates that ataluren for nmDMD brings no clinical added value for the overall population of patients aged 5 years and older compared with placebo. On this point, conscious of the structural limitations of trials in rare orphan disease and especially in DMD, PTC Therapeutics wants to firmly communicate its disagreement with the support of the experts and medical community.

CHMP assessed the clinical efficacy based on 007 and 020 studies and it is stated in the SmPC that "results indicate that ataluren 40 mg/kg/day slows the loss of walking ability in nmDMD patients." SmPC 5.1 section. CHMP also concludes "Over 48 weeks, ataluren-treated patients showed less decline in muscle function, as evidenced by smaller increases in the time to run/walk 10 meters, climb 4 steps, and descend 4 steps in the ataluren-treated group relative to placebo. The differences favoring ataluren versus placebo in mean changes in timed function tests at Week 48 in the ITT population reached the threshold for a clinically meaningful difference (changes ~1 to 1.5 seconds)."

Moreover, disease progression models have been evaluated by NICE in the UK. The current accepted estimate based on statistical trends in 6 MWT are that TRANSLARNA® could delay loss of ambulation to an extent ranging from 7 to 12 years. (reference https://www.nice.org.uk/guidance/hst3/documents/final-evaluation-determination-document). Assessing clinical data with TRANSLARNA® and considering opinions of the medical community (treating specialists), the evidence review group concluded that "ataluren was an

innovative treatment and could be likely to stimulate further research in this therapy area". Considering the evidence was limited based on 48 weeks follow up, NICE agreed to engage into a conditional reimbursement process with further local data collection.

Finally, more recent long-term evidence from 019 study and 025 study, initially not included in the Danish submission, demonstrates an average age of loss of ambulation at 16.3 years old (019 study) and median age of loss of ambulation at 16.5 years old (025 trial). These new elements confirm the delay in loss of ambulation of several years compared to alternative best supportive care without TRANSLARNA.

REFERENCES:

Delage A, et al. Effect of ataluren on age at loss of ambulation in nonsense mutation Duchenne muscular dystrophy: observational data from the STRIDE Registry. Poster presented at the 23rd International Annual Congress of the World Muscle Society, October 2–6, 2018, Mendoza, Argentina.

8) The quality of evidence has consequently been assessed as low.

It is stated in the DMC report that the quality of evidence has been assessed as low. PTC therapeutics considers this evaluation to be highly inappropriate for the following reasons.

When assessing the quality of evidence, the clinical trial was assessed positively both from a Good clinical practice standard perspective by EMEA as well as through the Cochrane Risk of Bias in annex 2 of the report. When conducting randomized double blinded placebo controlled clinical trials major Evidence Based Medicine rate these trials as high level of evidence (level 1). Since 007 and 020 are individually underpowered with wider confidence intervals, a moderate level of evidence rating would be more appropriate (level 2). Low level evidence base demonstrations are reserved to systematic reviews, case control studies or even expert opinion (Center of Evidence Based Medicine scope for example).

Since PTC Therapeutics has invested [redacted] in Research and Development for patients in Duchenne, an area where many industry sponsored trials have failed, and conducted 7 major clinical trials to date (004, 007, 016, 020, 030, 025, 041), it seems highly inappropriate and inaccurate to rank the quality of the evidence as low.

The main limitation of the pivotal evidence would rather reside on statistical power and follow up due to the rarity of the condition (approximately 1 case per 1.5 million population) and the short term follow up with phase 2 and 3 trials in a slowly progressing disease (48 week). These elements impact the certainty of efficacy results but not the quality of trial design.

9) Metaanalyse is not considered as methodological accepted.

DMC report states that the meta-analysis is not considered "methodically sound". On this point, PTC Therapeutics would like to emphasize that 2 major Health Technology Assessment bodies (NICE and G-BA) have accepted the methodology of the meta-analysis as supportive evidence. As an example, based on the meta-analysis and subgroup analysis, the ERG expert committee of NICE concluded for the 300-400m subgroup that "both sets of results for this subgroup showed statistically significant differences in the 6MWD at 48 weeks between ataluren and best supportive care ".

10) The expert committee attaches the greatest importance to the effect estimates from study 020, due the greater number of patients in that study compared to 007.

The findings that Study 007 showed a greater change from baseline compared with placebo at Week 42 in the 6-minute walk test (6MWT) than that observed in Study 020 (31.7 meters vs. 13.7 meters, respectively) likely reflect the fact that the inclusion criteria for Study 020 (ie, baseline 6MWD ≥150 meters and a maximum 6MWD <80% predicted) failed to exclude higher-functioning, more stable patients. Both the mean and median baseline 6MWD were higher in Study 020 (mean, 363 meters and median, 375 meters) than in Study 007 (mean, 356 meters and median, 360 meters). Even when comparing the Study 020 population to Study 007 ambulatory decline phase population, defined as having the same inclusion criteria as Study 020, the baseline 6MWD in Study 020 was still 23 meters greater. More stable patients, regardless of treatment arm, are less likely to show measurable change in muscle function over 48 weeks. To evaluate treatment effect in these more stable patients would require much longer studies than 48 weeks.

Clinical study results indicate that treatment effects using the 6MWT are more likely to be observed in patients in the gradual declining stage of the disease (ie, ≥300 to <400-meter baseline 6MWD) than in patients in the stable phase (≥400-meter baseline 6MWD) or the rapid decline phase (<300 meters baseline 6MWD) of the disease (McDonald 2017a).

Of note, the treatment effect observed in Study 007 and Study 020 were similar for the timed function tests (TFTs) (see Table below).

Table: Difference between Placebo and Ataluren Treatment Arms in 6MWD of Change from Baseline at Week 48

Timed function tests	Study 007	Study 020
10-meter walk run	-1.4 (-3.5, 0.8)	-1.1 (-0.3, 2.4)
4-stair climb	-2.6 (-4.8, -0.3)	-1.4 (-0.1, 29)
4-stair descend	-1.7 (-4.2, 0.7)	-2.0 (0.43, 3.5)

It is important to understand that, although TFTs and the 6MWT are highly correlated, the two tests evaluate different properties of muscle function. The 6MWT assesses endurance, which is difficult in patients with severely compromised ambulatory function (McDonald 2013a). In contrast, TFTs measure muscle burst activity (McDonald 2013a). Timed function tests assess functional aspects of proximal muscle strength required for everyday activities, can predict wheelchair dependency, and are prognostic for loss of ambulation (Straub 2018). The 6MWT is a validated outcome for evaluating ambulatory DMD patients (McDonald 2017a, Straub 2018). The 6MWT may be less sensitive to changes in muscle performance in certain subgroups of patients, as it does not measure muscle power but rather is reflective of cardiopulmonary function and a patient's overall "well-being" (Arora 2018). In addition, given the duration of the test, the performance of 6MWT may be more subject to compensatory strategies than TFTs (Arora 2018). While severely affected patients may not be able to perform a 6MWT, they may still be able to perform the 10-meter run/walk test. In addition, TFTs require less motivation from a patient compared with the 6MWT (Arora 2018).

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Straub, V and Mercuri, E. Report on the workshop: Meaningful outcome measures for duchenne muscular dystrophy, london, uk, 30-31 january 2017. Neuromuscul Disord 2018.

11) The expert committee do the evaluation that ataluren does not provide clinical added value due to that it does not meet minimal clinically relevant difference in 020-study.

A predefined target for the minimum clinically relevant difference of 30 meters cannot be defined across the entire study population since the MCID (Minimal Clinically Important Change) in DMD patients appears to vary with individual patient-level considerations, depending on age and baseline walking ability (*Goemans N, Kirschner J, Mercuri E. New Perspectives in the Management of Duchenne Muscular Dystrophy [Internet]. 2014 [cited 10th NOV 2018]. Available from: http://www.touchneurology.com/articles/new-perspectives-management-duchenne-muscular-dystrophy*).

According to Henricson et al. (2013) the change in therapeutically relevant 6MWD was dependent on baseline mobility for constant clinically relevant changes in PODCI (Pediatric Outcomes Data Collection Instrument). For example, a clinically meaningful improvement in the PODCI score (4.5 m) from a low PODCI range from 30 to 34.5 was associated with a change of only 5.6 m in the 6MWD. Based on a PODCI score of 90 points, a change of 4.5 points was associated with an increase of the relevant 6MWD by almost 46 m. (*Henricson E, Abresch R, Han JJ, Nicorici A, Goude Keller E, de Bie E, et al. The 6-minute walk test and person-reported outcomes in boys with duchenne muscular dystrophy and typically developing controls: longitudinal comparisons and clinically-meaningful changes over one year. PLoS Curr. 2013;5*.)

Therefore, even lower MCID as shown in the clinical trials 007 and 020 can be considered clinically meaningful.

12) Evaluation of no clinical value when evaluating motoric function with NSAA.

The North Star Ambulatory Assessment (NSAA) is a functional scale that measures gross motor function in ambulant children based upon 17 different functional milestones (Mazzone 2009). The NSAA was developed specifically to measure DMD disease progression. However, the NSAA is limited when evaluating heterogenous populations of DMD patients as it shows a “ceiling effect” (ie, upper limit) in patients with >400-meter 6MWD and a “floor effect” (ie, lower limit) in patients with 6MWD of <300 meters, and hence, is not sensitive to evaluating these two populations.

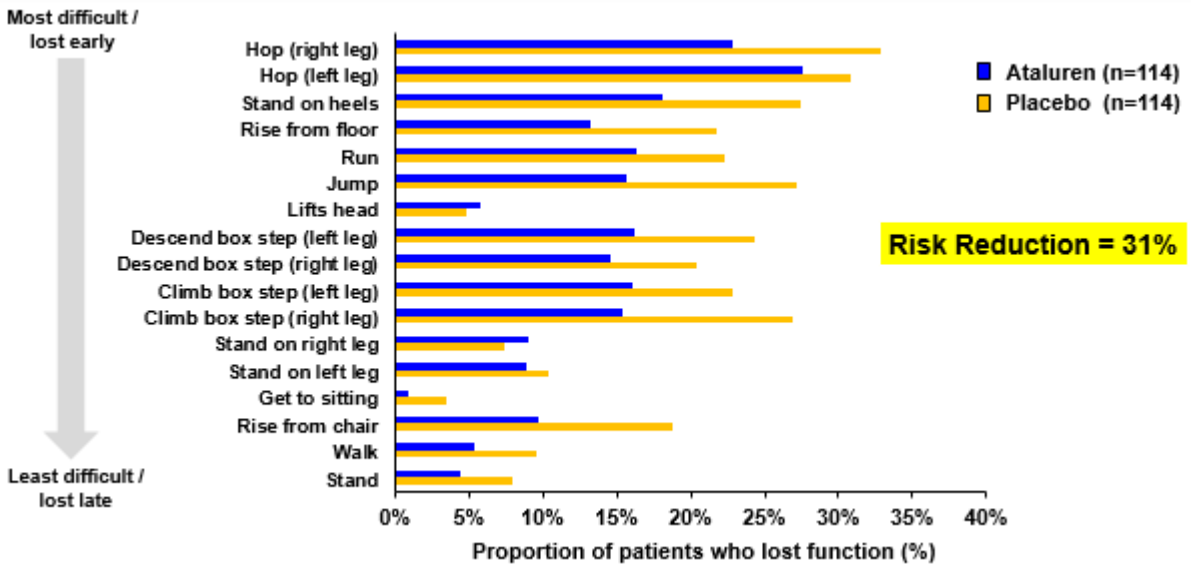
Although the NSAA total score gives important insight into gross motor function, recent analysis of the instrument has shown that evaluation of complete loss of function of one or more of the individual 17-evaluated functions may be the best way to assess treatment effect in Duchenne muscular dystrophy (DMD)

(McDonald 2017a). Patients tend to lose higher functions, such as hopping and running, first and through analysis of loss of individual functions it may be possible to determine important treatment effects that would not be apparent when considering only the total score. In addition, scoring a difference from 2 ("normal" with no obvious modification of activity) to 1 (modified method to achieve goal independent of physical assistance from another) can be subjective to the opinion of the assessor. Hence, a change from 2 or 1 to 0 (unable to perform a function) is a clearer definitive change as opposed to a decrease in function.

The results from Study 020 ae striking when comparing the loss of individual functions preserved in ataluren-treated patients versus placebo-treated patients (see Figure below). In nearly all measures, muscle function was retained in more patients in the ataluren group than the placebo group. The level of preservation was quantified by calculating the proportion of patients who lost the ability to perform individual functions in each treatment arm to obtain the risk ratio of losing a motor function. The risk ratio for ataluren versus placebo was 0.69 (p=0.010, post-hoc permutation test) across the 17 -functional outcome measures (McDonald 2017a). This means that among patients who could carry out an activity either normally or with compensation at baseline, ataluren-treated patients had a 31% reduction in risk of losing that activity, demonstrating ataluren preserved meaningful functions in patients with nmDMD.

Loss of an individual function is important as loss of any of these functional milestones are irreversibly in DMD patients and significantly impact the patients and their families (McDonald 2017a). Hence, the observation that a lower percentage of patients treated with ataluren loss a motor function compared with placebo is important.

Figure: NSAA Loss of Function Results in Study 020 (ITT)



Abbreviations: ITT, intent-to-treat; NSAA, North Star Ambulatory Assessment
Source: PTC124-GD-020-DMD Table 92

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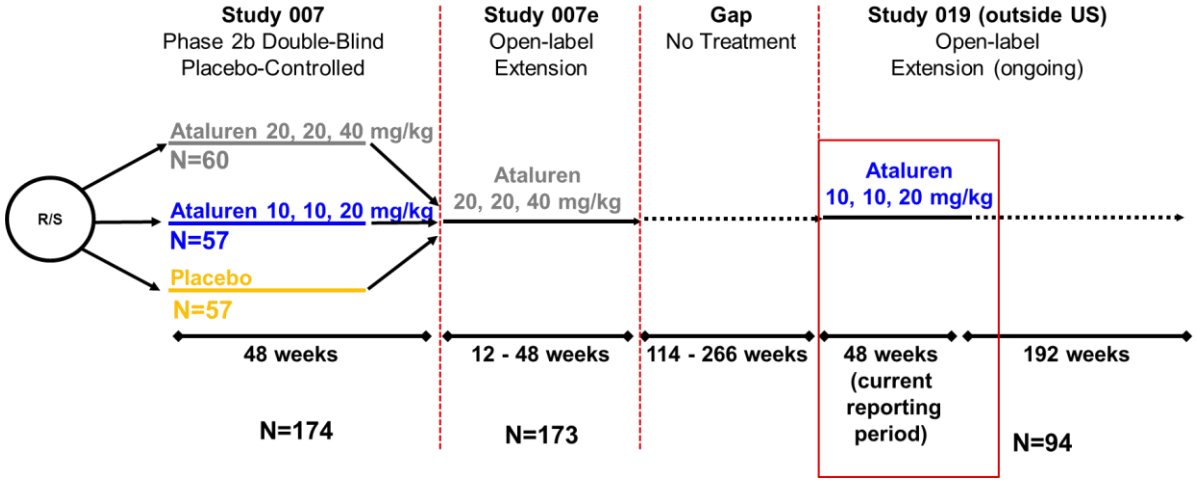
13) No data found in lungfunction in ambulatory patients

Early-onset respiratory failure is the primary cause of death in a significant proportion of the DMD population, indicating the importance of preservation of lung function. Abnormal respiratory function is present in DMD almost as soon as it can be measured reliably, from around age 8 onward [Phillips 2001]. Serial measurements of forced vital capacity (FVC) provide a simple, reliable and clinically useful measure of assessing disease progression in DMD [Phillips 2001] and is frequently used in everyday clinics, especially during the non-ambulatory stage where pulmonary function declines more rapidly in DMD patients. An FVC decrease below a threshold of 1 litre (L) is strongly associated with mortality [Phillips 2001, Finder 2004], as illustrated in Figure 2. The median age at which the FVC reaches 1 L is 17 (range 13 – 25.5) years in DMD patients and this signals a high probability of death within the next 3 years [Phillips 2001]. Contemporary natural history data also shows progression below a forced vital capacity of 1 litre to be associated with a 4-fold increased risk of death (McDonald 2017b).

The age at which FVC starts to decline is prognostic for long-term progression of pulmonary function in DMD patients. In the CINRG patient cohort the average maximum FVC **peaked at age 12.5 years** and then started to decline, marking the onset of progressive pulmonary decline.

Study 019 is a long-term extension of study 007 with the following design:



FVC function has been captured. Patients who had been receiving ataluren continued to see an increase in FVC **until 16.5 years of age**. This represents a 4-year delay in onset of lung function decline in the population treated with ataluren relative to patients treated with standard of care. The inflection point shift by 4 years in ataluren treated patients means they are closer to a normal inflection point of 19 to 21 years for healthy controls.

Study 025 is being conducted to evaluate the long-term safety and effectiveness and utilization pattern of ataluren in routine clinical practice. In Study 025, pulmonary function was assessed via spirometry, according to the clinical routine. The interim analyse after 1.4 years of treatment with ataluren show the annualized change in % predicted FVC of -1.4%, much lower than that reported in natural history studies, with the annual decline ranging from 4.7-8.8% in studies of DMD patients not using corticosteroids and ranging from 4.4-5.9% in studies of patients mainly using corticosteroids [Meyer 2017].
Further analysis was carried out to compare FVC decline in ambulatory patients aged 6 to 16 years in Study 025, suggesting the preservation of lungfunction >80% threshold for FVE% predicted.

Taken together, the real world data from Study 025 and the results from Study 019 show that ataluren is having an additional benefit in stabilising pulmonary function in ambulatory patients beyond delaying the time to loss of ambulation.

The conclusion from the expert group not to put this data into context in the evaluation of ataluren clinical value of lungfunction is highly unfortunate, where the evaluation don´t assess critical clinical meaningful data into the overall evaluation of Translarna.

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Mayer, O.H., et al., Efficacy of Idebenone to Preserve Respiratory Function above Clinically Meaningful Thresholds for Forced Vital Capacity (FVC) in Patients with Duchenne Muscular Dystrophy. J Neuromuscul Dis, 2017. **4**(3): p. 189-198.

14) Estimates in loss of ambulation are generally associated with major uncertainties.

DMC rightfully mentions loss of ambulation as being the key criteria in ambulatory patients aged 5 years and older. New results from the ambulatory patients in 019 show an average age of loss of ambulation at 16.3 years old and recent real-world evidence trials in Europe (study 025) demonstrated a median age of loss of ambulation of 16.5 years old. In comparison CINRG data set, a reflection of natural history of the disease indicated age of loss of ambulation without TRANSLARNA® of 10 to 11 years old.

Loss of ambulation is a devastating negative milestone in DMD, with a host of consequences for patients and their families. Less independence for the patient and more burden for the parent/caregiver impairs quality of life. Full-time wheelchair dependence increases risk for onset of scoliosis, often requiring surgery. Age at loss of ambulation correlates with age at loss of upper limb function, such as the ability to feed oneself, and age at need for mechanical ventilation. For these reasons, prolongation of walking ability is a major goal of treatment in DMD. A delay of even 2 years can dramatically benefit patients and their families, particularly given the relatively short-life span of this patient population.

In both Study 007 and Study 020, loss of ambulation was observed less frequently in ataluren-treated patients versus placebo in the overall study population, as well as the <300 meters group and the ≥300 to <400 meters group (see Table below). No cases of loss of ambulation in the ≥400 meters group occurred, highlighting the stability of this higher-functioning patient population over a 1-year period.

The small number of subjects who lost ambulation both Study 007 and Study 020 limits the interpretation of the results, and highlights the need of long-term studies, such as PTC124-GD-019-DMD (Study 019) and PTC124-GD-025o-DMD (Study 025o), to evaluate the ability of ataluren to delay loss of ambulation. An Interim analysis of Study 019 indicates that after 4 years ataluren therapy was associated with a ≥1.5-year delay in loss of ambulation compared with natural history controls (see Clinical Efficacy Summary document).

Table: Loss of Ambulation by Baseline 6MWD Category (Study 007 and Study 020)

Study	<300 m	≥300 to <400	≥400 m	Overall
Study 007				
Placebo	4/13 (31%)	2/22 (9%)	0/22	6/57 (11%)
Ataluren 10, 10, 20 mg/kg	4/15 (27%)	0/22	0/20	4/57 (7%)
Study 020				
Placebo	10/21 (48%)	4/52 (8%)	0/41	14/114 (12%)
Ataluren 10, 10, 20 mg/kg	9/24 (38%)	0/47	0/43	9/114 (8%)
Overall				
Placebo	**14/34 (41%)**	**6/74 (8%)**	**0/63**	**20/171 (12%)**
Ataluren 10, 10, 20 mg/kg	**13/39 (33%)**	**0/69**	**0/63**	**13/171 (8%)**

Abbreviations: 6MWD = 6-minute walk distance
Sources: PTC124-GD-007-DMD Table 28a, PTC124-GD-020-DMD Table 27

15) Adverse event and comment on long term safety requirement.

As of 31 July 2018, >2000 unique subjects have been exposed to ataluren either in clinical trials investigating the use of ataluren for various indications or exposed to commercial ataluren since the marketing date in July 2014.

Based on the cumulative review of adverse event data and the most recent PBRER (Periodic Benefit Risk Evaluation Report) (time-period 01 Aug 2017 to 31 July 2018), no new safety signals or trends have been identified. The adverse events reported are consistent with underlying disease progression or known risks with the use of ataluren. PTC Therapeutics will continue to monitor all new safety data and safety concerns per Risk Management Plan which includes important identified risks of "potentiation of aminoglycoside renal toxicity" and important potential risks of "long-term cardiovascular effects including changes in lipid profile", "hypertension with use of concomitant systemic corticosteroids", "renal toxicity", "hepatic toxicity", "hibernoma", and "general malignancies".

16) Absence of dose response in study 007.

The lack of dose response observed in Study 007 likely reflects the fact that ataluren shows a bell-shaped concentration response-relationship, which has also been observed in other premature codon readthrough agents. Drugs like ataluren and aminoglycosides that interact with the ribosome to modulate translation readthrough can demonstrate bell-shaped dose response relationships. In general, such bell-shaped dose responses are indicative of complex interactions with the ribosome, ie, they imply the existence of more than one binding site for the respective drugs. Considering that the translation machinery includes large and small ribosomal subunits, four ribosomal ribonucleic acids (rRNAs), over 100 ribosomal proteins, multiple transfer ribonucleic acids (tRNAs) for each amino acid, and numerous other factors that regulate initiation, elongation, termination, and recycling, it is not surprising that small molecules may have complicated interactions with the ribosome.

The nonsense-suppressing activity of aminoglycosides in prokaryotic ribosomes is well understood. Aminoglycosides bind to the bacterial 16S rRNA of the small ribosomal subunit in such a way that two bases normally involved in maintaining ribosomal A site fidelity are "flipped" to a state that allows tRNA mismatches

with the codon in the A site. When a nonsense codon is in the ribosome's A site, this relaxation of the stringency of A site fidelity allows a near cognate tRNA with imperfect tRNA-mRNA matches to be inserted into the ribosomal A site and promote nonsense suppression.

Aminoglycosides also demonstrate bell-shaped curves when enabling nonsense suppression (Burke 1985, Lai 2004, Bellais 2010). Only recently, however, have studies been performed that explain why low doses of aminoglycosides enable nonsense suppression while higher doses inhibit nonsense suppression. It had always been thought that there was a single aminoglycoside binding site on the ribosome, but now it is clear that there are two such sites, one with high affinity for aminoglycosides and the other with low affinity (Borovinskaya 2007, Wang 2012). While high affinity aminoglycoside binding at the A site (the "first" site) enables nonsense suppression, the reduced readthrough activity seen with elevated doses of aminoglycosides is attributable to inhibitory effects caused by binding at the second site. The second aminoglycoside-binding site is associated with a unique region of the large ribosomal subunit (Borovinskaya 2007, Wang 2012) and ribosome conformational changes caused by binding at the second site override the effects of drug-binding at the A site. The second binding site has lower binding affinity for aminoglycosides than the first site, explaining why binding there requires higher concentrations of drug.

These results suggest a parallel model for ataluren's activity. Ataluren is active in cell-free translation systems (Welch 2007) so it likely targets the translation apparatus. Data suggest that ataluren interacts with human but not bacterial ribosomes (Study report PTC124-16057). Thus, in the presence of a nonsense codon, and in the absence of drug, the ribosome would be in a conformational state that allows premature translational termination to occur. However, in patients and animals undergoing ataluren therapy, ataluren binding, like that of the aminoglycosides, would initially reduce A site fidelity and increase nonsense suppression. We hypothesize that ataluren, like aminoglycosides, also has a second, weaker binding site that alters the ribosome's conformation, such that ataluren binding at this site changes the conformation of the ribosome and dominantly antagonizes the nonsense suppression effects of ataluren's high affinity site. Thus, the bell-shaped curve can be explained by increased nonsense suppression as ataluren fills the high affinity site and inhibition of nonsense suppression when ataluren binds the second site.

The relationship of ataluren dose and readthrough activity has been observed to be bell-shaped in a number of in vitro and nonclinical model systems consistent with a 2-site interaction model observed for other classes of readthrough agents.

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Westfall, PH and Young, SS (1993). The minp method for multiple comparison under heteroscedasticity. In Re-sampling-based multiple testing. Examples and methods for p-value adjustments; New York, Wiley:285-288.

17) In study 007, statistically significant effects in the overall population (CITT analysis) are seen, but the efficacy is not statistically significant in the ITT assay, which expert group attribute to the greatest weight.

Prior to the market authorization, the EMA performed a scientific review of the available data leading to the conditional approval in the EU. Although the efficacy data available lacked robustness, the beneficial effects of ataluren were considered plausible and clinically relevant for this rare disease with high unmet medical need. The observed safety profile of ataluren was overall comparable to that of placebo (Haas et al 2015).

In the most recent EPAR, Aug 31 2018 (EMA/423254/2018), EMA reconfirmed that Translarna's benefits are greater than its risks and it continues to be authorized for use in the EU. This is also based on the findings in 020-study.

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EPAR Translarna, last updated 31/08/2018. https://www.ema.europa.eu/medicines/human/EPAR/translarna

Conclusion:

EMA states in the current EPAR, *"despite the need for further data, the Agency considered that the evidence suggests that Translarna slows the progression of the disease and that its safety profile is not of major concern. The Agency acknowledged that patients with Duchenne muscular dystrophy have an unmet need for treatment of this serious condition."*

The clinical research shows multiple lines of evidence, demonstrating that ataluren is well tolerated and clinically effective in promoting dystrophin production and in delaying loss of muscle function in boys with nmDMD.

In the two 48-week randomized controlled trials (Study 007 and Study 020), ataluren produced clinical benefit compared with placebo across multiple muscle function tests (table 1 in the annex 1). The positive effects occurring by chance across primary and key timed function tests secondary endpoints is <1%.

The totality of the data across studies demonstrates the ability of ataluren to slow the rate of disease progression in patients with nmDMD, and indicate it is well tolerated. These findings support the positive benefit-risk profile of ataluren. Given the inherent challenges in clinical development of drugs for rare diseases, including limited patient population, heterogeneity of patients within the disorder, natural history not well (or incompletely) understood, and endpoints/outcome measures not well defined, the FDA agrees that the totality of the evidence is appropriate to consider when evaluating the benefit of a drug.
The updated clinical efficacy summary is a part of this formal response and are attached as **Annex 1**, which summarize the totality of evidence across two ataluren nmDMD placebo-controlled studies and well as data generated from long-term studies and the registry Study025o provide compelling evidence of the significant benefit ataluren is providing to nmDMD patients

Under current standard of care, nmDMD remains a disease with devastating consequences and bleak prognosis. The progressive and irreversible effects of DMD underscore the importance of early intervention with treatments that have the potential to slow physical deterioration and delay the natural course of this ultimately fatal disease. The consequence of not giving access to Translarna in Denmark is of outmost concern for the remaining patients that still have no access to Translarna. The proposed evaluation; **No clinical value** for ataluren is strongly disagreed and missleading by not taking all available scientific data into consideration.

Kind regards

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ANNEX 1

Part of the formal response to Danish Medicin Council drafted evaluation evaluation of clinical value for ataluren in Duchenne muscle dystrophy

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1 INTRODUCTION

Duchenne muscular dystrophy (DMD) is a rare, debilitating, progressive, and ultimately fatal childhood genetic disease; the average life expectancy of a DMD patient is 25 years (Eagle 2002, Bushby 2010a, Bushby 2010b, Henricson 2013). Currently, there are no medications that cure or reverse the effects of DMD. The goal of current interventions is to help slow or stabilize disease progression, prolong patients' ability to manage activities of daily living, and delay the onset of subsequent deterioration. As loss of muscle tissue is irreversible, hence, early treatment is imperative to stall muscle degeneration and preserve muscle tissue while it is still intact. Recent clinical guidelines recommend treatment with glucocorticoids, which have beneficial effects on prolonging ambulation as well as muscle and respiratory function (Bushby 2010a, Bushby 2011, Henricson 2013, McDonald 2017b). While corticosteroids can address the inflammatory component of the disease, boys with DMD still lose muscle function resulting in loss of ambulation and permanent wheelchair dependency at around 12 to 15 years of age (Goemans 2013, Ricotti 2013). In addition, the benefits of corticosteroids must be balanced with a side effect profile that presents significant challenges. Hence, treatment options, such as Translarna® (ataluren), are needed to treat the lack of dystrophin protein.

The goal of ataluren treatment is to produce a sufficient amount of the dystrophin protein to alter disease progression in patients with nmDMD. In nonsense mutation DMD (nmDMD) a single base variation in a patient's DNA results in a premature stop codon within the corresponding mRNA, thereby terminating translation before a full-length protein is generated. Approximately 10% of DMD cases are due to a nonsense mutation in the dystrophin gene (Bladen 2015).

Ataluren allows ribosomes to read through the premature stop codon present in the dystrophin gene in patients with nmDMD, whilst respecting the normal stop codon, to restore the synthesis of full-length functional dystrophin protein (Translarna-SmPC 2017). Multiple lines of compelling evidence exist that demonstrate that even low levels of dystrophin protein can alter disease progression. Dystrophin replacement studies in a DMD mouse model have demonstrated that low levels of dystrophin protect mice from eccentric contraction-induced muscle injury (Sharp 2011, Wu 2011, Kayali 2012). Furthermore, patients with specific genetic lesions in exon 44 produce very low levels of dystrophin protein, due to exon skipping, and demonstrate a milder DMD phenotype than those with nonsense mutations (Anthony 2014). There is increasing consensus within the DMD academic community and among regulatory authorities that small increases in dystrophin predict clinical benefit in patients with DMD (FDA 2016b), and serve as an important proof-of-mechanism to support evidence of clinical efficacy of dystrophin-restoring therapies.

At the outset of the ataluren clinical development program, little to no information regarding the natural history of DMD or understanding of appropriate treatment outcome measures for clinical trials was available. PTC Therapeutics (PTC) was the first to conduct a registration directed, randomized, placebo, controlled study in nmDMD patients which contributed to a clearer understanding of the natural history of the disease. In addition, several natural history studies have recently given greater insight into DMD. Through these studies, a clearer understanding of the most appropriate efficacy outcomes for assessing treatment effect has emerged.

In addition, it has become apparent that DMD populations are heterogenous, which may impact the assessment of therapeutic effect. Patients who have a baseline 6-minute walk distance (6MWD) of ≥400 meters are typically in the "**Stable Phase**," characterized by negligible changes or improvement in 6MWD over the 1-year period of most DMD clinical trials. This stable phase can last for several years during which muscle loss may occur but the DMD patient can compensate and remains stable. The stable phase is followed by a "**Transition Phase**" in which the patient's 6MWD declines at a steady rate. Typically, transition phase patients have a baseline 6MWD in the 300≥ to <400-meter range. During the transition a phase of the disease muscle function is steadily lost; and hence, a phase that is more sensitive to possible therapeutic effect within 1-year trial. The transition phase is followed by the "**Accelerated Decline Phase**" which commonly occurs when patients' 6MWD drops <300 meters and is typified by very rapid loss of muscle function. Muscle loss continues and reaches a threshold (~80% of muscle replacement with fat) at which patients show large and often abrupt declines in walking ability as measured in the 6-minute walk test (6MWT), leading to loss of ambulation (McDonald 2017b).

As is common in rare diseases, the specific outcome measures and study designs required to evaluate a drugs ability to delay disease progression in DMD is evolving. Recent natural history and clinical study results indicate that evaluation of a drugs effect in patients in the stable phase of the disease requires long term studies (ie, >1 year). Moreover, it has recently become apparent that a single endpoint, such as the 6MWT may not be appropriate for evaluating all phases of DMD, such as patients with 6MWD <300 meters (Arora 2018).

FDA briefing materials for drisapersen and eteplirsen (other therapeutic agents targeting dystrophin restoration in DMD) implicitly support the validity of using the ≥300- to <400-meter baseline 6MWD criteria as the most sensitive for detecting beneficial drug effect in a year-long clinical study (FDA 2016a).

1.1 Overview of clinical efficacy

Multiple lines of evidence demonstrate that ataluren is well tolerated and clinically effective in promoting dystrophin production and in delaying loss of muscle function in boys with nmDMD.

The key findings that substantiate ataluren's efficacy and favorable benefit-risk profile are briefly summarized below:

- Ataluren promotes production of functional, full-length dystrophin protein in skeletal muscle in nmDMD patients and across multiple muscle types including the tibialis anterior, diaphragm, and heart muscles in animal models of nmDMD (Peltz 2013).
- In two 48-week randomized controlled trials (studies PTC124-GD-007-DMD [Study 007] and PTC124-GD-020-DMD [Study 020]), ataluren produced clinical benefit compared with placebo across multiple muscle function tests (Table 1) (Bushby 2014, McDonald 2017a). The positive effects occurring by chance across primary and key timed function tests secondary endpoints is <1%.
    - In both RCTs, ataluren dosed 10, 10, 20 mg/kg (morning, midday, and evening) preserved muscle function in patients; fewer patients on ataluren

relative to placebo experienced loss of discrete motor abilities and complete loss of ambulation.

  - In both RCTs, the benefit on the muscle function tests with ataluren 10, 10, 20 mg/kg therapy was most apparent in the subgroup of patients in the transition phase of the disease; the phase of the disease that is more sensitive to possible therapeutic effect within a 48-week trial.
  - A meta-analysis, which pooled the data from both RCTs, found a significant treatment benefit with ataluren across multiple tests of muscle function.

- In the long-term open-label extension Study 019, ataluren demonstrated a 4-year preservation of pulmonary function in non-ambulatory patients compared with matched external controls from a concurrently conducted natural history study. Ataluren was also associated with a delay in loss of ambulation compared with historical controls.
- Ataluren is well-tolerated and has a favorable safety profile for patients with nmDMD based on a comprehensive safety database and post-marketing experience.

The totality of the data across studies demonstrates the ability of ataluren dosed 10, 10, 20 mg/kg to slow the rate of disease progression in patients with nmDMD, and indicate it is well tolerated. These findings support the positive benefit-risk profile of ataluren. Given the inherent challenges in clinical development of drugs for rare diseases, including limited patient population, heterogeneity of patients within the disorder, natural history not well (or incompletely) understood, and endpoints/outcome measures not well defined, the FDA agrees that the totality of the evidence is appropriate to consider when evaluating the benefit of a drug (Rossi 2018).

Table 1 Summary of Results from Study 007 and Study 020

	Study	Population	Favors Placebo	Favors Ataluren
6MWT				
	Study 007	cITT		+
	Study 020	ITT		+
	Meta-analysis	cITT/ITT		**+***
	Study 007	≥300 to <400 6MWD		**+***
	Study 020	≥300 to <400 6MWD		**+***
	Meta-analysis	≥300 to <400 6MWD		**+***
Risk of 10% 6MWD worsening	Study 007	cITT		+
Timed function tests				
Time to run/walk 10 meters	Study 007	cITT		+
	Study 020	ITT		+
	Meta-analysis	cITT/ITT		**+***
	Study 007	≥300 to <400 6MWD		**+***
	Study 020	≥300 to <400 6MWD		+
	Meta-analysis	≥300 to <400 6MWD		**+***
Time to climb 4 stares	Study 007	cITT		+
	Study 020	ITT		+
	Meta-analysis	cITT/ITT		**+***
	Study 007	≥300 to <400 6MWD		+
	Study 020	≥300 to <400 6MWD		**+***
	Meta-analysis	≥300 to <400 6MWD		**+***
Time to descend 4 stairs	Study 007	cITT		+
	Study 020	ITT		**+***
	Meta-analysis	cITT/ITT		**+***
	Study 007	≥300 to <400 6MWD		**+***
	Study 020	≥300 to <400 6MWD		**+***
	Meta-analysis	≥300 to <400 6MWD		**+***
Loss of ambulation	Study 007	≥300 to <400 6MWD		+

	Study	Population	Favors Placebo	Favors Ataluren
	Study 020	≥300 to <400 6MWD		+
	Study 019[1]	total		+
NSAA (Total score)	Study 020	ITT		+
Loss of individual NSAA functions	Study 020	ITT		+
	≥300 to <400 6MWD			+*
FVC[1]	Study 019	total		+
Age when FVC <1 liter[1]	Study 019	total		+

2 OVERVIEW OF DATA FROM PLACEBO-CONTROLLED RANDOMIZED STUDIES

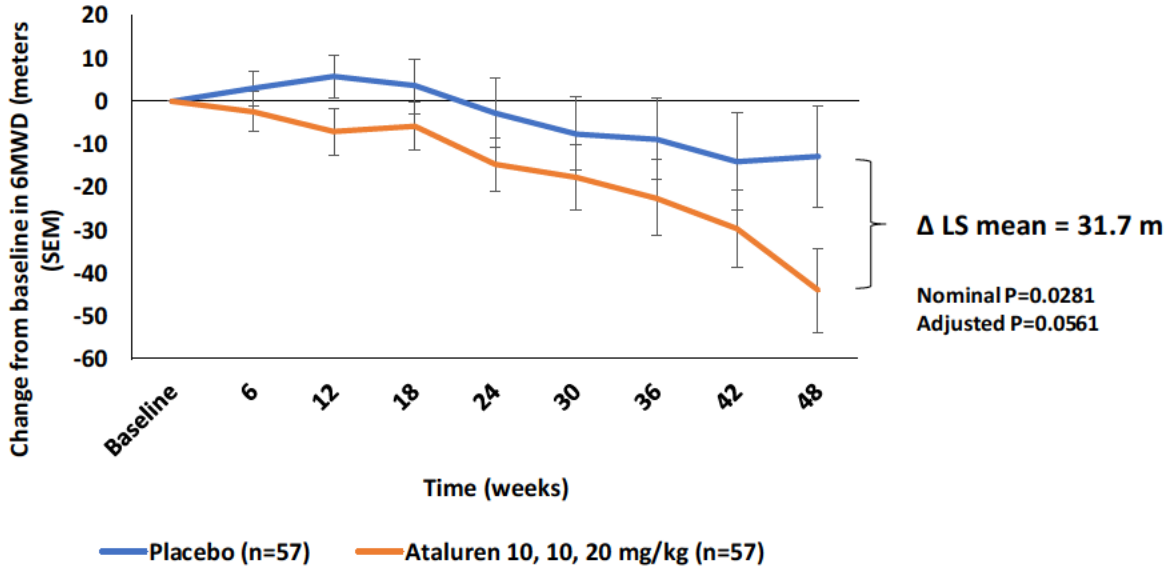
To date, two 48-week randomized placebo-controlled trials have been performed to demonstrate the benefit of ataluren in nmDMD: Study 007 and Study 020 (Bushby 2014, McDonald 2017a).

2.1 Efficacy Findings of Study 007

Study 007 was the first randomized, placebo-controlled dystrophin restoration therapy study ever conducted in nmDMD. Subjects meeting eligibility criteria were randomized to receive ataluren 20, 20, 40 mg/kg, 10, 10, 20 mg/kg, or placebo for 48 weeks. As the 10, 10, 20 mg/kg dose is the commercially available dose, the data presented below focuses on this dosing regimen.

A clinically meaningful and nominally statistically significant treatment benefit was observed with the 10, 10, 20 mg/kg dose. The difference in the mean change in observed 6MWD from baseline to Week 48 between ataluren and placebo was 31.7 meters (adjusted p=0.0561) (Figure 1). Separation of ataluren from placebo was seen at all post-baseline visits. These results were used to support the conditional approval of ataluren in nmDMD in the EMA in 2015.

Figure 1 **Mean Change in Observed 6MWD by Visit (Study 007 cITT)**



Abbreviations: cITT, corrected intent to treat; LS, least squares; 6MWD = 6-minute walk distance; SEM, standard error of mean
Mean changes in the ataluren 10, 10, 20 mg/kg and placebo arms were -12.86 and -44.14 meters, respectively, resulting in an observed difference of 31.3 meters.
Nominal P value = 0.0281; Dunnett's adjustment for multiplicity P value = 0.0561
Source: PTC124-GD-007-DMD CSR Figure 6 and Table 14.2.1.3.1S, Table 14.2.2.12.3S

Timed function test

In Study 007, timed function tests (TFTs) outcomes consistently demonstrated a trend in favor of ataluren 10, 10, 20 mg/kg dosing (Table 2). These tests take an average 6 to 7 seconds to complete at baseline. The benefit of ataluren over placebo on these measures ranged from 1.5 seconds for the time run/walk 10 meters to 2.4 seconds for the 4-stair climb and translate into a 21% to 37% preservation of function. Importantly, the observed differences are clinically relevant and greatly meaningful to patients and their families because they translate in preservation of walking ability; a change of 1 to 1.5 seconds is considered clinically meaningful (Escolar 2011).

Table 2 Summary of Timed Function Test Results for Study 007 (cITT population)

Endpoint, sec	Mean Change from Baseline at Week 48, mean (SD)		Difference, mean	Difference, LS mean (95% CI)	
	Placebo	Ataluren			P value
Time run/walk 10 meters	3.2 (6.6)	1.7 (5.6)	-1.5	-1.4 (-3.5, 0.8)	0.205
Time to climb 4 stairs	4.8 (7.9)	2.4 (4.6)	-2.4	-2.6 (-4.8, -0.3)	0.025
Time to descend 4 stairs	4.1 (7.8)	2.4 (6.2)	-1.6	-1.7 (-4.2, 0.7)	0.163

Abbreviations: CI, confidence interval; cITT, corrected intent-to-treat; LS, least squares; SD, standard deviation
Reference: PTC124-GD-007-DMD CSR Table 14.2.3.2.15, Table 14.2.3.2.2S, Table 14.2.3.3.17, Table 14.2.3.3.2.2S, Table 14.2.3.4.15, Table 14.2.3.4.2.2S

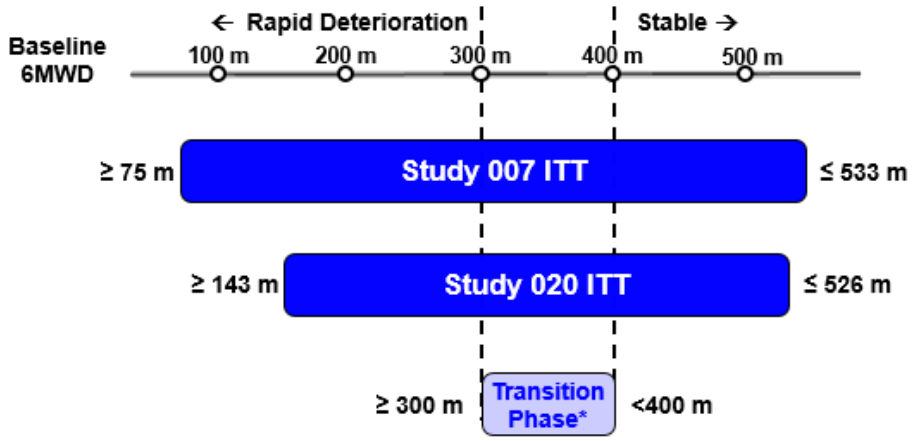
2.2 Efficacy Findings of Study 020

Based on results from Study 007 and greater understanding of the distinct phases of the disease, enrollment criteria were developed for Study 020 to enroll a more enriched patient population. Patients were required to be 7 to 16 years of age and have a screening 6MWD of at least 150 meters but not >80% of the predicted 6MWD. The maximum 6MWD value of 80% of the predicted 6MWD was used in an attempt to remove stable phase patients. However, the 80% predicted 6MWD inclusion criteria failed to adequately exclude these patients.

The failure to exclude stable phase patients is important for understanding the results of Study 020. The patient population of Study 020 had baseline 6MWDs ranging from 143 to 526 meters, indicating that the overall study population was heterogeneous and included patients in the stable, transition, and accelerated decline phases the disease. Of note, while the goal was to reduce the number of stable patients, the 80% of predicted 6MWD inclusion criteria was set too high to adequately exclude these patients. Consequently, a large number of stable patients who are not expected to decline were included in the study (

Figure 2).

Figure 2: Patients' Baseline 6MWD in Study 020 Relative to Study 007



Abbreviations: 6MWD, 6-minute walk distance; ITT, intent to treat
* Pre-specified analysis subgroup in Study 020

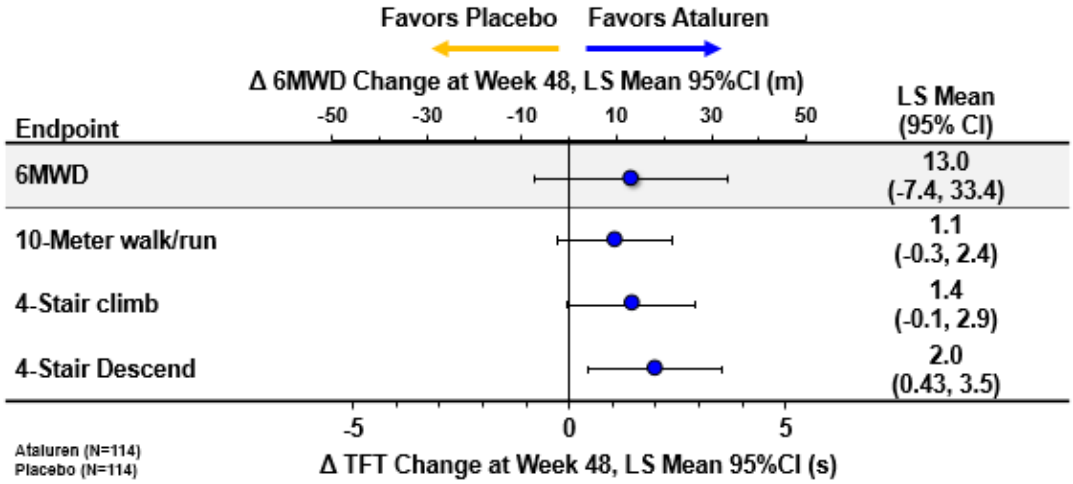
2.2.1 The results favored ataluren in both the primary and secondary endpoints

The summary of the results for Study 020 are shown in (Figure 3). At Week 48, treatment with ataluren demonstrated a favorable trend in 6MWD, with an observed treatment difference of 15.4 meters compared with placebo in the intent to treat (ITT) population (LS mean: 13.0 meters, p=0.213). While the 6MWD results did not reach statistical significance, the nominal improvement on the primary endpoint was supported by results from other study endpoint measures. A treatment benefit was observed for the 10-meter walk/run, 4-stair climb, and 4-stair descend; the stair-climbing and stair-descending results approached and reached statistical significance, respectively. The hazard ratio for 10% persistent worsening in 6MWD was 0.75 for ataluren versus placebo (p=0.160).

The observed effect size for both the 4-stair climb and descend tests was 1.8 seconds, representing a 29% and 37% preservation of function, respectively, based on the mean baseline values of in 6.1 seconds (climb) and 4.9 seconds (descend). The results were similar to those in Study 007.

Although stair-climbing and stair-descending were secondary endpoints in Studies 007 and 020, these results in the ITT populations of two randomized control trials (RCTs) support the efficacy of ataluren, especially considering the known limitations of the primary outcome 6MWT in this disease, such as the 6MWT takes patient cooperation/motivation and evaluates endurance not muscle burst activity.

Figure 3: 6MWT and TFT Results in Study 020 (ITT)



Abbreviations: 6MWD, 6-minute walk distance; CI, confidence interval; ITT, intent to treat; LS, least squares; TFT, timed function test

Ataluren-treated patients also demonstrated greater preservation of the ability to climb or descend stairs. Over the 48-week study, 20% of patients in the placebo group compared with 11% of patients in the ataluren group lost the ability to perform the 4-stair climb, and 18% and 11% of patients on placebo and ataluren, respectively, lost the ability to perform the 4-stair descend.

2.3 The results from the NSAA favored ataluren.

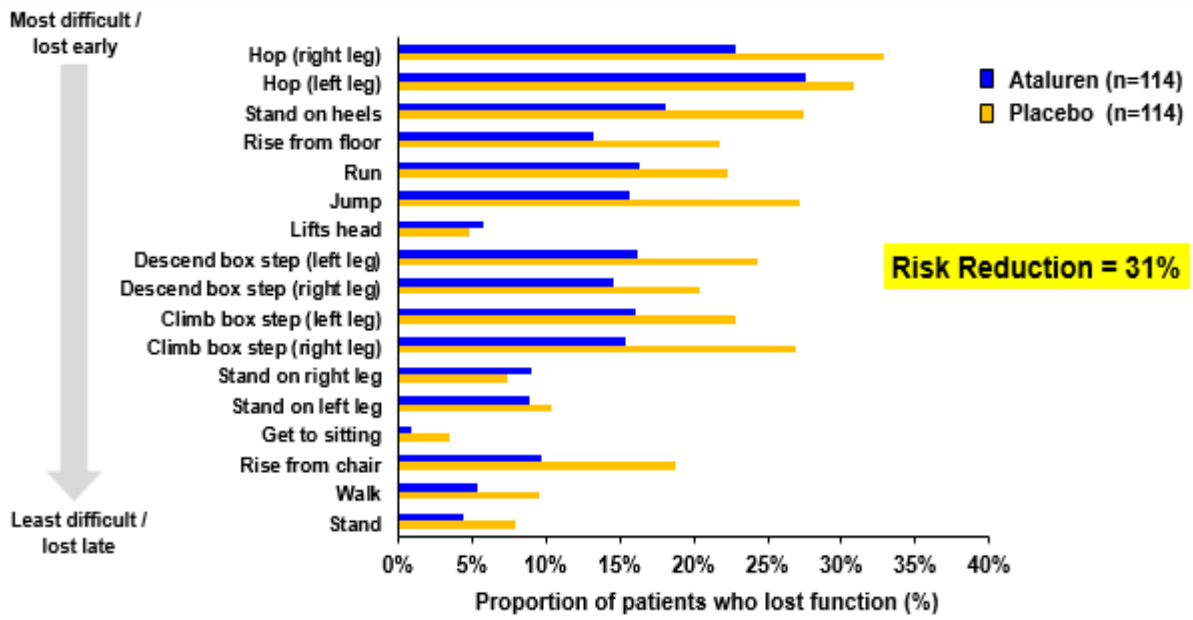
The North Star Ambulatory Assessment (NSAA) is a scale that measures 17 different functional milestones ranging from those that are easier to those that are harder to perform. Each function is scored zero, one, or two, where zero indicates the patient is unable to perform the function, and one and two indicate the patient can perform the function, either with or without difficulty, respectively. The results can be evaluated in two ways. One method is to sum the scores from all 17 measurements, obtaining a total score of 0 to 34. The challenge of the total score is that it is difficult to interpret the meaning of the result. The second approach is to determine the number of functions that were preserved by calculating the proportion of patients that lost the ability to perform a specific individual function (ie, change from a score of 2 or 1 to a score of zero) over the course of the study. This approach is more meaningful in that it allows a comparison of the degree of preservation of function in treated versus placebo patients (Larkindale 2017).

The results for the total NSAA score demonstrated an observed treatment difference of about 1.0 point favoring ataluren in the ITT population (LS mean: 0.8 points, p=0.128). A 1.0-point difference relates directly to the change from performing an item normally to performing it with compensation, or from performing an item with compensation to inability to perform the function (Bello 2016a).

When assessing the loss of function, the results were striking when comparing the individual functions preserved in ataluren-treated patients versus placebo-treated patients (Figure 4). In nearly all measures, muscle function was retained in more patients in the ataluren group compared with the placebo group. The level of preservation was quantified by calculating the

proportion of patients who lost the ability to perform individual functions in each treatment arm to obtain the risk ratio (RR) of losing a motor function. The risk ratio for ataluren versus placebo was 0.69 (p=0.010, post-hoc permutation test) across the 17 functional outcome measures (McDonald 2017a). This means that among patients who could carry out an activity at baseline either normally or with compensation, ataluren-treated patients had a 31% reduction in risk of losing a motor ability. The importance of this result is that it demonstrates that ataluren substantially preserves functions that are meaningful in DMD.

Figure 4: NSAA Results in Study 020 (ITT)



Abbreviations: NSAA, North Star Ambulatory Assessment; TFT, timed function test

2.4 Efficacy Findings in Subgroup Analyses of Studies 007 and 020

As described above, understanding of the natural history of DMD continued to evolve through the course of both studies. The identification of DMD patients in the transition phase, defined as having a baseline 6MWD of ≥300 to <400 meters, was established after the completion of Study 007 and the full enrollment in Study 020. Consequently, both studies enrolled a substantial proportion of stable patients with a baseline 6MWD ≥400 meters and patients with baseline 6MWD <300 meters who are rapidly declining and who are likely to become non-ambulatory. This ultimately contributed to the smaller than expected effect size observed over the 48-week trial period. Importantly, both studies had a substantial number of transition phase patients with which to perform subgroup analyses, with approximately 39% and 43% of subjects in Study 007 and Study 020, respectively, having a baseline 6MWD of ≥300 to <400 meters. Pre-specified analyses of the ≥300 to <400-meter baseline 6MWD subgroup were performed for Study 020; post-hoc analyses of the transition phase subgroup were performed for Study 007.

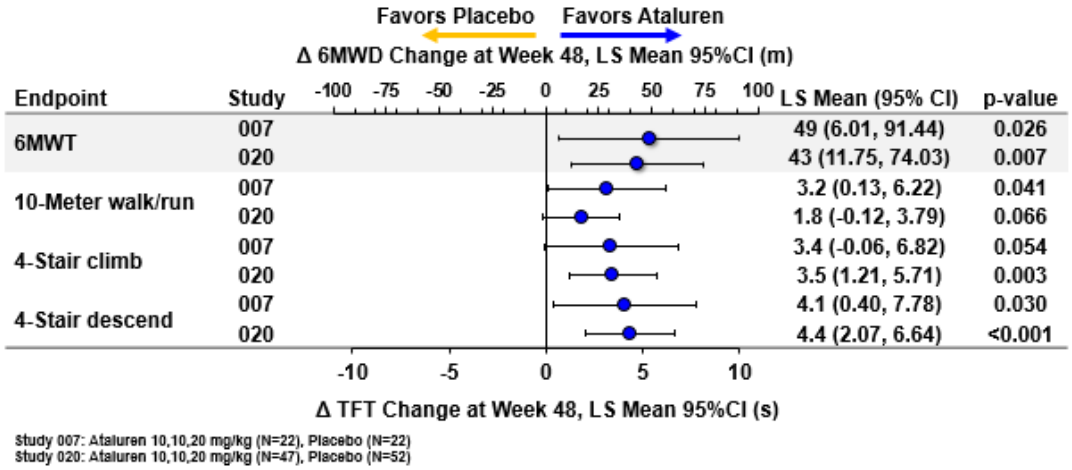
In both studies, the effect of ataluren in the transition phase subgroup demonstrated larger benefits in both the 6MWT and TFTs.

In the 6MWT, ataluren-treated patients in the transition phase subgroup showed a 49-meter (LS mean, p=0.026) and a 43-meter (LS mean, p=0.007) benefit in Study 007 and Study 020, respectively (Figure 5).

The hazard ratio for 10% worsening in 6MWD was 0.29 (p=0.045) and 0.79 (p=0.418) for ataluren versus placebo in Study 007 and Study 020, respectively. Improvements in TFTs were also larger; the differences in change between ataluren and placebo were 3.2 to 4.1 seconds in Study 007 and 1.8 to 4.4 seconds (LS means) in Study 020 (Figure 5).

It should be noted that all patients in Study 020 and ~70% of patients in Study 007 were on steroids; thus, these results are independent of the benefits achieved with steroid therapy.

Figure 5: 6MWT and TFT Results for Patients with Baseline 6MWD ≥300 to <400 Meters

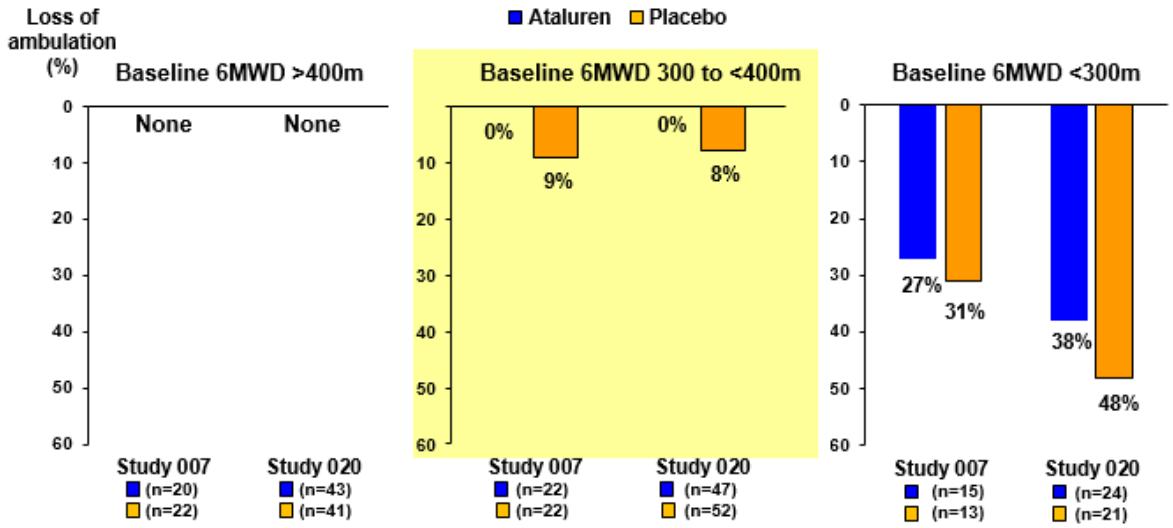


Abbreviations: 6MWT, 6-minute walk test; 6MWD, 6-minute walk distance; LS, least square; TFT, timed function tests
Note: Findings for Study 007 are from the cITT population
Source: PTC124-GD-020-DMD CSR, Tables 14.2.1.3.3.2, 14.2.2.2.8, 14.2.2.3.8, 14.2.2.4.8; PTC124-GD-007-DMD CSR, Table 14.2.1.36C, 14.2.3.2.2.5C, 14.2.3.3.2.5C, 14.2.3.4.2.5C

Ataluren preserved ambulation over the course of the study in patients in the transition phase.

In addition to monitoring the outcome measures described above, the preservation of ambulation was compared in ataluren-treated patients to placebo patients in both Study 007 and Study 020. As shown in Figure 6 (center graph), the results showed that, within the ≥300 to <400 group, no ataluren-treated patients lost ambulation in either study, whereas 8% to 9% of placebo-treated patients lost ambulation. In the accelerated decline phase (baseline 6MWD <300 meters) subgroup, many patients lost ambulation, but a smaller proportion did so in the ataluren arm in both studies (27% to 38% of ataluren patients vs. 31% to 48% of placebo patients); (Figure 6, right graph). As expected, no patients in the stable phase (with baseline 6MWD >400 meters) lost ambulation over the 48-week studies (Figure 6Figure 6, left graph).

Figure 6: Loss of Ambulation by Baseline 6MWD in Study 007 and Study 020



Abbreviations: 6MWD, 6-minute walk distance

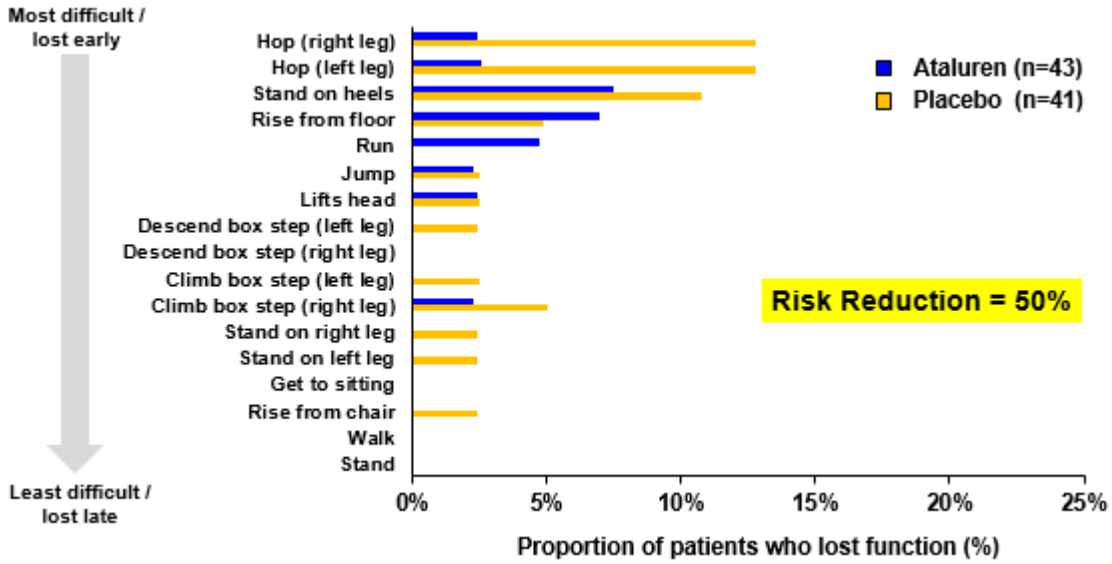
Ataluren patients in the transition phase demonstrated larger treatment benefits in the NSAA.

For the NSAA, which was included as an outcome measure in Study 020, the subgroup of patients with a baseline 6MWD of ≥300 to <400 meters who were treated with ataluren had a 1.7-point advantage on the total NSAA score over those treated with placebo (p=0.037).

The NSAA function preservation analysis method shows that ataluren is active in stable phase nmDMD patients with 6MWD ≥400 meters.

While there is a general expectation that patients with 6MWD ≥400m at baseline remain relatively stable on a number of muscle function measures, the disease itself continues to progress. The NSAA may be useful to monitor the effects of drugs in the stable subgroup, as this functional scale was deliberately designed to avoid “ceiling effects” (upper limit) in high-functioning patients (Mazzone 2009). This group was analyzed for the number of functions preserved in ataluren-treated patients compared with placebo patients. The results demonstrated that there was a 50% risk reduction in loss of function across all components of the NSAA in this subgroup (RR=0.50, p=0.252, post-hoc permutation test; (Figure 7).

Figure 7: NSAA Results in Patients with Baseline 6MWD of ≥400 Meters in Study 020



Abbreviations: NSAA, North Star Ambulatory Assessment

2.5 Efficacy Findings in Meta-Analysis of Studies 007 and 020

The objective of the meta-analysis was to provide an estimate of the benefit of ataluren in a larger, heterogenous population and to contribute to the totality of evidence of the benefit of ataluren therapy. The meta-analysis methodology was based on inversed-variance weighting as described in the Study 020 statistical analysis plan. A meta-analysis of the ITT population of Study 020 and all subjects in Study 007 who received treatment with ataluren 10, 10, 20 mg/kg or placebo is presented below, reflecting the most conservative method of analysis. The meta-analysis comprised a total of 171 patients treated with ataluren 10, 10, 20 mg/kg and 171 patients treated with placebo.

The meta-analysis results showed clinically meaningful and statistically significant benefit across primary and secondary endpoints. For the primary endpoint of change in 6MWD, a 20.0-meter LS mean difference favoring ataluren over placebo was observed (p=0.0152) (**Fejl! Henvisningskilde ikke fundet.**). The hazard ratio for 10% worsening in 6MWD was 0.68, favoring ataluren (p=0.022). In addition, clinically meaningful and statistically significant benefit was seen on the 4-stair climb and 4-stair descend timed function tests.

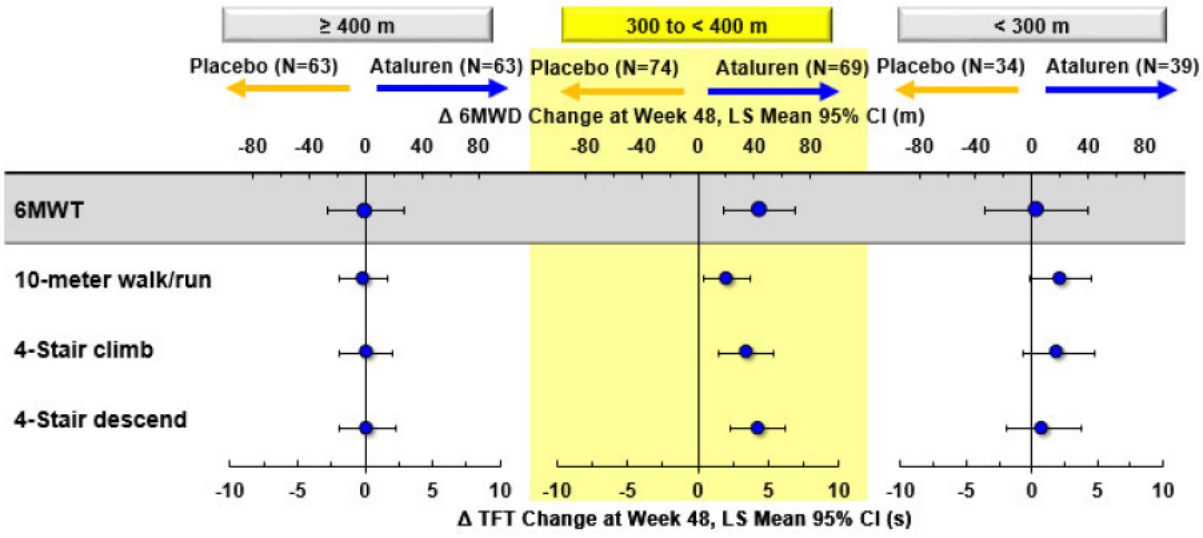
Table 3 **Summary of Results for the Pre-specified Meta-Analyses of Study 007 and Study 020**

Endpoint	Meta-Analysis		
	LS Mean Δ	SE	P value
N (ataluren, placebo)		171, 171	
Change in 6MWD, meters	20.0	8.237	0.0152
Change in time to run/walk 10 m, seconds	-1.3	0.564	0.0262
Change in time to climb 4 stairs, seconds	-1.8	0.626	0.0041
Change in time to descend 4 stairs, seconds	-1.9	0.663	0.0038

Abbreviations: ADP, ambulatory decline phase; 6MWD, 6-minute walk distance; ITT, intent-to-treat, LS, least squares; SE, standard error
[a]Values are hazard ratios
Note: Data for Study 007 is from the cIIT population and for Study 020 from the ITT population
For each study, the point estimate from the model (mean Δ) was given a weight equal to the inverse of its variance. ADP subgroup includes patients ≥7 to ≤16 years of age, baseline 6MWD ≥150 m and ≤80%-predicted, on stable regimen of corticosteroids.
Source: ISE Table 3.1.2

The meta-analysis also compared the ataluren treatment effect in patients based on baseline 6MWD categories. In the baseline 6MWD ≥300 to <400-meter transition phase subgroup a pronounced treatment benefit in ataluren relative to placebo patients of >40 meters in the 6MWT was observed (Figure 8, center panel). As expected, the stability of the ≥400-meter 6MWD subgroup over a 48-week period obscures the ability to see a drug effect and no change was observed (Figure 8, left panel). A modest treatment benefit was observed in the <300-meter subgroup containing patients with accelerated and variable disease progression (Figure 8, right panel).

Figure 8 **6MWT and TFT Results from the Meta-Analysis of Study 020 and Study 007 by Baseline 6MWD Subgroups (Ataluren 10, 10, 20 mg/kg TID)**



Abbreviations: 6MWD, 6-minute walk distance; 6MWT, 6-minute walk test; CI, confidence interval; ITT, intent to treat; LS, least squares; TFT, timed function test; TID, three times a day

3 SUMMARY OF LONG-TERM EFFICACY DATA

Clinical studies in DMD present significant challenges due to the rarity of the disorder, the heterogeneity and the variable nature of the decline in endpoints like 6MWD and TFTs over a relative short period of 48 weeks. Ambulatory functional decline in DMD occurs progressively over a 10- to 13-year period, hence to truly understand the clinical benefits of a therapy long-term outcomes data on clinical milestones, like loss of ambulation and respiratory function are required. This has been highlighted by the fact that it has taken more than a decade to truly understand the benefits of corticosteroids in the treatment of DMD (McDonald 2018). For this reason, long-term outcomes data generated in the open-label extension study PTC124-GD-019-DMD (study 019) and the registry study (PTC124-GD-025o-DMD [Study 25o]) provide the most compelling evidence on the true benefit ataluren offers to nmDMD patients. These data are present in the sections below.

3.1 Long-term Open-label Study (Study 019)

Study 019 includes patients (≥5 years of age) not in the United States who had received ataluren in prior ataluren studies. The primary objective of this study is to assess the long-term safety and tolerability of ataluren 10, 10, 20 mg/kg in nmDMD patients. Secondary objective included exploration of efficacy. Clinic visits are every 12 weeks. Study 019 started (first patient first visit) on 20 May 2012 and has recently concluded.

3.1.1 Baseline Patient Characteristics for Study 019

Baseline characteristics for Study 019 are summarized in Table 4Table 4. A total of 94 boys were included. Fifty patients were ambulatory, and 44 patients were non-ambulatory at study entry. Mean age of enrolled patients at baseline in Study 019 was 12.8 years representing an older patient population with more advanced progression. Of the 50 ambulatory patients in Study 019, 47 patients (94%) were using corticosteroids.

Table 4: Demographics and Baseline Characteristics for Study 019 (All Patients)

Parameter, n (%)	Ambulatory n=50[a]	Non-ambulatory n=44	Overall N=94
Male, n (%)	49 (98.0)	44 (100.0)	93 (98.9)
Age (years)			
Mean (SD)	12.1 (2.08)	13.6 (2.48)	12.8 (2.39)
Median (Min, Max)	12.0 (9.0, 18.0)	13.0 (9.0, 21.0)	13.0 (9.0, 21.0)
Age groups, n (%)			
6 to ≤11 years	17 (34.0)	7 (15.9)	24 (25.5)
12 to ≤17 years	31 (62.0)	33 (75.0)	64 (68.1)
≥18 years	1 (2.0)	4 (9.1)	5 (5.3)
Race, n (%)			
Caucasian	46 (92.0)	41 (93.2)	87 (92.6)
Black	0	0	0
Asian	3 (6.0)	1 (2.3)	4 (4.3)
Other	0	2 (4.5)	2 (2.1)
Corticosteroid use, n (%)	47 (94.0)	36 (81.8)	83 (88.3)

Parameter, n (%)	Ambulatory n=50[a]	Non-ambulatory n=44	Overall N=94
Baseline 6MWD (meters) Mean (SD) Median (Min, Max)	341.6 (108.1) 355.00 (36.0, 552.0)	N/A	N/A
Baseline Time to Stand from Supine (seconds) Mean (SD) Median (Min, Max)	11.4 (9.5) 7.20 (2.3, 30.0)	N/A	N/A
Baseline Time to Walk/Run 10 Meters (seconds) Mean (SD) Median (Min, Max)	8.4 (4.7) 7.2 (3.5, 26.4)	N/A	N/A
Baseline FVC Mean (SD) Median (Min, Max)	N/A	2.0 (0.5) 2.0 (1.0, 3.1)	N/A
Baseline %-predicted FVC Mean (SD) Median (Min, Max)	N/A	74.1 (18.4) 74.1 (32.6, 110.3)	N/A

Abbreviations: FVC, forced vital capacity; Max, maximum; Min, minimum; 6MWD, 6-minute walk distance; N/A, not applicable; SD, mean
[a]One male patient (062-007) had not participated in a previous ataluren study and his demographic data were not collected.
[b]Height values for some non-ambulatory patients were not collected.
Source: PTC124-GD-019-DMD Table 16, Table 14.1.3.1.1, Table 14.1.3.1.1.1, Table 14.2.1.1, Table 14.2.2.1, Table 14.2.3.1, Table 14.2.4.1, Table 14.2.5.1; Table 161

3.1.2 Forced Vital Capacity in Non-ambulatory Patients in Study 019

Forced vital capacity (FVC) is a clinically useful measure in non-ambulatory patients with DMD, as an FVC decrease below a threshold of 1 liter is associated with mortality; when FVC is <1 liter, the median survival is 3.1 years and the 5-year survival is only 8% (Phillips 2001). The Cooperative International Neuromuscular Research Group (CINRG) contemporary natural history data show that risk of death in DMD is increased 4-fold when absolute FVC drops below 1 liter (McDonald 2017). The median age of patients with DMD at which the FVC reaches 1 liter is 17 years (range 13.0 to 25.5) (Phillips 2001).

The long-term 4-year FVC findings for Study 019 were compared with the CINRG natural history study (McDonald 2016). Patients in the CINRG database were treated with the standard of care and were matched with those enrolled in Study 019 according to the following criteria: patients were non-ambulatory, ≤25 years old, had corticosteroid exposure ≥24 months, and were assessed in 2012 and thereafter.

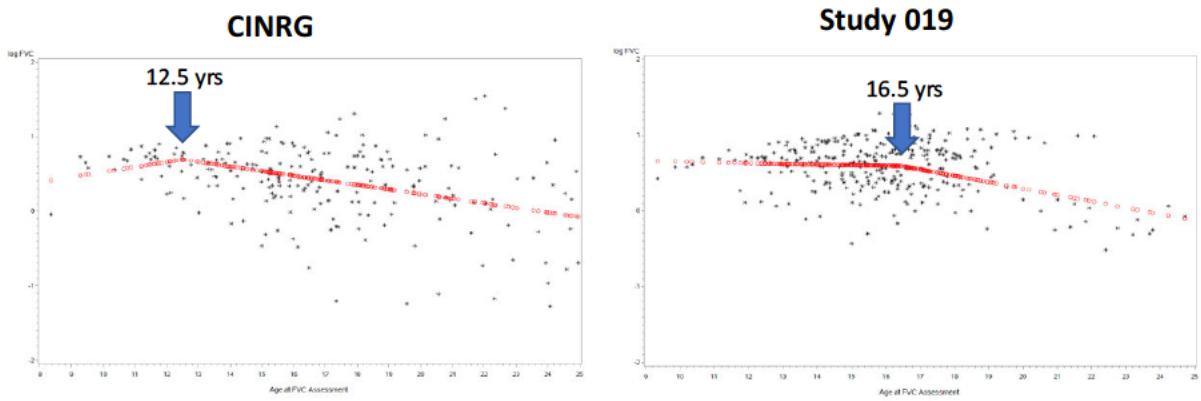
The absolute FVC rather than percent-predicted FVC was used because height, required for the conversion to percent-predicted FVC, is difficult to measure in non-ambulant DMD patients. Although, ulna length can be used instead of height, it is highly variable.

Among the non-ambulatory patients in Study 019, the mean baseline percent-predicted FVC was 74.1% (Table 4).

As of July 31, 2017, overall, lung function was preserved by 10.4% (p=0.0204) in Study 019 ataluren-treated patients across ages versus untreated patients in the CINRG natural history study (McDonald 2016).

To evaluate when patients start to decline in pulmonary function, FVC by age was analyzed for each cohort based on a piecewise regression model. A total of 238 assessments from 114 CINRG patients were included in the analysis (McDonald 2016). This analysis found that CINRG patients reached an average maximum FVC at 12.5 years of age followed by the onset of progressive pulmonary decline (Figure 9, left panel). In contrast, patients taking ataluren really did have a defined inflection point as found to have a later, estimated to possible be as late as 16.5 years of age (Figure 9; right panel).

Figure 9: FVC in Non-ambulant DMD Patients Treated Under Standard Care (CINRG Database) or with Ataluren (Study 019)



Abbreviations: CINRG, Cooperative International Neuromuscular Research Group; DMD, Duchenne muscular dystrophy; FVC, forced vital capacity
Note: Study 019 cut-off 31JUL2017 and CINRG transfer 18NOV2016
Data from cut-off of July 31, 2017

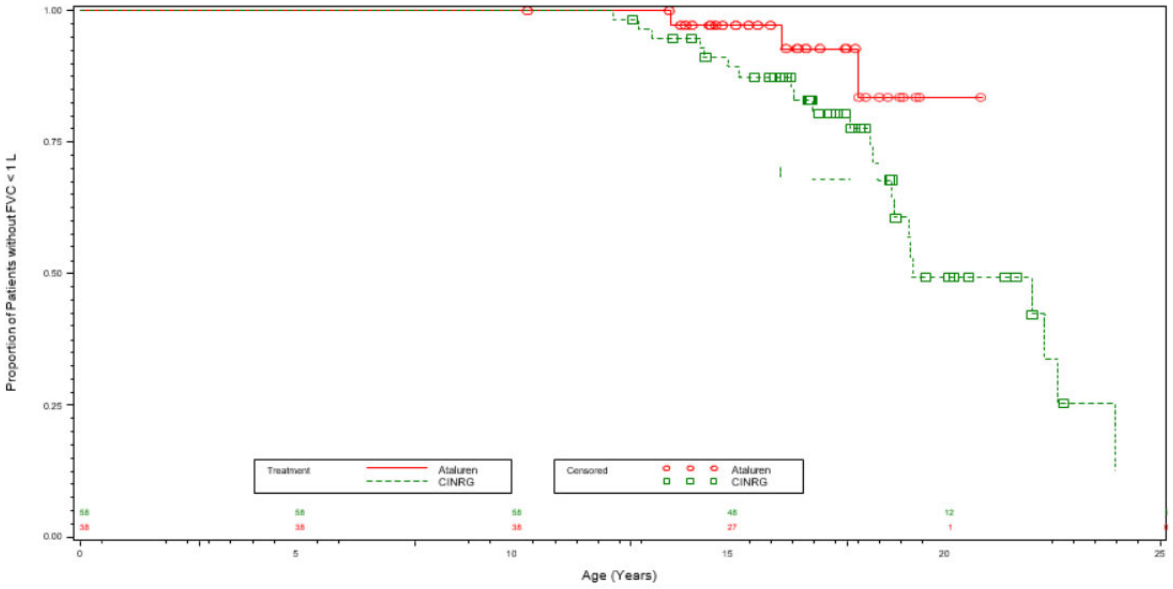
It should be noted that all patients included in these analyses were on concomitant corticosteroids; thus, the difference in FVC observed between Study 019 and CINRG cohorts indicates a treatment benefit with ataluren in addition to the standard of care.

A Kaplan-Meier analysis of the time to the FVC <1L was performed for the subgroup of patients who were non-ambulatory at baseline in Study 019 and the CINRG dataset (

Figure 10) and (Table 5).

Of the 38 patients in Study 019 with FVC data (all of whom where non-ambulatory at study entry), 3 (7.9%) experienced a transition to FVC <1 liter. In comparison, among the 58 non-ambulatory patients in the CINRG dataset, 23 (39.7%) experienced such a transition at a median age of 18.8 years. A median age was not reached for Study 019 patients. Given the critical importance of this milestone and its strong association with mortality, the ~32% difference in the proportion of patients who experienced a transition to FVC <1 L represents a demonstrable and clinically meaningful benefit for ataluren in non-ambulatory patients.

Figure 10: Kaplan-Meier Plot of Age at Transition to FVC <1 Liter



Abbreviations: CINRG, The Cooperative International Neuromuscular Research Group; FVC, forced vital capacity
Note: CINRG subjects matched based on age and corticosteroid use.
Source: Figure 5A

Table 5: Kaplan-Meier Analysis of Age (years) at FVC < 1 Liter

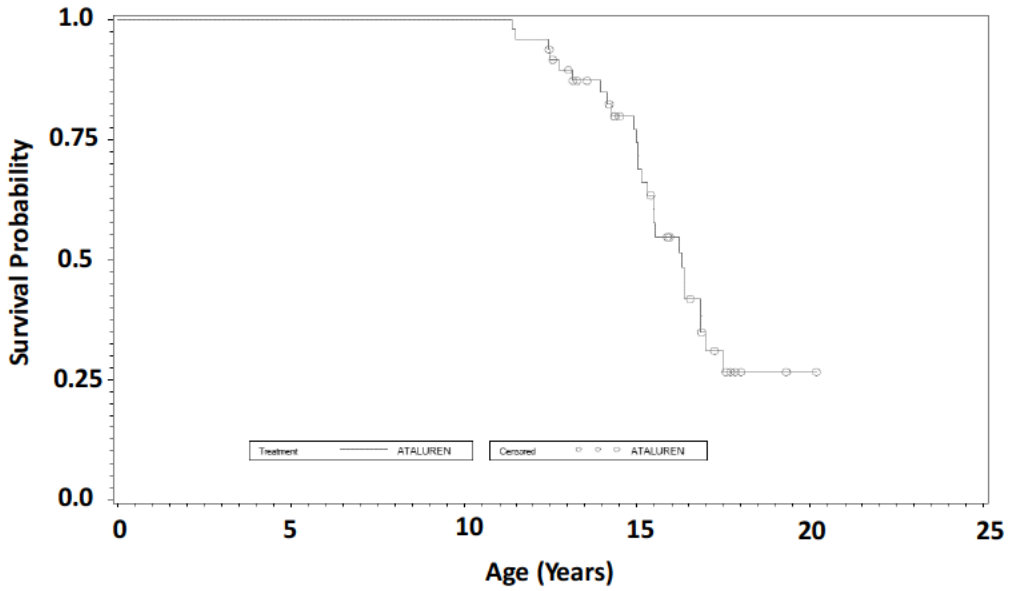
	Ataluren N=38	CINRG N=58
Transition to FVC <1 L		
Patients assessed	38 (100.0)	58 (100.0)
Patients with events	3 (7.9)	23 (39.7)
Patients censored	35 (92.1)	35 (60.3)
Age at FVC <1 L		
25% Quantile (95% CI)	NA (16.2, NA)	18.3 (16.5, 18.9)
Median (95% CI)	NA (NA, NA)	19.3 (18.8, 22.6)
75% Quantile (95% CI)	NA (NA, NA)	24.0 (22.0, NA)
Minimum, Maximum	10.4+, 20.9+	12.4, 26.4+

Abbreviations: CI, confidence interval; CINRG, Cooperative International Neuromuscular Research Group; FVC, forced vital capacity; NA, not analyzed
Source: Table 5ATable

3.1.3 Loss of Ambulation

As of the 31 July 2017, 54% of patients (26/48) in Study 019 lost ambulation (Table 6).Table 6 The median age when patients became non-ambulatory was 16.3 years in Study 019 compared with published historical controls who were treated with the standard of care (with or without corticosteroids) ataluren delayed loss of ambulation by 1.8 to 7 years (Table 6) (Brooke 1989, Eagle 2002, Ricotti 2013, McDonald 2013c, Bello 2015).

Figure 11: Loss of ambulation in Study 019



Note: In Study 019, ambulatory patients aged 9-18 years at baseline. Date cut-off for both studies 31 July 2016.
Reference: Appendix Figure 14.2.1 31-JUL-2017 and Figure 2B 31-JUL-2016

Table 6: Loss of Ambulation in Studies Study 019 Compared with Historical Controls

Group	Average Follow-up	N	Loss of Ambulation n (%)	Age of LOA, yrs
Study 019	4.0 yrs	48	26 (54.2)	16.3[a]
(McDonald 2013c)	1 yr	80	23 (16.0)	10.8[b]
(Ricotti 2013)	3.9 yrs	All: 360[c]		
		Intermittent prednisolone: 184	51 (27.7)	12[a]
		Daily prednisolone:168	39 (23.2)	14.5[a]
(Bello 2015)	3.8 yrs	All: 340	229 (67.6)	
		No treatment or <1 year of corticosteroid tx: 88	—	10[a]
		≥1 yr corticosteroid treatment: 252	—	13[a]
(Eagle 2002)	35 yrs[d]	197[e]	197 (100.0)	9.3[b]
(Brooke 1989)	3.6 yrs	293[e]	—	12-13

Abbreviations: CINRG, Cooperative International Neuromuscular Research Group; LOA, loss of ambulation; tx, treatment; yrs, years
Note: Ambulatory patients in Study 019 were age 9-18 years at study entry and CINRG study patients were matched to Study 019 based on age and steroid use. Data for Study 019 are from data as of 31 July 2017
[a]Median age
[b]Mean age

[c]Patients included are ≥6 years of age
[d]Patients treated between1967 and 2002 at Newcastle Muscle Center
[e]All patients were steroid naive

Summary

Analysis of FVC in Study 019 indicates that ataluren therapy preserves lung function for about 4 years in non-ambulant nmDMD patients. These results are important because the age at which peak FVC occurs and then begins to decline is prognostic for long-term progression of pulmonary function in DMD patients. Reduction of FVC to <1 liter remains the strongest negative predictor of survival in patients with DMD (Finder 2017).

Ataluren therapy was also associated with delay in the loss of ambulation in nmDMD patients Delay in loss of ambulation observed in Study 019 compared with historical controls suggest that, in ambulatory patients, ataluren 10, 10, 20 mg/kg therapy slows disease progression. This finding is particularly significant as loss of ambulation is a devastating milestone for patients and their families alike, as children in the non-ambulatory stage require much greater assistance with normal activities of daily living.

4 EFFICACY FINDINGS OF THE OBSERVATIONAL REGISTRY STUDY (STUDY 025o)

Study 025o is an ongoing, multicenter, observational study in patients with nmDMD who are being treated with commercial ataluren (Translarna®) based on inclusion of their data in a registry. The study is designed to collect information on the safety and effectiveness of ataluren in the real world setting as part of routine clinical practice. Enrolled patients will be followed for ≥5 years from their data or enrollment into the registry. Data is collected during this time period in conjunction with all routine care visits; there are no protocol-mandated procedures or mandated diagnostic tests. For patients who initiated Translarna prior to enrollment into the registry, data were obtained retrospectively from their medical records for the time period between Translarna initiation and enrollment.

In order to analyze change in efficacy parameters over time in the context of this non-interventional study with heterogeneity in assessment timepoints, change from first assessment to last assessment was summarized for patients with at least 2 assessments, with first assessment defined as the first available value since the first dose date in the registry. To normalize for differences in duration from enrollment in the study among patients, the efficacy outcome of 6MWD, NSAA, TFTs (time to rise from supine and time to run/walk 10 meters) and percent predicted FVC are presented as annualized change.

The findings presented below are from a data cut-off of 31 January 2018.

The efficacy endpoints of 6MWD, NSAA, and TFTs were compared with the findings of nmDMD placebo treated patients from Studies 007 and 020. Evaluation of FVC was not performed in either Study 007 of Study 020.

4.1 Results

As of 31 January 2018, 179 patients had been included in Study 025o at 51 sites in 9 European member states: Austria, Czech Republic, France, Germany, Hungary, Italy, Romania, Sweden, United Kingdom and Israel.

The median age of enrolled patients was 11 years (Table 7). Of the 126 patients for whom ethnic origin was obtained, 113 (63.1%) were identified as Caucasian. A total of 176 (98.3%) of patients were male; 3 patients (1.7%) were female. Most patients (70.4%) had not participated in a PTC-sponsored ataluren clinical study. Thirty-three of the patients (18.4%) were not receiving corticosteroids (PTC124-GD-025o-DMD Third Interim Report)

Patient baseline characteristics in Studies 007 and 020 were similar to that of Study 025o, except Study 007 and 020 tended to have younger population (about a mean of 8.4 and 9.0 years, respectively). All placebo-treated patients in Study 020 and about 70% of these patients in Study 007 were treated with corticosteroids (PTC124-GD-007-DMD and PTC124-GD-020-DMD CSRs).

Table 7: Demographic and Patient Characteristics at First Assessment (As-treated Population)

Variable[a]	All (N=179)
Age, (years)	11.1 (4.4)
Age groups, n (%)	
≥5	179 (100.0)
≥5 - <12	113 (63.1)
≥12 - <18	58 (32.4)
≥18	8 (4.5)
Sex, n (%)	
Male	176 (98.3)
Female	3 (1.7)
Ethnicity, n (%)	
Caucasian	113 (63.1)
Arab/Middle Eastern	6 (3.4)
Arab/ Middle Eastern, Asian	1 (0.6)
Asian	4 (2.2)
North African	1 (0.6)
Unknown	1 (0.6)
Weight (kg)	31.0 (14.0)
Height (cm)	124.2 (16.3)
BMI (kg/m^2)	18.7 (4.0)
Naïve to PTC ataluren studies, n (%)	
Yes	126 (70.4)
No	53 (29.6)

Abbreviations: BMI, body mass index; SD, mean
Note: The As-treated Population consists of all patients who had at least 1 dose of Translarna.
All percentages are calculated based on the number of patients in the As-treated Population.

Given the observational nature of this study, the patient characteristics summarized within reflect status at the first assessment captured in the database, which may include retrospectively collected data from timepoints that precede the inclusion visit.
[a]Values are mean (SD) unless indicated otherwise

4.2 6-minute walk distance, NSAA, and Timed-function Tests

At first assessment (baseline), 6MWD was similar across Study 007, Study 020, and the registry Study 025o (Table 8). Patients in the registry were associated with a smaller reduction in annualized 6MWD (-32.6 meters) compared with placebo treated patients in Study 007 (-43.7 meters) and Study 020 (-59.6 meters), consistent with ataluren being associated with slowing of disease progression.

Similarly, ataluren treatment in Study 025o was associated with a less annualized reduction in the NSAA score compared with Study 020 placebo treated patients (-2.3 for Study 025o vs -4.0 for Study 020 placebo) (Table 8). Better treatment outcomes with ataluren therapy were also observed with the TFTs; annualized increases in the time for a patient to rise from supine or run/walk 10 meters were less in the registry Study 025o (2.2 sec and 2.1 sec, respectively) than observed for placebo treated patients in Study 007 (3.4 sec and 3.2 sec) and Study 020 (5.2 sec and 3.7 sec) (Table 8).

Of note, the mean (SD) duration of treatment in the registry Study 025o across the different assessments was longer compared with that of Studies 007 and 020 (≥85 days) (Table 7), indicating persistence of the positive treatment effect of ataluren.

Table 8: Annualized Change in Six-minute Walk Distance, NSAA, and Timed-function Tests

Assessments[a]	Study 007 Placebo (n=57)	Study 020 Placebo (n=115)	Study 025o All (N=179)
6MWD	n=57	n=114	n=87
First Assessment (baseline), meters	359.6 (87.7)	363.5 (81.3)	355.6 (98.7)
Annualized Change, meters/year	-43.7 (97.1)	-59.6 (111.0)	-32.6 (108.7)
Treatment Duration, days	336.4 (8.9)	331.7 (31.0)	520.8 (299.3)
NSAA	—	n=114	n=179
First Assessment (baseline)	—	21.9 (8.03)	21.3 (8.2)
Annualized Change	—	-4.0 (4.6)	-2.3 (5.7)
Treatment Duration, days	—	333.4 (26.9)	418.2 (273.2)
TFTs			
Rise from supine	n=57	n=112	n=69
First Assessment (baseline), sec,	11.5 (11.4)	9.9 (8.2)	6.9 (6.3)
Annualized Change, sec/year	3.4 (7.8)	5.2 (8.3)	2.2 (5.6)
Treatment Duration, days	337.1 (7.50)	317.2 (55.89)	532.1 (373.36)
Time to run/walk 10 meters	n=57	n=114	n=79
First Assessment (baseline), sec,	6.9 (2.8)	6.8 (2.9)	6.7 (4.3)
Annualized Change, sec/year	3.2 (7.2)	3.7 (7.1)	2.1 (4.3)
Treatment Duration, days	337.1 (7.5)	331.4 (32.4)	548.3 (371.0)

Abbreviations: 6MWD, 6-minute walk distance; NSAA, North Star Ambulatory Assessment; SD, mean; TFT, timed-function tests
Note: Change from first to last assessment was summarized for patients with at least 2 assessments, with first assessment defined as the first available value since the first dose date in the study.
Annualized change was defined as the difference between the last and first assessments divided by the number of days in between × 365.25.
For patients who lost ambulation, the six-minute walk distance (6MWD) was imputed as 0.
For 6MWD, any patient who lost ambulation within 30 days of the prior assessment was not counted in the analysis of annualized change.
Duration is defined as days between the first and last assessments during the Translarna use period
[a]Values are mean (SD)

4.3 Pulmonary Function

In the Study 025o, pulmonary function was evaluated using spirometery in accordance with routine clinical practice. Mean (SD) baseline percent predicted FVC (first assessment) was 84.5% (19.6) (Table 9). After a mean treatment duration of 1.4 years, reduction in percent predicted FVC was 1.4%.

Table 9: Annualized Change in Percent Predicted FVC

Assessment[a]	Study 025o All (n=69)
% Predicted FVC	
First Assessment (baseline),	84.4 (19.6)
Annualized Change	-1.4 (12.8)
Mean (SD) Treatment Duration, days	497.5 (239.2)

Abbreviations: FVC, forced vital capacity; SD, mean
Note: Change from first to last assessment and annualized change were summarized for patients with ≥2 assessments and in which ≥1 assessment was >24 weeks (168 days), to reduce bias resulting from the annualization of short time frames and the variability of FVC measurements. The first assessment was defined as the first available value since the first dose date in the study.
Annualized change was defined as the difference between the last and first assessments divided by the number of days in between × 365.25.

4.4 Discussion

Study 025o is being conducted to evaluate the long-term safety and effectiveness and utilization pattern of ataluren in routine clinical practice.

As of the 31 January 2018 cut-off date for this third interim report, ataluren, as used in routine clinical practice, was associated benefit in slowing nmDMD disease progression across multiple clinically meaningful endpoints over a mean duration considerably longer than that evaluated in the 48-week placebo-controlled trials Study 007 and Study 020.

5 CONCLUSION

Under current standard of care, nmDMD remains a disease with devastating consequences and bleak prognosis. The progressive and irreversible effects of DMD underscore the importance of early intervention with treatments that have the potential to slow physical deterioration and delay the natural course of this ultimately fatal disease. The totality of evidence summarized below supports the benefit of ataluren:

- Clinically meaningful benefits over placebo in the ITT population of each study under multiple functional assessments
- Clinically meaningful treatment effects in the overall study population on walking (6MWD), stair-climbing, and stair-descending. A treatment effect of greater than 1.0 to 1.5 seconds on a timed function test translates to differences in physical and social activity in patients with DMD (Escolar 2011, Bendixen 2014)

- More pronounced treatment benefits in transition phase patients, a population which minimizes the impact of the floor and ceiling effect of the 6MWT and other endpoints
- Significant treatment effect in the 6MWT and TFTs when the study populations were combined in a meta-analysis
- Clinically meaningful preservation of multiple muscle functional milestones
    - Preservation of ambulation in the ataluren group, which was observed across both RCTs
    - Higher percentages of ataluren-treated patients who maintained the ability to climb and descend stairs in both RCTs
    - Greater preservation of functions as measured by the NSAA; the risk of losing motor ability as measured by the NSAA was markedly reduced in the ITT population in Study 020
- Preservation of pulmonary function and loss of ambulation (LOA) as compared with natural history and other published literature was observed in Study 019
- Additional real-world evidence from the ongoing registry study 025o also supports the benefit ataluren provides in slowing the progression of nmDMD across multiple outcomes

In summary the totality of evidence across two ataluren nmDMD placebo-controlled studies and well as data generated from long-term studies and the registry Study025o provide compelling evidence of the significant benefit ataluren is providing to nmDMD patients

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Medicinrådets vurdering af klinisk merværdi af ataluren til Duchennes muskeldystrofi

Handelsnavn	Translarna
Generisk navn	Ataluren
Firma	PTC Therapeutics
ATC-kode	M09AX03
Virkningsmekanisme	Ataluren promoverer ribosomal gennemlæsning af mRNA indeholdende præmature stopkodons, hvilket faciliterer produktionen af fuldlængdeprotein
Administration/dosis	Administreres som granulat til oral suspension hver dag i 3 doser. Total daglig dosis på 40 mg/kg legemsvægt
EMA-indikation	Behandling af Duchennes muskeldystrofi, der er forårsaget af en nonsensmutation i dystrofingenet hos gående patienter i alderen 5 år og derover
Godkendelsesdato Offentliggørelsesdato Dokumentnummer Versionsnummer	14. november 2018 14. november 2018 29266 1.0
Fagudvalgets sammensætning og sekretariatets arbejdsgruppe	Se bilag 1

Medicinrådets konklusion

Medicinrådet vurderer, at ataluren til Duchennes muskeldystrofi, forårsaget af nonsensmutation, giver:

- **Ingen klinisk merværdi** for den samlede population af gående patienter i alderen 5 år og derover, sammenlignet med placebo.

Evidensens kvalitet er samlet vurderet som værende **lav**.

Definition af klinisk merværdi:

Medicinrådet kategoriserer lægemidlets kliniske merværdi i en af følgende kategorier:

Kategori 1. Stor merværdi: Vedvarende og stor forbedring i effektforhold der ikke tidligere er opnået med et relevant behandlingsalternativ. Eksempler herpå er sygdomsremission, markant stigning i overlevelsestid, langvarigt fravær af alvorlige sygdomssymptomer eller udtalt fravær af alvorlige bivirkninger.

Kategori 2. Vigtig merværdi: Markant forbedring, eksempelvis lindring af sygdomstilstand, moderat stigning i overlevelsestid, lindring af alvorlige symptomer, fravær af alvorlige bivirkninger og væsentligt fravær af andre bivirkninger.

Kategori 3. Lille merværdi: Moderat forbedring, f.eks. reduktion i ikkealvorlige sygdomssymptomer eller fravær af bivirkninger.

Kategori 4. Ingen merværdi: Ingen merværdi sammenlignet med standardbehandling/andre behandlinger.

Kategori 5. Negativ merværdi: Negativ merværdi sammenlignet med standardbehandling/andre behandlinger.

Kategori 6. Ikkedokumenterbar merværdi: Ikkedokumenterbar merværdi sammenlignet med standardbehandling/ andre behandlinger. Effektforskellen kan ikke kvantificeres ud fra det videnskabelige datagrundlag.

Om Medicinrådet:

Medicinrådet er et uafhængigt råd, som udarbejder anbefalinger og vejledninger om lægemidler til de fem regioner.

Medicinrådet vurderer, om nye lægemidler og nye indikationer kan anbefales som standardbehandling og udarbejder fælles regionale behandlingsvejledninger.

Nye lægemidler vurderes i forhold til effekt, eksisterende behandling og pris. Det skal give lavere priser og lægemidler, der er til størst mulig gavn for patienterne.

De fælles regionale behandlingsvejledninger er vurderinger af, hvilke lægemidler der er mest hensigtsmæssige til behandling af patienter inden for et terapiområde og dermed grundlag for ensartet høj kvalitet for patienterne på tværs af sygehuse og regioner.

Forkortelser

6MWT:	6-minutters gangtest
6MWD:	6-minutters gangdistance
CHMP:	*Committee for Medicinal Products for Human Use* (komité i EMA)
CI:	Konfidensinterval
DMD:	Duchennes muskeldystrofi
EMA:	*European Medicines Agency*
EPAR:	*European public assessment report*
FVC:	Forceret vitalkapacitet
GRADE:	System til vurdering af evidens (*Grading of Recommendations Assessment, Development and Education System*)
HR:	*Hazard ratio*
KRIS:	Koordineringsrådet for ibrugtagning af sygehusmedicin
nmDMD:	Duchennes muskeldystrofi forårsaget af nonsensmutation
NSAA:	*North Star Ambulatory Assessment*
OR:	*Odds ratio*
PedsQL:	*Pediatric Quality of Life Inventory*
PODCI:	*Pediatric Outcomes Data Collection Instrument*
RR:	Relativ risiko
SD:	Standardafvigelse

Indhold

1 Formål

Formålet med Medicinrådets vurdering af klinisk merværdi af ataluren til Duchennes muskeldystrofi, der er forårsaget af nonsensmutationer i dystrofingenet, er at vurdere den kliniske merværdi i forhold til et eller flere lægemidler til samme patientgruppe (komparatorer).

Formålet med vurderingsrapporten er at vurdere den kliniske merværdi af ataluren, der gives i tillæg til nuværende standardbehandling (se afsnit 2) til behandling af Duchennes muskeldystrofi forårsaget af nonsensmutationer i dystrofingenet sammenlignet med placebo i tillæg til nuværende standardbehandling.

Med udgangspunkt i den kliniske merværdi og en omkostningsanalyse udarbejdet af Amgros vurderer Medicinrådet, om ataluren anbefales som mulig standardbehandling.

2 Baggrund

Duchennes muskeldystrofi

Duchennes muskeldystrofi (DMD) er en af de hyppigste muskelsvindssygdomme hos børn. DMD er en progredierende sygdom, hvor der sker en tiltagende, symmetrisk svækkelse i alle kroppens muskler, fordi muskelfibrene gradvist ødelægges. Som en konsekvens heraf optræder der med tiden respiratoriske, ortopædkirurgiske, gastrointestinale, kardiale og, hos nogle patienter, kognitive problemer. Alder ved symptomdebut varierer. Hos nogle ses de første tegn på sygdommen i 2-3-årsalderen, hos andre lidt senere. Svækkelse af respirations- og hjertemuskulaturen medfører i sidste ende respirations- og hjertesvigt, der medfører en nedsættelse af den forventede levealder [1].

Sygdommen er arvelig og forårsages af forskellige typer af mutationer på X-kromosomet i genet, der koder for proteinet dystrofin [2]. Den hyppigste årsag til DMD er deletioner/duplikationer i dystrofingenet. Hos en mindre andel (10-15 %) skyldes DMD nonsensmutationer i dystrofingenet. Dette medfører inkomplet ribosomal transskription, hvilket resulterer i varierende grader af trunkeret, ikkefunktionelt protein [3].

I Danmark findes aktuelt 157 personer i alderen 2-52 år med DMD ifølge RehabiliteringsCenter for Muskelsvinds register. 52 er under 18 år, hvoraf 62 % (32/52) fortsat er gående. Gennemsnitsalderen for de 32 gående drenge er 9 år (2-17). Ud af de 32 har 9 patienter DMD forårsaget af en nonsensmutation (nmDMD). På landsplan påvises 1-2 nye tilfælde af nmDMD/år.

Nuværende behandling

Den nuværende medicinske behandling af nmDMD omfatter behandling med kortikosteroider, som primært sigter mod at forsinke eller mindske de komplikationer, der opstår som følge af sygdommen. Hovedparten af patienterne får steroidbehandling, men enkelte patienter fravælger steroidbehandling grundet præferencer eller bivirkninger. Den medicinske behandling suppleres med en række andre interventioner såsom fysioterapi, overvågning og støtte af hjerte- og respiratorisk funktion, ortopædkirurgiske indgreb, rygkirurgi og rehabilitering [2].

Anvendelse af det nye lægemiddel

Ataluren er et oralt lægemiddel, som forbedrer ribosomal gennemlæsning af nonsensmutationer i forskellige gener. I nmDMD er formålet med atalurenbehandling at fremme produktion af fuld længde dystrofin og dermed genoprette dets funktion i muskelcellerne [4].

Ataluren doseres som oral suspension tre gange daglig efter legemsvægt: Morgen: 10 mg/kg, middag: 10 mg/kg og aften: 20 mg/kg. Den totale døgndosis er 40 mg/kg legemsvægt. Et svar på molekylærgenetisk analyse med påvisning af nonsensmutation i dystrofingenet skal foreligge forud for behandlingsstart [5]. Ataluren gives sammen med steroidbehandling. Behandling med ataluren forventes at være langvarig, som udgangspunkt indtil patienten mister sin gangfunktion, jf. EMAs indikation for lægemidlet.

I 2014 fik ataluren en betinget godkendelse fra det europæiske lægemiddelagentur (EMA) til behandling af gående patienter med nmDMD i alderen 5 år og derover. På baggrund af det daværende datagrundlag afviste Koordineringsrådet for ibrugtagning af medicin (KRIS) brugen af ataluren som standardbehandling, men godkendte behandling i særlige tilfælde og under protokollerede rammer. To patienter har siden modtaget ataluren og er aktuelt fortsat i behandling. KRIS ønskede at revurdere behandlingen, når data fra et igangværende fase 3-studie forelå. Dette studie foreligger nu og danner baggrund for vurderingen i Medicinrådet. Den betingede markedsføringstilladelse blev fornyet i november 2016 på baggrund af det foreliggende fase 3-studie med krav om yderligere at belyse balancen mellem gavnlige og uønskede virkninger i endnu et nyt fase 3-studie.

3 Metode

Ansøger (PTC-therapeutics) har sendt en endelig ansøgning om vurdering af ataluren, som Medicinrådet modtog den 14. marts 2018. Under sagsbehandling har ansøger den 3. oktober 2018 valgt at trække sin endelig ansøgning tilbage. Medicinrådet besluttede på sit møde den 10. oktober 2018 at tage vurderingen op af egen drift. Vurderingen er baseret på de studier, der blev identificeret ved ansøgers litteraturgennemgang, der er valideret af Medicinrådet.

Fagudvalget har følgende bemærkninger til datagrundlaget:

- For hvert effektmål har Medicinrådet i det omfang, det er muligt, medtaget subgruppeanalyser baseret på baseline gangdistance (6MWD). Subgrupperne er fastsat i Medicinrådets protokol på baggrund af opdelingen i fase-III studiet for ataluren (studie-020). Fagudvalget betragter subgruppeanalyserne som prædefinerede, eksploratoriske analyser, da der blandt andet ikke er udført korrektion for multiplicitet i analyserne. Subgrupperne er samtidig ikke anvendt som stratificeringsfaktor i randomiseringen, og da studiet er negativt på det primære effektmål, er alle øvrige effektmål og subgruppeanalyser pr. definition eksploratoriske.
- Datagrundlaget for subgrupperne har flere metodiske svagheder, og effektestimaterne er behæftet med stor usikkerhed. På denne baggrund vurderer fagudvalget, at det ikke er muligt at udtale sig særskilt om den kliniske merværdi i de enkelte subgrupper. I denne vurderingsrapport vil fagudvalget i stedet foretage en særskilt narrativ vurdering af resultaterne i subgrupperne i fase-III-studiet for at understøtte en mere nuanceret vurdering af atalurens effekt i forhold til sygdommens naturhistorie og separate sygdomsstadier (se afsnit 7.1.1).
- For effektmålet ”andelen af patienter der undgår en forværring på ≥ 8 % fra baseline” har Medicinrådet fundet data for en forværring på ≥ 10 % fra baseline fremfor de ≥ 8 % som angivet i protokollen. Forskellen vurderes ikke at have betydning for kategoriseringen.
- Der er ikke fundet data på effektmålet ”lungefunktion” i den gående population som specificeret i protokollen.
- For livskvalitet er der i studie-020 rapporteret data på Pediatric Outcomes Data Collection Instrument’s (PODCI) to domæner ”Transfers/Basic Mobility” og “Sports/Physical Function” fremfor instrumentets totalscore. Fagudvalget vurderer, at de to domæner er tilstrækkelige i vurderingen.

Der er ikke publiceret tilstrækkeligt data på livskvalitet fra fase-II studiet (studie-007) til at kunne foretage en vurdering af livskvalitet fra dette studie.

- Det har ikke været muligt at finde data for sekundært stratificerede subgrupper i analysen af tab af gangfunktion og lungefunktion for den præspecificerede subgruppe af patienter med en 6MWT < 300 m. Dette vurderes ikke at have betydning for kategoriseringen.

4 Litteratursøgning

Ansøger har foretaget en systematisk søgning efter kliniske studier på behandling med ataluren indenfor indikationen Duchennes muskeldystrofi som beskrevet i protokollen. Ansøger fandt to publicerede artikler og et publiceret abstract (tre kliniske studier). De to publicerede artikler opfyldte Medicinrådets præspecificerede kriterier og kunne således besvare det kliniske spørgsmål i protokollen [6,7]. Det publicerede abstract indeholder ikke data på den relevante population og indgår således ikke i Medicinrådets vurdering [8]. Dog har fagudvalget inddraget overvejelser fra dette studie i forbindelse med vurdering af lungefunktion.

Medicinrådets sekretariat har ikke fundet det nødvendigt at supplere ansøgers litteratursøgning. I afsnit 6.1.1 følger en gennemgang af de identificerede studier.

Identificerede publikationer:

Medtaget af Medicinrådet:

McDonald CM, Campbell C, Torricelli RE, Finkel RS, Flanigan KM, Goemans N, et al. Ataluren in patients with nonsense mutation Duchenne muscular dystrophy (ACT DMD): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. Lancet (London, England). 2017;390(10101):1489–98. [6]

Bushby K, Finkel R, Wong B, Barohn R, Campbell C, Comi GP, et al. Ataluren treatment of patients with nonsense mutation dystrophinopathy. Muscle Nerve. 2014;50(4):477–87. [7]

Committee for Medicinal Products for Human Use (CHMP). Translarna: EPAR - Public assessment report. 2014 [4]

Committee for Medicinal Products for Human Use (CHMP). Translarna: EPAR - Public assessment report. 2017 [9]

Ekskluderet af Medicinrådet da studiet ikke omhandlede relevant population, speficiceret i protokollen. Dog medtaget i overvejelser om lungefunktion:

Luo X, McIntosh J, Trifillis P, Gill A, Ong T, Riebling P, et al. Lung function in ataluren-treated, non-ambulatory patients with nonsense mutation Duchenne muscular dystrophy from a long-term extension trial versus untreated patients from a natural history study. Neuromuscul Disord. 2017;27:S6. [8]

Fra evidens til kategori. Medicinrådet vurderer den kliniske merværdi af et lægemiddel ud fra den indsendte endelige ansøgning, evt. suppleret med andet materiale. I protokollen blev effektmålene angivet som "kritiske", "vigtige" og "mindre vigtige". I vurderingen af klinisk merværdi vægter de kritiske højest, de vigtige næsthøjest og de mindre vigtige indgår ikke.

Den kliniske merværdi kategoriseres først enkeltvis per effektmål, hvorefter der foretages en vurdering af den samlede kategori for lægemidlet på tværs af effektmålene. Kategoriseringen pr. effektmål foretages på baggrund af

absolutte og relative værdier for det enkelte effektmål. Den relative effekt beskrives med et estimat og et konfidensinterval, der sammenholdes med generiske væsentlighedskriterier. Den absolutte effekt sammenholdes med den i protokollen beskrevne "mindste klinisk relevante forskel". Den endelige kategorisering af lægemidlets kliniske merværdi er en delvis kvalitativ proces, hvor der foretages en vurdering af det samlede datagrundlag på tværs af effektmålene.

Vurdering af evidensens kvalitet foretages med udgangspunkt i GRADE og udtrykker tiltroen til evidensgrundlaget for de enkelte effektstørrelser og den endelige kategori for klinisk merværdi. Evidensens kvalitet inddeles i fire niveauer: høj, moderat, lav og meget lav. GRADE-metoden er et internationalt anerkendt redskab til systematisk vurdering af evidens og udarbejdelse af anbefalinger. I denne vurdering er metoden anvendt til at vurdere evidensens kvalitet.

5 Databehandling

For at fastslå den mindste klinisk relevante forskel på effektmålet livskvalitet, der i protokollen er defineret som 0,5 SD af baselinemålingen, har Medicinrådets sekretariat udregnet en pooled SD (SDp) baseret på SD i intervention og komparatorgruppen for PODCI. Udregningen er foretaget på baggrund af følgende formel: SDp = sqrt [((n1-1) * (SD1)^2 + (n2-1)*(SD2)^2) / (n1+n2-k)], her er n1 og n2 antal patienter i de to grupper, SD1 og SD2 angiver SD i de to grupper, og k er antallet af SD, der kombineres og er i dette tilfælde 2.

Medicinrådets sekretariatet har udregnet absolutte og relative effektestimater med tilhørende konfidensintervaller for tab af gangfunktion og alvorlige uønskede hændelser ved hjælp af antal patienter i behandlingsgrupperne (N) og antal hændelser i grupperne (n). De absolutte effektestimater med tilhørende konfidensintervaller for livskvalitet i studie-020 er udregnet ud fra den gennemsnitlige ændring fra baseline til uge 48 i hver af behandlingsgrupperne.

6 Klinisk merværdi

6.1 Konklusion klinisk spørgsmål

Hvad er den kliniske merværdi af ataluren til gående patienter i alderen 5 år eller derover med nmDMD?

Fagudvalget vurderer, at ataluren til Duchennes muskeldystrofi forårsaget af nonsensmutation giver:

- **Ingen klinisk merværdi** for den samlede population af gående patienter i alderen 5 år og derover, sammenlignet med placebo.

Evidensens kvalitet er samlet vurderet som værende **lav**.

6.1.1 Gennemgang af studier

Karakteristika

Søgningen identificerede to randomiserede kliniske forsøg (RCT), som direkte sammenligner ataluren med placebo.

Studie-007 (NCT00592553): Fase 2b, internationalt, multicenter, randomiseret, dobbeltblindet, placebo-kontrolleret studie. Patienter blev randomiseret 1:1:1 til at modtage placebo (n = 57); ataluren i døgndosis på 40 mg/kg i 48 uger (n = 57); eller ataluren i døgndosis på 80 mg/kg i 48 uger (n = 60). Randomisering blev

stratificeret på baggrund af alder (< 9 år vs. ≥ 9 år), anvendelse af glukokortikoider (ja vs. nej) og baseline 6MWD (≥ 350 vs. ≤ 350 meter). Da EMAs anbefalede dosis er 40 mg/kg, medtages data fra studiearmen med 80 mg/kg ikke.

Studie-020 (NCT02090959): Fase 3, internationalt, multicenter, randomiseret, dobbeltblindet, placebo-kontrolleret studie. Patienterne blev randomiseret 1:1 til at modtage placebo (n = 115) eller ataluren i døgndosis på 40 mg/kg i 48 uger (n = 115). I alt 230 patienter indgik i studiet. Randomisering blev stratificeret på baggrund af alder (< 9 år vs. ≥ 9 år), varigheden af glukokortikoidbehandling (6 måneder til < 12 måneder vs. ≥ 12 måneder) og baseline 6MWD (< 350 m vs. ≥ 350 m).

Population

Tabel 1: Baselinekarakteristika for interventionsgrupperne i studie-007 og studie-020.

	Studie-007 (fase-II)		**Studie-020 (fase-III)**	
Karakteristika	**ataluren 40 mg/kg** n = 57	**placebo** n = 57	**ataluren 40 mg/kg** n = 115	**placebo** n = 115
Alder, median (range) / median (IQR)*	8 (5-20)	8 (5-15)	9 (7-10)	9 (8-10)
6MWD, mean (SD) / median (IQR)*	350 (97,6)	361 (87,5)	375 (314-421)	370 (314-422)
Anvendelse af glukokortikoider, %	72 %	70 %	100 %	100 %
Vægt, median (range) / median (IQR)*	27 (16-76)	26 (16-55)	29 (23-37)	27 (24-34)
Alder ved diagnose, median (IQR)*	Ikke oplyst	Ikke oplyst	4 (3,3-6,8)	4 (2,3-6,9)

* Inter-quartile range (IQR) er opgivet for studie-020

Baselinekarakteristika i studie-007 og studie-020 er sammenlignelige mellem placebo og ataluren 40 mg/kg/dag-grupperne. Baselinekarakteristika for studiepopulationerne synes at være sammenlignelig på tværs af de to studier.

Fagudvalget finder, at baselinekarakteristika internt i studierne er velbalancerede i de sammenlignede grupper og finder ikke grund til at tro, at nogle af effekterne er forårsaget af confounding. Studiepopulation vurderes samlet set at være i god overensstemmelse med den danske population.

Inklusionskriterierne var ikke ens i studierne, som angivet nedenfor.

Tabel 2: Inklusionskriterier studie-007 og studie-020.

Kriterier	**Studie-007 (fase-II)**	**Studie-020 (fase-III)**
Sygdom/diagnose	Beckers muskeldystrofi eller nmDMD	nmDMD
6MWT	≥ 75 meter	≥ 150 m og ≤ 80 % af den forventede distance i 6MWT baseret på vægt og højde
Glukokortikoider	Tilladt, stabil dosis i mindst 3 måneder	Anvendelse af systemiske glukokortikoider i mindst 6 måneder før indtrædelse i studiet og stabil dosis i mindst 3 måneder
Alder	≥ 5 år	≥ 7 ≤ 18 år

PTC-Therapeutics (Indehaver af markedsføringstilladelsen for ataluren) har anvendt fase-II-studiet, der var negativt på det primære effektmål, til at lave en række post hoc-analyser med det formål at identificere en

subgruppe med bedre effekt af ataluren. Herved identificerede PTC-Therapeutics ADP-subgruppen (ambulatory decline phase). PTC-Therapeutics' hypotese var, at ADP-subgruppen havde størst risiko for at tabe gangfunktion over studiets opfølgningstid, og at subgruppen dermed er bedst i forhold til at vurdere, hvorvidt patienter med nmDMD har gavn af atalurenbehandling. ADP-subgruppen har følgende karakteristika: 1) alder ≥ 7 til ≤ 16 år, 2) baseline 6MWD ≥ 150 m og ≤ 80 % af prædiktereret 6MWD og 3) en stabil dosis af kortikosteroid ved baseline. Disse afgrænsninger blev anvendt som inklusionskriterier for fase-III-studiet (studie-020).

Nedenstående tabel viser, hvilke kritiske og vigtige effektmål der indgår i de udvalgte studier, og hvilken dataanalyse der er anvendt.

Tabel 3: Oversigt over de inkluderede studier og effektmål relateret til protokollen.

	Studie-007 (fase-II)	***Studie-020 (fase-III)***
Dataanalyse	cITT	ITT
Samlet population (n)	Ataluren, n =57 Placebo, n = 57	Ataluren, n = 114 Placebo, n = 114
Subgrupper (n) < 300 m 300-400 m > 400 m	Ataluren/placebo 15/13 22/22 20/22	Ataluren/placebo 24/21 47/52 43/41
Kritiske effektmål	Motorisk funktion • Ændring i 6MWT fra baseline Livskvalitet • PedsQL	Motorisk funktion • Ændring i 6MWT fra baseline • Ændring i NSAA score fra baseline Livskvalitet • PODCI
Vigtige effektmål	Tab af gangfunktion • Andel patienter med tab af gangfunktion fra baseline Alvorlige uønskede hændelser (SAE) • Andel patienter der oplever ≥ 1 SAE	Tab af gangfunktion • Andel patienter med tab af gangfunktion fra baseline Alvorlige uønskede hændelser (SAE) • Andel patienter der oplever ≥ 1 SAE
Opfølgningstid	48 uger	48 uger

*Dataanalysen fra studie-007 er foretaget på baggrund af corrected ITT-population (cITT). Korrektionen indebærer, at baselineværdierne for 2 patienter (1 i placebogruppen og 1 i atalurengruppen, 80 mg/kg) blev erstattet af deres screeningsværdier, fordi deres baseline 6MWD var markant lavere end deres screeningsværdier grundet skader på deres underekstremiteter før baselinetesten. Korrektion indebærer ligeledes, at den præspecificerede statistiske analyse blev modificeret.

7 Resultater og vurdering

Resultater og vurdering af de effektmål, som fagudvalget har præspecificeret som hhv. kritiske og vigtige, følger nedenfor.

Motorisk funktion (kritisk)

Motorisk funktion vurderes i forhold til den aktuelle population at være helt centralt for patienternes generelle funktionsniveau og livskvalitet. Den motoriske funktion vurderes ved hjælp af to standardiserede testinstrumenter, henholdsvis 6-minutters gangtest (6MWT) og North Star Ambulatory Assessment (NSAA).

6-minutters gangtest

6MWT er en simpel test, der vurderer patienternes funktionstilstand. Målet med testen er, at patienten skal gå så langt som muligt på 6 minutter uden at løbe. Foruden standardiseret beskrivelse af gangdistance, har 6MWT vist at korrelere med sygdomsprogression, skeletmuskelstyrke, grovmotoriske færdigheder, tidspunkt for tab af gangfunktion og livskvalitet. På baggrund af en række studier vedrørende effektmål ved DMD angiver internationalt anerkendte eksperter, at en forskel på omkring 30 meter i 6MWT over en kort periode (< 1 år) er markant og betydende. For at fastsætte den relative effektforskel har fagudvalget foruden forskel i antal tilbagelagte meter ønsket 6MWT opgjort som forskellen mellem andelen af patienter i de to behandlingsarme, som i opfølgningstiden undgår en forværring på ≥ 8 % fra baseline til endt opfølgning.

Tabel 4. Vurdering af klinisk merværdi: Motorisk funktion, angivet som reduktion i tab af gangdistance fra baseline målt ved 6MWT. I den nedenstående tabel angives der ændring i meter for de absolutte forskelle, mens den for de relative forskelle angives som forskellen mellem ataluren og placebo i andelen af patienter, der undgår en forværring på ≥ 10 % fra baseline til endt opfølgning i de to behandlingsarme.

	Forhåndsdefineret grundlag for vurdering		Resultater (**baseret på studie-007 og -020**)
Absolutte forskelle	30 meter		<u>Studie-020:</u> Samlet population: 15,4 m (−7,44; 33,39) <u>Studie-007:</u> Samlet population (cITT, post hoc): 31,71 m [5,13; 58,28] Samlet population (ITT, prædefineret): 26,4 m [-4,2; 57,1] ADP-subgruppen (post hoc): 49,9 m, p = 0,001*
Relative forskelle	Stor merværdi	Øvre konf.gr. < 0,75	
	Vigtig merværdi	Øvre konf.gr. < 0,90	
	Lille merværdi	Øvre konf.gr. < 1,00	<u>Studie-007:</u> Samlet population (cITT, post hoc): 0,51, p = 0,03*
	Ingen merværdi	Øvre konf.gr. ≥ 1,00	<u>Studie-020:</u> Samlet population: 0,75 [0,51; 1,12]
	Negativ merværdi	Nedre konf.gr. > 1,00	
Evidensens kvalitet	Lav		

Første kolonne indeholder de i protokollen og metodehåndbogen præspecificerede grundlag for vurderingen. Anden kolonne indeholder data på de absolutte og relative værdier fra resultatafsnittet, som indgår i Medicinrådets vurdering.
*Konfidensintervaller ikke tilgængelige.

Samlet population:

Effektmålet 6MWT baseres på de individuelle effektestimater fra studie-007 og studie-020 for den samlede population, da en metaanalyse ikke anses som metodisk forsvarlig. Fagudvalget lægger størst vægt på effektestimaterne fra studie-020, da studiet inkluderede et væsentligt større antal patienter. Både patienter, der blev behandlet med ataluren og placebo, tabte gangfunktion i løbet af studierne og gik en kortere distance i 6MWT end ved baseline. I hhv. studie-020 og studie-007 reducerede ataluren i gennemsnit den samlede populations tab af gangfunktion med 15,4 m [−7,44; 33,39] og 26,4 m [-4,2; 57,1] sammenlignet med placebogruppen (ITT-analyser). I studie-007 ses statistisk signifikant effekt i den samlede population (cITT-analyse), men effekten er ikke statistisk signifikant i ITT-analysen, der tillægges størst vægt. I studie-020 går de atalurenbehandlede patienter i gennemsnit 15,4 meter længere end de placebobehandlede efter 48 ugers behandling i fase-III-studiet (studie-020). Dette er under det prædefinerede mål for den mindste klinisk relevante forskel på 30 meter. I studie-020 er den relative effektforskel på andelen af patienter, der oplever en forværring af gangfunktion på ≥ 10 % fra baseline, 0,75 [0,51; 1,12] hvilket svarer til ingen klinisk merværdi.

Fagudvalget bemærker, at effektestimaterne fra fase-II (studie-007) favoriserer ataluren i væsentligt højere grad end i fase-III-studiet (studie-020). Effekten af ataluren på 6MWT i den samlede population i fase-III (konfirmatorisk, prædefineret) er ca. en tredjedel af effekten i den sammenlignelige ADP-subgruppe (eksploratorisk, post-hoc) i fase-II hhv. 15,4 m (p = 0,213) mod 49,9 m (p = 0,001), hvilket tydeliggør svagheden ved at basere konklusioner på eksploratoriske analyser.

Fagudvalget vurderer, at ataluren giver **ingen klinisk merværdi** i den samlede population, baseret på at effektestimatet ikke lever op til kravet for den mindste klinisk relevante forskel i studie-020, og at det relative effektestimat ligeledes ikke er statistisk signifikant. Fagudvalget ønsker at fremhæve, at effektestimatet i den samlede population er påvirket af, at en stor andel (36 % i studie-020) af patienter tilhører subgruppen med 6MWD > 400 m. Patienter med en baseline 6MWD > 400 m vil sjældent opleve relevante ændringer i deres gangfunktion over 48 uger, da patienterne, jævnfør sygdommens naturhistorie, ikke befinder sig i den progressive fase (se i øvrigt afsnit 7.1.1 vedrørende subgrupperne). Subgruppen vil dermed trække effektestimatet for den samlede population mod nuleffekten.

North Star Ambulatory Asssessment

NSAA er et valideret værktøj specielt udviklet til at vurdere gående drenge med DMD. NSAA er opbygget af en skala med 17 elementer, hvor individuelle motoriske funktioner scores med enten 2, 1 eller 0, hvor scoren 2 er den bedst opnåelige score. Fagudvalget har vurderet på basis af deres erfaring med brugen af NSAA, at en forskel på 2 point mellem grupperne er den mindste klinisk relevante forskel over en periode på 48 uger. En forskel på 2 point svarer i praksis til, at patienten går fra at kunne udføre en motorisk funktion selvstændigt (f.eks. at løfte hovedet) til slet ikke at kunne udføre denne funktion længere, eller alternativt at patienten mister evnen til selvstændigt at udføre to motoriske funktioner normalt, men kan udføre dem i modificeret/kompenseret udgave.

Tabel 5. Vurdering af klinisk merværdi: Ændring i NSAA totalscore fra baseline

	Forhåndsdefineret grundlag for vurdering	Resultater (**baseret på studie-020**)
Absolutte forskelle	2 point	Samlet population: 0,8 point [-0,23-1,82]
Relative forskelle	Ikke muligt at udregne relative forskelle baseret på ændring i effekt på ordinalskala.	
Evidensens kvalitet	Lav	

Samlet population:

I studie-020 er effektmålet NSAA opgjort, mens dette ikke blev målt i studie-007. Vurderingen af effektmålet baseres derfor udelukkende på data fra studie-020. Ændringen i NSAA totalscore var negativ i begge behandlingsarme. Dette indikerer, at der sker en forværring af patienternes motoriske funktion i opfølgningsperioden på 48 uger. Den samlede population af patienter med nmDMD, der behandles med ataluren, vurderes i gennemsnit at tabe 0,8 point færre i NSAA-score end placebogruppen, men effektestimatet er ikke statistisk signifikant. Den absolutte forskel er dermed mindre end de 2 point, der er vurderet som den mindste klinisk relevante forskel.

Fagudvalget vurderer, at ataluren har **ingen klinisk merværdi** sammenlignet med placebo for effektmålet motorisk funktion målt ved NSAA.

For effektmålet motorisk funktion vurderer fagudvalget samlet på baggrund af 6MWT og NSAA, at ataluren har **ingen klinisk merværdi** sammenlignet med placebo.

Livskvalitet (kritisk)
Til vurdering af livskvalitet anvendes PODCI (studie-020), som er et instrument til vurdering af børns funktion og livskvalitet. For livskvalitet anvendes en mindste klinisk relevant forskel mellem grupperne på 0,5 standardafvigelser (SD), som er udregnet ved brug af SD for hele studiepopulationen ved baseline.

PODCI omfatter syv dimensioner: Funktioner i overekstremiteter, mobilitet, fysisk funktion og sport, komfort (mangel på smerte), lykke, tilfredshed og forventninger. Der er fundet data fra to domæner, mobilitet og sport, da disse domæner har vist sig at være associeret med sygdomsprogression hos patienter med DMD, og det er disse data, som er opsamlet og dermed tilgængelige fra studiet. En høj PODCI-score repræsenterer en bedre livskvalitet.

Tabel 7. Vurdering af klinisk merværdi: Livskvalitet målt ved PODCI transfers/basic mobility og sports/physical function.

	Forhåndsdefineret grundlag for vurdering	Resultater (**baseret på studie-020**)
Absolutte forskelle	Forskel på 0,5 SD	PODCI Transfers/basic Mobility: Total population: 1,7 [-2,8-6,2]

	PODCI Transfers/basic Mobility: 7,25 point PODCI - Sports/physical Function: 9,95 point	<u>PODCI - Sports/physical Function:</u> Total population: 2,2 [-2,6-7,0]
Evidensens kvalitet	Lav	

Første kolonne indeholder de i protokollen og metodehåndbogen præspecificerede grundlag for vurderingen. Anden kolonne indeholder data fra ansøgning, som indgår i Medicinrådets vurdering.

<u>Samlet population:</u>

PODCI-mobilitet

I studie-020 oplever patienterne generelt en reduktion i livskvalitet i begge behandlingsarme. Den samlede population af patienter, der behandles med ataluren, har i gennemsnit 1,7 point [-2,8-6,2] højere score i PODCI-mobilitetsscore end placebogruppen, og effektestimatet er ikke statistisk signifikant. Den absolutte forskel er dermed mindre end de 7,25 point, der er vurderet som den mindste klinisk relevante forskel.

PODCI-sport

Den samlede population af patienter, der behandles med ataluren, har i gennemsnit 2,2 point [-2,6-7,0] højere score i PODCI-sportscore end placebogruppen, og effektestimatet er ikke statistisk signifikant. Den absolutte forskel er dermed mindre end de 9,95 point, der er vurderet som den mindste klinisk relevante forskel.

For livskvalitet vurderer fagudvalget samlet, at ataluren har **ingen klinisk merværdi** sammenlignet med placebo.

Lungefunktion (vigtig):

Data for lungefunktion som forespurgt i protokollen er ikke tilgængelig, og derfor kan merværdien ikke dokumenteres for dette effektmål. Patienterne i studiet har en alder, hvor lungefunktionen fortsat forventes at være nær normal og er dermed ikke den primære årsag til funktionsnedsættelse. Sammenholdt med den relativt korte opfølgningstid forklarer dette sandsynligvis, at effekten på lungefunktion ikke er undersøgt.

Der er ikke fundet data på lungefunktion, som vedrører den gående population. PTC-Therapeutics identificerede et open-label single-arm extensionstudie i ikkegående patienter tidligere behandlet med ataluren. Resultaterne for dette studie er beskrevet i et abstract [8]. Lungefunktionen hos patienter behandlet med ataluren er sammenlignet med tilsvarende patienter fra et igangværende observationelt studie. Fagudvalget ønsker at fremhæve en potentiel positiv langsigtet effekt på patienternes lungefunktion ved behandling med ataluren afspejlet i en udskydelse af tidspunktet, hvor patienternes lungefunktion (målt med FVC) falder til under 1 L. Denne grænse er prædiktiv for mortalitet [10], og fagudvalget vurderer den for klinisk betydende.

Fagudvalget vurderer dog, at ataluren har **ikkedokumenterbar merværdi** sammenlignet med placebo for effektmålet lungefunktion, da der ikke er nogle data tilgængelig for den gående patientpopulation.

Tab af gangfunktion (vigtig):

Tab af gangfunktion er udtryk for, hvor længe patienterne opretholder deres gangfunktion. Det har stor betydning for patientens overordnede funktionsniveau, hvis tidspunktet for tab af gangfunktion udskydes. Tab af gangfunktion er centralt for målpopulationens sygdomsforløb og samtidig prædiktivt for senere

komplikationer. Tab af gangfunktion måles her ved andelen af patienter, der fuldstændig mister evnen til at gå.

Tabel 8. Vurdering af klinisk merværdi: Andel af patienter som taber gangfunktion.

	Forhåndsdefineret grundlag for vurdering		Resultater
Absolutte forskelle	5 %-point		Studie-020: Samlet population: -4,4 %-point [-12; 3,4] Studie-007: Samlet population: -3,5 %-point [-14; 6,9]
Relative forskelle	Stor merværdi	Øvre konf.gr. < 0,75	
	Vigtig merværdi	Øvre konf.gr. < 0,90	
	Lille merværdi	Øvre konf.gr. < 1,00	
	Ingen merværdi	Øvre konf.gr. ≥ 1,00	Studie-020: Samlet population: 0,64 [0,29; 1,43] Studie-007: Samlet population: 0,67 [0,20; 2,24]
	Negativ merværdi	Nedre konf.gr. > 1,00	
Evidensens kvalitet	Moderat		

Samlet population:
Der ses en ikkestatistisk signifikant reduktion i andelen af patienter, som mister deres gangfunktion på ca. 4 %-point (-4,4 %-point i studie-020 og -3,5 %-point i studie-007). Dette indikerer, at der er færre patienter, som helt mister gangfunktion i studiernes opfølgningsperiode ved behandling med ataluren sammenlignet med placebo. Fagudvalget havde præspecificeret en reduktion på 5 %-point som værende den mindste klinisk relevante forskel, og reduktionen på ca. 4 %-point lever dermed ikke op til den mindste klinisk relevante forskel. Den relative effektforskel i er ikke statistisk signifikant og falder dermed i kategorien for ingen klinisk merværdi. Estimaterne er overordnet forbundet med stor usikkerhed grundet meget få hændelser, og fagudvalget finder derfor, at datagrundlaget ikke tillader en kvantificering af den kliniske merværdi og indplacerer derfor lægemidlet i kategorien **ikkedokumenterbar merværdi** for dette effektmål.

Alvorlige uønskede hændelser (vigtig):

Tabel 9. Vurdering af klinisk merværdi: Alvorlige uønskede hændelser (SAE)

	Forhåndsdefineret grundlag for vurdering	Resultater
Absolutte forskelle	5 %-point	Studie-020: Samlet population: 0 %-point [-4,8; 4,8] Studie-007:

			Samlet population: -1,8 %-point [-9,3; 5,8]
Relative forskelle	Stor merværdi	Øvre konf.gr. < 0,75	
	Vigtig merværdi	Øvre konf.gr. < 0,90	
	Lille merværdi	Øvre konf.gr. < 1,00	
	Ingen merværdi	Øvre konf.gr. ≥ 1,00	Studie-020: Samlet population: 1,00 [0,26;3,90] Studie-007: Samlet population: 0,67 [0,12;3,84]
	Negativ merværdi	Nedre konf.gr. > 1,00	
Evidensens kvalitet	Moderat		

For effektmålet alvorlige uønskede hændelser ses en absolut forskel på henholdsvis 0 %-point og -1,8 %-point mellem patienter behandlet med ataluren og patienter behandlet med placebo, hvilket betyder, at i studie-007 var der 1,8 %-point færre patienter i atalurengruppen, der fik SAE. Dette overstiger ikke den prædefinerede grænse for den mindste klinisk relevante forskel på 5 %-point.

Den relative effektforskel lever op til kravet for ingen klinisk merværdi, da konfidensintervallet fra begge studier overlapper med nuleffekten. Dette indikerer, at der ikke er en øget frekvens af alvorlige uønskede hændelser ved behandling med ataluren sammenlignet med placebo. Fagudvalget vurderer, at ataluren har **ingen merværdi** sammenlignet med placebo for effektmålet alvorlige uønskede hændelser.

Kvalitativ gennemgang af bivirkninger
Bivirkningsprofilen er baseret på bivirkningsdata fra 007 og 020 i den gående population, hvor i alt 232 patienter har modtaget ataluren samt et åbent forlængelsesstudie på 48 uger i ikkegående patienter. Fagudvalget vurderer, at ataluren har en favorabel sikkerhedsprofil. Bivirkningerne var generelt milde eller moderate i sværhedsgrad, og der blev ikke rapporteret nogen behandlingsrelaterede alvorlige bivirkninger blandt de atalurenbehandlede patienter i disse to studier.

Fagudvalget ønsker at påpege, at langtidssikkerhedsdata ikke er tilgængelige grundet den begrænsede opfølgningstid. I kraft af lægemidlets virkningsmekanisme (mRNA-translation) kan det ikke udelukkes, at lægemidlet kan påvirke translation af mRNA kodende for andre funktionelle proteiner.

Fagudvalget bemærker desuden, at lægemidlet kan påvirke nyrefunktionen som angivet i lægemidlets produktresume afsnit 4.4. Fagudvalget anbefaler, at patienternes nyrefunktion kontrolleres forud for opstart af behandling og overvåges jævnligt i behandlingsforløbet.

Der er rapporteret ændringer i lipidprofilen for visse patienter i de kliniske studier, hvorfor eventuelle kardiovaskulære langtidseffekter er uafklarede.

Overordnet er den nuværende standardbehandling i form af steroider forbundet med en betydelig bivirkningstyngde, og behandling med ataluren vurderes af fagudvalget ikke at medføre en yderligere belastning for patienterne, hvorfor bivirkningsprofilen ikke påvirker atalurens merværdikategorisering.

7.1.1 Vurdering af subgrupper

Fagudvalget har diskuteret den kliniske relevans af subgruppeanalyserne baseret på patienternes baseline 6MWD. Fagudvalget finder, at subgrupperne overordnet er i overensstemmelse med sygdommens naturhistorie og repræsenterer separate sygdomsstadier. Afgrænsningen af de respektive sygdomsstadier er dog arbitrær og kan i klinisk praksis ikke udelukkende baseres på en 6MWT, der er forbundet med stor variation, da der ligeledes er andre faktorer, der er betydende for patientens prognose. Overordnet vurderer fagudvalget, at de valgte afgrænsninger kan være behjælpelige med at afgrænse subgrupper, hvor gangfunktionen er mere eller mindre tilbøjelig til at forværres over 48 uger.

Subgruppen med baselinegangfunktion på > 400 m er kendetegnet ved at være i en stabil fase, hvor der over kortere tidsperioder ikke forventes væsentlige ændringer i funktionsniveauet. Subgruppen med baselinegangfunktion 300-400 m repræsenterer patienter i den progressive fase, hvor forværring i gangfunktion accelereres. Subgruppen med baselinegangfunktion under 300 m er kendetegnet ved en lille residual gangfunktion og dermed en høj risiko for tab af gangfunktion. Behandlingssigtet i denne subgruppe er at opretholde gangfunktion længst muligt, da tab af gangfunktion er en signifikant betydende milepæl for patienter og er tæt relateret til senere komplikationer relateret til lungefunktion, hjertefunktion mv. For de kritiske og vigtige effektmål er effektestimaterne for subgrupperne angivet i tabel 10.

Subgruppen med 6WMD: < 300 m

Generelt ses ingen signifikante effekter på hverken motorisk funktion målt ved 6MWT (-1,0 m [−54,9; 39,5]) eller på tab af gangfunktion (-10 %-point [-39;19]). Der ses en nominel signifikant effekt 0,48 [0,24; 0,93] på andelen af patienter, der får ≥ 10 % forværring i deres 6MWT i studie-020. Subgruppen med baselinegangfunktion under 300 m er kendetegnet ved at have fremskreden sygdom med en lille residual gangfunktion og dermed en høj risiko for tab af gangfunktion. Resultaterne kan derfor indikere, at atalurenbehandling er virkningsløs, når den indledes sent hos patienter med fremskreden sygdom eller alternativt, at opfølgningstiden i studierne ikke har været tilstrækkelig lang tid at opfange eventuelle forskelle i subgruppen.

Subgruppen med 6MWD: ≥ 400 m

Der ses ingen signifikant effekt på effektmålene motorisk funktion målt ved 6MWT (-9,6 m [−43,2; 24,2]), og ingen af patienterne taber gangfunktionen i denne subgruppe. Der er ligeledes ingen forskel på andelen af patienter, der får ≥ 10 % forværring i deres 6MWT, RR 1,52 [0,59; 3,91]. Dette er i tråd med, at patienterne i denne subgruppe overordnet forventes at være i en stabil sygdomsfase, hvor ændringer ikke forventes over studiernes korte opfølgningstid på 48 uger.

Subgruppen med 6MWD ≥ 300 m til < 400 m:

Overordnet ses den største effekt i 6MWT i subgruppen med 6MWD 300-400 m. Patienter behandlet med ataluren går i gennemsnit 47,2 m [11,75; 74,03] længere end patienter behandlet med placebo. Ligeledes er der tendens til at færre patienter helt taber deres gangfunktionen -7,7 %-point [-16; 0,3] eller får en ≥ 10 % forværring af deres 6MWT 0,79 [0,44; 1,41]. FDA har udført sensitivitetsanalyser, der viser, at effekten i 300-400 m-gruppen især er drevet af, at nogle få patienter helt mister gangfunktionen i placebogruppen (n = 4) [11]. Ved en anden afgrænsning på 230-400 m ses der ingen nominel signifikant forskel i 6MWT, da denne afgrænsning inkluderer patienter fra atalurengruppen, der helt mister gangfunktionen [11].

Fagudvalget bemærker derudover, at det kun er 300-400 m-subgruppen, der har effekt i 6MWT, mens de øvrige komplementære subgrupper (6MWD < 300 m og 6MWD ≥ 400 m) udviser modsatrettede tendenser

og således favoriserer disse subgruppeanalyser placebogruppen i studie-020. For effektmålet tab af gangfunktion er der ikke er nogen patienter i atalurengruppen, der taber gangfunktion. I placebogruppen taber 8 % (n = 4) gangfunktion. Der er stor usikkerhed for effektmålet tab af gangfunktion, da der er for få hændelser, og studiet ikke har tilstrækkelig opfølgningstid og patientantal til at belyse effektmålet.

Overordnet vurderer fagudvalget, at der ses et muligt signal for en positiv behandlingseffekt af ataluren i subgruppen med 6MWD på 300-400 m grundet de nominelt signifikante resultater, der favoriserer ataluren på det kritiske effektmål 6MWT. , De komplementære subgrupper udviser modsatrettede effektestimater, og favorisere placebo Effekten i 300-400 subgruppen er observeret i en subgruppeanalyse med betydelige metodiske svagheder, og det er rent biologisk er svære at forklare, at der ses stor variation i behandlingseffekten selv ved mindre justeringer af subgruppernes afgrænsninger. Ligeledes er det svært at forklare, hvorfor effektestimaterne i subgruppen med 6MWD på > 400 m har tendens til at favorisere placebo.

Set i lyset af de mange metodiske svagheder (se afsnit 6.1.1) ved subgruppeanalyserne, er det overordnet meget vanskeligt at vurdere validiteten af fundene i subgruppen med 6MWD 300-400 m.

7.1.2 Evidensens kvalitet

Evidensens kvalitet er samlet set vurderet som værende **lav**. Overvejelser vedrørende evidensens kvalitet kan ses i bilag 2.

7.1.3 Konklusion

Fagudvalget vurderer, at ataluren til Duchennes muskeldystrofi forårsaget af nonsensmutation giver:

- **Ingen klinisk merværdi** for den samlede population af gående patienter i alderen 5 år og derover, sammenlignet med placebo.

Evidensens kvalitet er samlet vurderet som værende **lav**.

Baseret på de kritiske og vigtige effektmål vurderer fagudvalget, at den samlede population af patienter ikke opnår nogen klinisk betydende effekt af atalurenbehandling sammenlignet med placebo og tildeler dermed ataluren **ingen klinisk merværdi**. Dette baseres primært på, at der ikke vises statistiske signifikante eller kliniske relevante effekter på særligt de kritiske effektmål motorisk funktion og livskvalitet i hverken fase-III-studiet (studie-020) eller fase-II-studiet (studie-007).

Baseret på subgruppeanalyserne ses effekten at være størst i subgruppen med 6MWD 300-400 meter, hvor der er nominel signifikant effekt på effektmålene 6MWT, som beskrevet i afsnit 7.1.1. Fagudvalget har svært ved at vurdere disse effekter i lyset af de mange metodiske svagheder, der er behæftet ved subgruppeanalyserne, hvorfor validiteten af fundene i subgruppen for nuværende er uvis. Fagudvalget bemærker, at ansøger har indledt et nyt fase-III-studie med længere opfølgningstid, der forventes afrapporteret i september 2021. Dette studie forventes at være bedre egnet til at opfange en behandlingseffekt af ataluren, grundet en længere opfølgningstid på 18 måneder.

8 Andre overvejelser

Manglende dosisrespons i studie-007.

Fagudvalget bemærker, at ataluren er testet i to forskellige doseringer (40 mg/kg/dag og 80 mg/kg/dag) i studie-007. I studie-007 var der ved behandling med 80 mg/kg/dag totalt fravær af klinisk respons

sammenlignet med placebo. Ansøger har fremsat en hypotese om en klokkeformet dosisresponssammenhæng på baggrund af en række in vitro-test og test i larver fra zebrafisk. Ifølge CHMP i EMA var denne sammenhæng imidlertid ikke tydeligt påvist i de prækliniske in vivo-data og fase-IIa kliniske data.

Da dosisresponssammenhængen ikke er fuldt afklaret, vurderer fagudvalget, at uklarheden om dosis-effekt-forholdet kan føre til et suboptimalt behandlingsrespons, hvis ikke patientens vægt monitoreres kontinuerligt.

9 Fagudvalgets vurdering af samlet klinisk merværdi og samlet evidensniveau

Fagudvalget vurderer, at ataluren til Duchennes muskeldystrofi forårsaget af nonsensmutation giver:

- **Ingen klinisk merværdi** for den samlede population af gående patienter i alderen 5 år og derover, sammenlignet med placebo.

Evidensens kvalitet er samlet vurderet som værende **lav**.

10 Rådets vurdering af samlet klinisk merværdi og samlet evidensniveau

Medicinrådet vurderer, at ataluren til Duchennes muskeldystrofi forårsaget af nonsensmutation giver:

- **Ingen klinisk merværdi** for den samlede population af gående patienter i alderen 5 år og derover, sammenlignet med placebo.

Evidensens kvalitet er samlet vurderet som værende **lav**.

11 Relation til eksisterende behandlingsvejledning

Der foreligger ingen behandlingsvejledning fra RADS eller Medicinrådet på området.

12 Referencer

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13 Bilag 1: Sammensætning af fagudvalg og kontaktinformation til Medicinrådet

Medicinrådets fagudvalg vedrørende Duchennes muskeldystrofi

Formand	*Indstillet af*
Charlotte Olesen *Overlæge*	Lægevidenskabelige Selskaber
Medlemmer	*Udpeget af*
Lise Lotte Bjerregaard *Overlæge*	Region Nordjylland
Karen Markussen Linnet *Overlæge, ph.d.*	Region Midtjylland
Niels Ove Illum *Specialeansvarlig overlæge*	Region Syddanmark
Jens Erik Klint Nielsen *Overlæge*	Region Sjælland
Henrik Simonsen *Overlæge, ph.d.*	Region Hovedstaden
Søren Bisgård Johansen *Farmaceut*	Dansk Selskab for Sygehusapoteksledelse
Espen Jimenez Solem *Overlæge, lektor, ph.d.*	Dansk Selskab for Klinisk Farmakologi
Suzanne Lindquist *Overlæge, ph.d.*	Dansk Selskab for Medicinsk Genetik
Nanna Witting *Overlæge, ph.d.*	Dansk Neurologisk Selskab
Anette Torvin Møller *Overlæge, ph.d.*	Dansk Neurologisk Selskab
Anne Helene Spannow *Afdelingslæge, ph.d.*	Dansk Pædiatrisk Selskab
Bjarne Møller-Madsen *Overlæge, professor*	Dansk Ortopædisk Selskab
Ulla Werlauff *Fysioterapeut, ph.d.*	RehabiliteringsCenter for Muskelsvind
Heidi Aagaard *Direktør, cheflæge*	RehabiliteringsCenter for Muskelsvind
Søren Ulrich *Patient/patientrepræsentant*	Danske Patienter
En patient/patientrepræsentant	Danske Patienter

Medicinrådets sekretariat

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Thomas Linemann (projekt- og metodeansvarlig)

Jesper Skov Neergaard (projektdeltager)

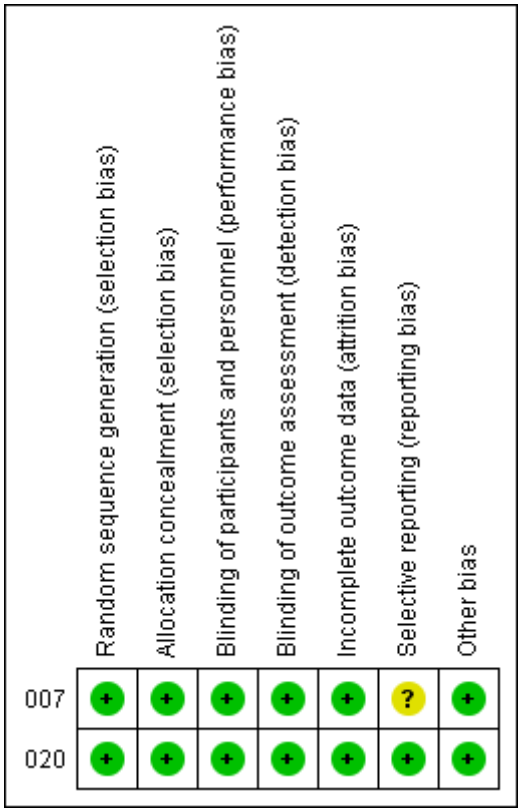
Anette Pultera Nielsen (koordinator)

Jan Odgaard-Jensen (biostatistiker)

Annemette Anker Nielsen (teamleder)

14 Bilag 2: GRADE-evidensprofiler

14.1 Cochrane Risk of Bias



14.2 GRADE-evaluering af evidenskvaliteten til vurdering af den kliniske merværdi af ataluren

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsis-tency	Indirect-ness	Impreci-sion	Other con-siderations	ataluren	placebo	Relative (95 % CI)	Absolute (95 % CI)		
Motorisk funktion: ændring i gangdistance målt i meter (assessed with: 6MWT)												
2	RCT	not serious	serious [a]	not serious	serious [b]	none	Studie-020: 114 Studie-007: 57	Studie-020: 114 Studie-007: 57	-	Studie-020: **15,4 m** (−7,44; 33,39) Studie-007: **31,71 m** [5,13; 58,28]	⨁⨁◯◯ LOW	CRITICAL
Motorisk funktion: andel af patienter der undgår forværring på 10 % eller mere (assessed with: 6MWT)												
1	RCT	not serious	serious [d]	not serious	serious [c]	none	Studie-020: 114 Studie-007: 57	Studie-020: 114 Studie-007: 57	Studie-020: **HR 0,66** (0,47 to 0,95)		⨁⨁◯◯ LOW	CRITICAL
Motorisk funktion: ændring i NSAA-totalscore fra baseline (assessed with: North Star Ambulatory Assessment; Scale from: 0 to 34)												
1	RCT	not serious	serious [d]	not serious	serious [c]	none	114	114	-	MD **0,8 points higher** (-0,23 to 1,82)	⨁⨁◯◯ LOW	CRITICAL
Livskvalitet: gennemsnitlig ændring fra baseline (assessed with: PODCI basal mobilitet; Scale from: 0 to 100)												
1	RCT	not serious	serious [d]	not serious	serious [c]	none	114	114	-	MD **1,7 points higher** (-2,8 to 6,2)	⨁⨁◯◯ LOW	CRITICAL
Livskvalitet: gennemsnitlig ændring fra baseline (assessed with: PODCI fysisk funktion; Scale from: 0 to 100)												
1	RCT	not serious	serious [d]	not serious	serious [c]	none	114	114	-	MD **2,2 points higher** (-2,6 to 7,0)	⨁⨁◯◯ LOW	CRITICAL
Lungefunktion: ændring fra baseline - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT
Tab af gangfunktion												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsis-tency	Indirect-ness	Impreci-sion	Other con-siderations	ataluren	placebo	Relative (95 % CI)	Absolute (95 % CI)		
2	RCT	not serious	not serious	not serious	serious [e]	none	Studie-020: 114 Studie-007: 57	Studie-020: 114 Studie-007: 57	Studie-020: RR 0,64 [0,29;1,43] Studie-007: RR 0,67 [0,20; 2,24]	Studie-020: 4 fewer per. 100 [12 fewer to 4 more] Studie-007: - 3,5 fewer per 100 [14 fewer to 7 more]	⊕⊕⊕◯ MODERATE	IMPORTANT
Alvorlige uønskede hændelser (SAE)												
2	RCT	not serious	not serious	not serious	serious [e]	none	Studie-020: 114 Studie-007: 57	Studie-020: 114 Studie-007: 57	Studie-020: 1,00 [0,26;3,90] Studie-007: 0,67 [0,12;3,84]	-	⊕⊕⊕◯ MODERATE	IMPORTANT

CI: Confidence interval; **MD:** Mean difference; **HR:** Hazard Ratio; **RR:** Risk ratio; **RCT**: Randomized controlled trial

Explanations

a. Studiernes konfidensintervaller overlapper ikke hinandens punktestimater
b. Konfidensintervallet krydser den mindste klinisk relevante forskel
c. Nedgradering af effektmålet møder ikke kriteriet for optimal information size
d. Nedgraderes på inconsistency da det ikke kan vurderes på baggrund af ét studie
e. Konfidensintervallet for den relative effekt indeholder 1

Protokol for vurdering af den kliniske merværdi af ataluren til behandling af Duchennes muskeldystrofi

Handelsnavn	Translarna
Generisk navn	Ataluren
Firma	PTC Therapeutics
ATC-kode	M09AX03
Virkningsmekanisme	Ataluren promoverer ribosomal gennemlæsning af mRNA indeholdende indeholdende præmature stopcodons, hvilket faciliterer produktionen af fuldlængdeprotein
Administration/dosis	Indgives oralt hver dag i 3 doser. Total daglig dosis på 40 mg/kg legemsvægt
EMA-indikation	Behandling af Duchennes muskeldystrofi, der er forårsaget af en nonsensmutation i dystrofingenet hos ambulante patienter i alderen 5 år og derover
Godkendelsesdato Offentliggørelsesdato Dokumentnummer Versionsnummer	30. januar 2018 5. februar 2018 14275 1.0
Fagudvalgets sammensætning og sekretariatets arbejdsgruppe	Bilag 1

Indhold

Forkortelser

6MWT:	6 minutters gangtest
CI:	Konfidensinterval
DMD:	Duchennes muskeldystrofi
EMA:	European Medicines Agency
EPAR:	European public assessment report
FVC:	Forceret vital kapacitet
GRADE:	System til vurdering af evidens (Grading of Recommendations Assessment, Development and Education System)
HR:	Hazard Ratio
KRIS:	Koordineringsrådet for ibrugtagning af sygehusmedicin
nmDMD:	Duchennes muskeldystrofi forårsaget af nonsensmutation
NSAA:	North Star Ambulatory Assessment
OR:	Odds Ratio
PedsQL:	Pediatric Quality of Life Inventory
PODCI:	Pediatric Outcomes Data Collection Instrument
RR:	Relativ Risiko

1 Formål

Protokollen har til formål at definere de kliniske spørgsmål, der ønskes belyst i vurderingen af ataluren med henblik på generel ibrugtagning til patienter med Duchennes muskeldystrofi. I protokollen angives en definition af populationer, komparator og effektmål, der skal præsenteres i den endelige ansøgning samt de metoder, der ønskes anvendt til den komparative analyse. Arbejdet med protokollen er igangsat på baggrund af den foreløbige ansøgning vedrørende ataluren modtaget den 23. oktober 2017.

Protokollen danner grundlaget for den endelige ansøgning for vurderingen af den kliniske merværdi af ataluren sammenlignet med dansk standardbehandling. Alle effektmål, der er opgivet i denne protokol, skal besvares med en sammenlignende analyse mellem ataluren og placebo af både absolutte og relative værdier for de udspecificerede populationer i de angivne måleenheder (se tabel 1). Litteratursøgning og databehandling udføres som beskrevet i protokollen.

2 Baggrund

Duchennes muskeldystrofi (DMD) er en af de hyppigste muskelsvindssygdomme hos børn. DMD er en progredierende sygdom, hvor der sker en tiltagende, symmetrisk svækkelse i alle kroppens muskler, fordi muskelfibrene gradvist ødelægges. Som en konsekvens heraf optræder der respiratoriske, ortopædiske, gastrointestinale, kardiale og hos nogle patienter også kognitive problemer. Alder ved symptomdebut varierer. Hos nogle ses de første tegn på sygdommen i 2-3-årsalderen, hos andre lidt senere. Svækkelse af respirations- og hjertemuskulaturen medfører i sidste ende respirations- og hjertesvigt, der fører til tidlig død [1].

Sygdommen er arvelig og forårsages af forskellige typer af mutationer på X-kromosomet i genet, der koder for proteinet dystrofin [2]. Den hyppigste årsag til DMD er deletioner/duplikationer i dystrofingenet. Hos en mindre andel (10-15 %) skyldes DMD nonsensmutationer i dystrofingenet. Dette medfører inkomplet ribosomal transskription, hvilket resulterer i varierende grader af trunkeret, ikke-funktionelt protein [3].

I Danmark findes aktuelt 157 personer i alderen 2-52 år med DMD ifølge RehabiliteringsCenter for Muskelsvinds register. Tooghalvtreds er under 18 år, hvoraf 62 % (32/52) fortsat er gående. Af disse har 9 patienter DMD forårsaget af en nonsensmutation (nmDMD). Gennemsnitsalderen for de 32 gående drenge er 9 år (2-17). På landsplan påvises 1-2 nye tilfælde af nmDMD/år.

2.1 Nuværende behandling

Den nuværende medicinske behandling af nmDMD omfatter behandling med kortikosteroider, som primært sigter mod at forsinke eller mindske de komplikationer, der opstår som følge af sygdommen. Hovedparten af patienterne får steroidbehandling, men enkelte patienter fravælger steroidbehandling grundet præferencer eller bivirkninger. Den medicinske behandling suppleres med en række andre interventioner såsom fysioterapi, overvågning og støtte af hjerte- og respiratorisk funktion, ortopædiske indgreb, rygkirurgi og rehabilitering [2].

2.2 Ataluren

Ataluren er et oralt lægemiddel, som forbedrer ribosomal gennemlæsning af nonsensmutationer i forskellige gener. I nmDMD er formålet med atalurenbehandling at fremme produktion af fuld længde dystrofin og dermed genoprette dets funktion i muskelcellerne [4].

Ataluren doseres som oral suspension tre gange daglig efter legemsvægt: Morgen: 10 mg/kg, middag: 10 mg/kg og aften: 20 mg/kg. Den totale døgndosis er 40 mg/kg legemsvægt. Et svar på molekylærgenetisk analyse med påvisning af nonsensmutation i dystrofingenet skal foreligge forud for behandlingsstart [5]. Ataluren gives sammen med steroidbehandling.

I 2014 fik ataluren en betinget godkendelse fra det europæiske lægemiddelagentur (EMA) til behandling af ambulante patienter med nmDMD i alderen 5 år og derover. På baggrund af det daværende datagrundlag vurderede Koordineringsrådet for ibrugtagning af sygehusmedicin (KRIS) en ansøgning om ibrugtagning af ataluren som standardbehandling i Danmark. KRIS afviste brugen af ataluren som standardbehandling, men godkendte behandling i særlige tilfælde og under protokollerede rammer. To patienter har siden modtaget, og er aktuelt fortsat i behandling med, ataluren. KRIS ønskede at revurdere behandlingen når data fra et igangværende fase 3-studie forelå. En vurdering der nu er overgået til Medicinrådet. Den betingede markedsføringstilladelse blev fornyet i november 2016 med krav om yderligere at belyse balancen mellem gavnlige og uønskede virkninger i et nyt fase 3-studie.

3 Kliniske spørgsmål

De kliniske spørgsmål skal indeholde specifikation af patientgruppen, interventionen, alternativet/-erne til interventionen og effektmål.

3.1 Klinisk spørgsmål 1

1. Hvad er den kliniske merværdi af ataluren til gående patienter i alderen 5 år eller derover med nmDMD?

Population
Gående patienter med nmDMD i alderen 5 år og derover, hvor en gående patient er defineret ved en selvstændig gangfunktion uden brug af ganghjælpemidler.

Fagudvalget ønsker desuden behandlingseffekten belyst i de prædefinerede subpopulationer baseret på patienternes 6-minutters gangtest ved baseline:

- Patienter med en gangdistance under 300 m*
- Patienter med en gangdistance mellem 300-400 m
- Patienter med en gangdistance over 400 m

*for denne patientgruppe ønskes desuden en yderligere opdeling for visse effektmål, som angivet i afsnit 5.

Intervention
Ataluren (som beskrevet under 2.2) + nuværende behandling (som beskrevet under 2.1)

Komparator
Placebo + nuværende behandling (som beskrevet under 2.1)

Effektmål
Se tabel 1.

3.2 Valg af effektmål

Tabel 1 summerer de valgte effektmål, deres vigtighed, mindste kliniske relevante forskel og kategori. For alle effektmål ønskes både absolutte og relative værdier, jævnfør ansøgningsskemaet. For de relative værdier vurderes den kliniske relevans (merværdi), jævnfør væsentlighedskriterierne beskrevet i Medicinrådets metodehåndbog for vurdering af nye lægemidler. De relative effektestimater kan angives i relativ risiko (RR), odds ratio (OR) eller hazard ratio (HR). Det skal begrundes i ansøgningen, hvis der afviges fra de ønskede effektmål.

Tabel 1. Oversigt over valgte effektmål. For hvert effektmål er angivet deres vigtighed. For kritiske og vigtige effektmål er desuden angivet den mindste klinisk relevante forskel samt indplacering i de fire kategorier (overlevelse, alvorlige symptomer og bivirkninger, livskvalitet og ikke-alvorlige symptomer og bivirkninger).
* For alle effektmål ønskes data med længst mulig opfølgningstid.

Effektmål*	**Vigtighed**	**Kategori**	**Måleenhed**	**Mindste klinisk relevante forskelle (absolutte værdier)**
Motorisk funktion	Kritisk	Alvorlige symptomer	Ændring i gangdistance fra baseline målt ved 6MWT	En forskel på 30 meter
			Andel af patienter undgår en forværring på ≥8% fra baseline	*Anvendes kun til bestemmelse af den relative effektforskel*
			Ændring i NSAA totalscore fra baseline	En forskel på 2 point
Livskvalitet	Kritisk	Helbredsrelateret livskvalitet	Gennemsnitlig ændring over tid på værktøjets totalscore - fra baseline til efter endt behandling - fra baseline til efter endt opfølgning	Forskel på 0,5 SD
Lungefunktion	Vigtigt	Alvorlige symptomer	Ændring fra baseline i FVC (udtrykt som % af normalværdien)	En forskel på 2%-point
Tab af gangfunktion	Vigtigt	Alvorlige symptomer	Andel patienter der fortsat er gående efter 48 uger	En forskel på 5 %-point
Bivirkninger/ uønskede hændelser	Vigtigt	Alvorlige bivirkninger	Andel patienter som får en eller flere alvorlige hændelser	En forskel på 5%-point
			Kendte bivirkninger til ataluren som angivet i produktresumé	Listen over bivirkninger, deres alvorlighed og frekvens vurderes narrativt af fagudvalget

Alle effektmål, der er opgivet i tabel 1, skal besvares med en sammenlignende analyse mellem ataluren og placebo af både absolutte og relative værdier og vurderes i henhold til de mindste klinisk relevante forskelle og væsentlighedskriterierne som angivet i Medicinrådets metodehåndbog.

På baggrund af den indsendte foreløbige ansøgning formodes det at den samlede kliniske merværdi af ataluren baseres på en tidshorisont på 48 uger. Med mindre andet er angivet nedenfor er de mindste klinisk relevante forskelle fastsat ud fra den forventede tidshorisont på 48 uger.

Kritiske effektmål

Motorisk funktion vurderes i forhold til den aktuelle population at være helt centralt for patienternes generelle funktionsniveau og livskvalitet og er derfor valgt som kritisk effektmål. Gående patienter er oftest karakteriseret ved velfungerende lunge- og hjertefunktion men aftagende motorisk funktion. Fagudvalget ønsker motorisk funktion vurderet ved henholdsvis 6 minutters gangtest (6MWT) og North Star Ambulatory Assessment (NSAA).

6MWT er en simpel test, der vurderer patienternes funktionstilstand. Målet med testen er, at patienten skal gå så langt som muligt på 6 minutter uden at løbe. Testen er valideret til brug hos børn fra omkring 5-års alderen. Testen har vist sig at være et mere følsomt klinisk endepunkt sammenlignet med andre simple funktions- og kvantitative muskelstyrkeundersøgelser. Foruden standardiseret beskrivelse af gangdistance, har 6MWT vist at korrelere med sygdomsprogression, skeletmuskelstyrke, grovmotoriske færdigheder, tidspunkt for tab af gangfunktion og livskvalitet. Mindste klinisk relevante forskel i 6MWT er vanskelig at angive eksakt. På baggrund af en række studier vedrørende effektmål ved DMD angiver internationalt anerkendte eksperter, at en forskel på omkring 28-30 meter i 6MWT over en kort periode (<1år) er markant og betydende [6]. Fagudvalget har derfor fastsat den mindste klinisk relevante forskel til 30 meter mellem grupperne.

For at fastsætte den relative effektforskel ønsker fagudvalget desuden 6MWT opgjort som andelen af patienter som i opfølgningstiden undgår en forværring på ≥8% fra baseline til endt opfølgning i de to behandlingsarme.

NSAA er et valideret værktøj specielt udviklet til at vurdere gående drenge med DMD [7]. NSAA er opbygget af en skala med 17 elementer. Hvert element scores med enten 2, 1 eller 0, hvor scoren 2 er den bedst opnåelige score. Summen af de 17 elementer er udtryk for den totale motoriske funktionsevne og kan give anledning til en total score mellem 0-34. Den årlige forværring og dermed tab af funktionsevne er aldersafhængig. Fagudvalget vurderer, baseret på deres erfaring med brugen af NSAA, at en forskel på 2 point mellem grupperne er den mindste klinisk relevante forskel over en periode på 48 uger.

Livskvalitet er centralt for patienterne og betragtes af fagudvalget som et kritisk effektmål. Fagudvalget ønsker som udgangspunkt at basere vurderingen af livskvalitet på *Pediatric Outcomes Data Collection Instrument (PODCI)* som et instrument til vurdering af børns funktion og livskvalitet. Instrumentet omfatter syv dimensioner: Funktioner i overekstremiteter, mobilitet, fysisk funktion og sport, komfort (mangel på smerte), lykke, tilfredshed og forventninger. For helbredsrelateret livskvalitet anvendes ofte en mindste klinisk relevant forskel på 0,5 standarddeviationer (SD), da det historisk set har vist sig at være en relevant forskel på tværs af adskillige kroniske sygdomme og instrumenter [8]. Fagudvalget har derfor valgt at anvende en ændring på 0,5 SD mellem grupperne som den mindste klinisk relevante forskel. Den mindste klinisk relevante forskel udregnes ved brug af SD for hele studiepopulationen ved baseline. Såfremt der i alle studier ikke foreligger data på PODCI foretrækkes data fra et andet valideret instrument, som er relevant for patienter med nmDMD, eksempelvis *Pediatric Quality of Life Inventory (PedsQL)*. Den mindste klinisk relevante forskel er også gældende for dette værktøj.

Vigtige effektmål

Lungefunktion vurderes i denne sammenhæng som et vigtigt effektmål, da nedsat lungefunktion hos DMD patienter er forbundet med morbiditet og nedsat levetid. Patienterne i populationen forventes at være på et stadie i deres sygdomsforløb hvor lungefunktionen fortsat er nærnormal, selvom der kan være individuel variation. Overordnet for patienterne med DMD er lungefunktion og bevarelse af denne meget afgørende. Lungefunktionen tabes i takt med nedsættelse af den generelle muskelfunktion. Fald i lungefunktion ses

oftest efter 13-14-årsalderen, og kan medføre øget forekomst af lungeinfektioner grundet nedsat hoste kraft, ændret vejrtrækningsmønster under søvn med deraf nedsat ventilation under søvn, og gør at patienten får brug for respirationsstøttende foranstaltninger. Fagudvalget ønsker lungefunktionen vurderet ved brug af *Forceret vital kapacitet (FVC)*. FVC er defineret som mængden af luft, der udåndes fra lungerne efter at have taget den dybest mulige indånding. Sygdommens naturhistorie viser et tab af FVC på 4-5 %-point per år [9,10]. Fagudvalget har på baggrund af dette fastsat den mindste klinisk relevante forskel til en ændring på 2 %-point mellem grupperne over 48 uger.

Tab af gangfunktion er udtryk for, hvor længe patienterne opretholder deres gangfunktion. Tab af gangfunktion uden behandling med steroid indtræder før det fyldte 13. år (gennemsnit: 9 år); med steroidbehandling kan ophør af gangfunktion udskydes minimum 2 år [2]. Det har stor betydning for patientens overordnede funktionsniveau, hvis tidspunktet for tab af gangfunktion udskydes. Tab af gangfunktion er centralt for målpopulationens sygdomsforløb og samtidig prædiktivt for senere komplikationer. Fagudvalget vurderer, at tab af gangfunktion supplerer de andre effektmål for motorisk funktion, da tab af gangfunktion er et mere objektivt mål med mindre variation end de motoriske funktionstests. Fagudvalget har fastsat den mindste klinisk relevante forskel til 5 %-point mellem grupperne.

Bivirkninger/uønskede hændelser har betydning for den enkelte patients livskvalitet og kompliance. Det er vigtigt, at bivirkningsprofilen belyses og er acceptabel, særligt i denne patientpopulation hvor behandlingen forventes at være langsigtet. Fagudvalget vurderer dette effektmål som vigtigt og ønsker bivirkningerne belyst ved nedenstående tre parametre.

Alvorlige uønskede hændelser (serious adverse events)
Andelen af patienter som oplever en eller flere alvorlige uønskede hændelser. Den mindste klinisk relevante forskel mellem grupperne er fastsat af fagudvalget til 5 %-point. Fagudvalget lægger vægt på, at patienten er alvorligt syg, men at der er lav tolerance for alvorlige hændelser, der kræver hospitalisering eller i værste tilfælde er fatale.

Kendte bivirkninger
Fagudvalget ønsker desuden en kvalitativ gennemgang af bivirkningstyperne med henblik på at vurdere alvorlighed, håndterbarhed og tyngde af bivirkningerne. Ansøger bedes derfor bidrage med bivirkningsdata fra både de kliniske studier samt produktresuméet for lægemidlet.

Mindre vigtige effektmål

Under udarbejdelsen af protokollen har fagudvalget vurderet, at nedenstående effektmål er mindre vigtige set i forhold til effektmålene i kategorierne ”Kritiske effektmål” og ”Vigtige effektmål”. Disse effektmål vil ikke indgå i vurderingen af den kliniske merværdi.

10 meters gangtest og **trappetest** (4-stair climb/4-stair descend) er relevante mål for motorisk funktion. Fagudvalget har vurderet, at 6MWT og NSAA er bedre mål for populationens funktionsniveau.

Hverdagsaktiviteter (activities of daily living) er helt centrale for patienten. Fagudvalget vurderer imidlertid, at en patientpopulation der fortsat er gående, evner at udføre hverdagsaktiviteter og samtidig i dette stadie har sammenhæng til patienternes motoriske funktion.

Hjertefunktion er ligeledes et relevant effektmål. I klinisk praksis fokuseres der mere på hjertet nu end tidligere hos patienter med DMD, da det er vigtigt at behandle kardiomyopati så tidligt som muligt. Det er fagudvalgets vurdering af effektmålet for den givne population og i den forventede tidshorisont er mindre egnet sammenlignet med de effektmål som fremgår i tabel 1.

Tid til assisteret ventilation og mortalitet anses for at være kritiske effektmål, om end ikke for at være effektive effektmål i vurderingen af ataluren i den pågældende population som kun omfatter gående. En effektiv sygdomsmodificerende behandling vil givetvis have effekt på disse effektmål, men indenfor den angivne tidshorisont og i den pågældende population må det forventes, at død og behovet for assisteret ventilation sjældent indtræder, og det anslås derfor ikke, at disse effektmål kan give nogen relevant information til vurderingen. Fagudvalget ønsker i stedet at basere vurdering på andre effektmål som motorisk funktion, lungefunktion og tab af gangfunktion som forventes at være prædiktive for de senere komplikationer.

4 Litteratursøgning

Databaser for søgningen

Relevant litteratur søges i databaserne MEDLINE (via PubMed eller Ovid) og CENTRAL (via Cochrane Library).

Derudover skal EMAs European public assessment reports (EPAR) konsulteres for både det aktuelle lægemiddel og dets komparator(er).

Søgetermer

Søgningen skal inkludere det generiske navn og handelsnavnet for både det aktuelle lægemiddel og dets komparator(er), som kombineres med termer for indikationen.

Søgningen skal som minimum indeholde termer, som er beskrivende for de områder, der er angivet i tabellen herunder. Både indekseret (f.eks. Medical Subject Headings, MeSH) og fritekst søgning skal anvendes.

Lægemiddel/komparator(er)	*Blokkene til venstre og højre kombineres med **AND***	**Indikation**
Ataluren, Translarna *Termer for det generiske navn, handelsnavn og alternative stavemåder og eventuelle MeSH/Supplementary Concepts kombineres med **OR**.*		Muscular Dystrophy, Duchenne *Termer for indikationen, alternative stavemåder og eventuelle MeSH kombineres med OR. AND kan bruges, hvor flere termer skal forekomme samtidigt for at beskrive indikationen korrekt.*

De anvendte søgetermer, og hvordan de er blevet kombineret, dokumenteres separat for hver af de to databaser.

Kriterier for udvælgelse af litteratur

Der ekskluderes først på titel- og abstractniveau, dernæst ved gennemlæsning af fuldtekstartikler. Artikler, der ekskluderes ved fuldtekstlæsning, skal fremgå med forfatter, årstal og titel i en eksklusionsliste, hvor eksklusionen begrundes kort. Som udgangspunkt skal alle prospektive interventionsstudier inkluderes, der opfylder det kliniske spørgsmål, som er specificeret i protokollen. Såfremt der ikke findes randomiserede direkte sammenlignende studier, som kan belyse det kliniske spørgsmål, skal der søges efter randomiserede eller kontrollerede studier, som muliggør indirekte sammenligninger. Såfremt det ikke findes, søges efter ukontrollerede studier.

Den samlede udvælgelsesproces skal afrapporteres ved brug af et PRISMA-flowdiagram (http://prisma-statement.org/PRISMAStatement/FlowDiagram.aspx).

Ved usikkerheder om hvorvidt en artikel på titel- og abstract-niveau lever op til inklusions- og eksklusionskriterierne, skal der anvendes et forsigtighedsprincip til fordel for artiklen, hvorved fuldtekstartiklen vurderes.

Inklusions- og eksklusionskriterier: Studier med andre populationer end de her beskrevne ekskluderes, studier som ikke rapporterer mindst et af de kritiske eller vigtige effektmål ekskluderes.

Vurderingen af klinisk merværdi baseres på data fra publicerede fuldtekst-artikler og data fra EMA's EPAR. Data skal derudover stemme overens med protokollens beskrivelser. Upublicerede data, og data fra fx abstracts kan fremsendes og vil indgå i vurderingen, såfremt Medicinrådet finder, at de er nødvendige for at sikre en fair sammenligning. Data skal i så fald stamme fra de forsøg, hovedpublikationerne rapporterer fra, og ansøger skal acceptere, at Medicinrådet offentliggør dem i ansøgningsskemaet og i rapporten vedr. klinisk merværdi.

5 Databehandling/analyse

De inkluderede studier og baseline-karakteristikken af studiepopulationerne beskrives i Medicinrådets ansøgningsskema. Det skal angives hvilke studier, der benyttes til at besvare hvilke kliniske spørgsmål.

Alt relevant data skal som udgangspunkt ekstraheres ved brug af Medicinrådets ansøgningsskema. Der skal udføres en komparativ analyse for hvert enkelt effektmål på baggrund af relevant data fra inkluderede studier. For hvert effektmål og studie angives analysepopulation (f.eks. intention-to-treat (ITT), per-protocol) samt metode. Resultater for ITT populationen skal angives, hvis muligt, hvis komparative analyser ikke i udgangspunktet er baseret på denne population. Alle ekstraherede data skal krydstjekkes med de resultater, der beskrives i EPAR'en. Findes uoverensstemmelser, gives en mulig grund herfor.

Hvis ekstraherede data afviger fra de forhåndsdefinerede PICO-beskrivelser specielt i forhold til præspecificeret population og effektmål, begrundes dette. Subgruppeanalyserne, baseret på 6MWT, ønskes udført for effektmålene: motorisk funktion, livskvalitet, tab af gangfunktion og lungefunktion.

For effektmålene tab af gangfunktion og lungefunktion ønsker fagudvalget en subgruppeanalyse i gruppen af patienter med dårligst gangfunktion (6MWT < 300 m ved baseline), hvor patienterne er opdelt i to grupper baseret på median 6MWT. Fagudvalget ønsker dette for at belyse behandlingseffekten i gruppen af patienter med mest fremskreden sygdom. Vurderingen af lægemidlets effekt på gangfunktion i denne gruppe af patienter er muligvis udfordret af, at patienterne forventeligt har en høj risiko for at miste gangfunktionen.

Hvis data for et effektmål ikke er tilgængelig for alle deltagere i et studie, vil der ikke blive gjort forsøg på at erstatte manglende data med en meningsfuld værdi. Det vil sige, at alle analyser udelukkende baseres på tilgængelige data på individniveau.

For effektmål (ORR, SAE, behandlingsstop på grund af bivirkninger og ikke-alvorlige bivirkninger) hvor det er naturligt at beregne både absolut og relativ forskel, vil den relative forskel være basis for statistiske analyser. Den absolutte forskel vil derefter blive beregnet baseret på den estimerede relative forskel for et antaget niveau på hændelsesraten i komparatorgruppen. Det antagne niveau vil afspejle det forventede niveau i Danmark ved behandling med komparator (hvis relativ risiko (RR) = 0,5 og antaget andel med

hændelse i komparatorgruppen er 30 %, da er den absolutte risiko reduktion (ARR) = 30 – 30 x 0,5 = 15 %-point).

Hvis der er mere end et sammenlignende studie, foretages en metaanalyse for de effektmål, hvor det er metodemæssigt forsvarligt. Hvis der ikke foreligger sammenlignende studier, kan data eventuelt syntetiseres indirekte (evt. i form af formelle netværksmetaanalyser eller ved brug af Buchers metode), hvis intervention og komparator er sammenlignet med samme alternative komparator i separate studier. Medicinrådet forbeholder sig retten til at foretage sensitivitets- og subgruppeanalyser på baggrund af studiernes validitet og relevans.

For effektmål, hvor forskellige måleinstrumenter er brugt på tværs af de inkluderede studier, vil eventuelle metaanalyser blive baseret på standardized mean difference (SMD). Den estimerede SMD vil blive omregnet til den foretrukne skala for effektmålet. Til dette formål anvendes medianen af de observerede standardafvigelser i de inkluderede studier.

Hvis det ikke er en mulighed at udarbejde metaanalyser (herunder netværksmetaanalyser), syntetiseres data narrativt. Studie- og patientkarakteristika samt resultater fra de inkluderede studier beskrives narrativt og i tabelform med angivelse af resultater per effektmål for både intervention og komparator(er). Forskelle i patientkarakteristika og studiekontekst (f.eks. geografi og årstal) mellem studier skal beskrives og vurderes for at afgøre, hvorvidt resultaterne er sammenlignelige.

Valget af syntesemetode (metaanalyse eller narrativ beskrivelse) begrundes, og specifikke analysevalg truffet i forhold til metoden skal fremgå tydeligt.

6 Referencer

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7 Bilag 1: Sammensætning af fagudvalg og kontaktinformation til Medicinrådet

Medicinrådets fagudvalg vedrørende Duchennes muskeldystrofi

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