Ataluren in patients with nonsense mutation Duchenne muscular dystrophy (ACT DMD): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial

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Summary

Background Duchenne muscular dystrophy (DMD) is a severe, progressive, and rare neuromuscular, X-linked recessive disease. Dystrophin deficiency is the underlying cause of disease; therefore, mutation-specific therapies aimed at restoring dystrophin protein production are being explored. We aimed to assess the efficacy and safety of ataluren in ambulatory boys with nonsense mutation DMD.

Methods We did this multicentre, randomised, double-blind, placebo-controlled, phase 3 trial at 54 sites in 18 countries located in North America, Europe, the Asia-Pacific region, and Latin America. Boys aged 7–16 years with nonsense mutation DMD and a baseline 6-minute walk distance (6MWD) of 150 m or more and 80% or less of the predicted normal value for age and height were randomly assigned (1:1), via permuted block randomisation (block size of four) using an interactive voice-response or web-response system, to receive ataluren orally three times daily (40 mg/kg per day) or matching placebo. Randomisation was stratified by age (<9 years *vs* ≥9 years), duration of previous corticosteroid use (6 months to <12 months *vs* ≥12 months), and baseline 6MWD (<350 m *vs* ≥350 m). Patients, parents and caregivers, investigational site personnel, PTC Therapeutics employees, and all other study personnel were masked to group allocation until after database lock. The primary endpoint was change in 6MWD from baseline to week 48. We additionally did a prespecified subgroup analysis of the primary endpoint, based on baseline 6MWD, which is reflective of anticipated rates of disease progression over 1 year. The primary analysis was by intention to treat. This study is registered with ClinicalTrials.gov, number NCT01826487.

Findings Between March 26, 2013, and Aug 26, 2014, we randomly assigned 230 patients to receive ataluren (n=115) or placebo (n=115); 228 patients comprised the intention-to-treat population. The least-squares mean change in 6MWD from baseline to week 48 was –47·7 m (SE 9·3) for ataluren-treated patients and –60·7 m (9·3) for placebo-treated patients (difference 13·0 m [SE 10·4], 95% CI –7·4 to 33·4; p=0·213). The least-squares mean change for ataluren versus placebo in the prespecified subgroups was –7·7 m (SE 24·1, 95% CI –54·9 to 39·5; p=0·749) in the group with a 6MWD of less than 300 m, 42·9 m (15·9, 11·8–74·0; p=0·007) in the group with a 6MWD of 300 m or more to less than 400 m, and –9·5 m (17·2, –43·2 to 24·2; p=0·580) in the group with a 6MWD of 400 m or more. Ataluren was generally well tolerated and most treatment-emergent adverse events were mild to moderate in severity. Eight (3%) patients (n=4 per group) reported serious adverse events; all except one event in the placebo group (abnormal hepatic function deemed possibly related to treatment) were deemed unrelated to treatment.

Interpretation Change in 6MWD did not differ significantly between patients in the ataluren group and those in the placebo group, neither in the intention-to-treat population nor in the prespecified subgroups with a baseline 6MWD of less than 300 m or 400 m or more. However, we recorded a significant effect of ataluren in the prespecified subgroup of patients with a baseline 6MWD of 300 m or more to less than 400 m. Baseline 6MWD values within this range were associated with a more predictable rate of decline over 1 year; this finding has implications for the design of future DMD trials with the 6-minute walk test as the endpoint.

Funding PTC Therapeutics.

Lancet 2017; 390: 1489–98

Published **Online** July 17, 2017 http://dx.doi.org/10.1016/S0140-6736(17)31611-2

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Introduction

Duchenne muscular dystrophy (DMD) is a severe, progressive, and rare neuromuscular, X-linked recessive disease.[1] Corticosteroids and better coordinated care have improved outcomes in patients with DMD in the past few decades,[2,3] but these approaches do not specifically target dystrophin deficiency—the underlying cause of disease.[4] Mutation-specific therapies aimed at restoring dystrophin protein production are therefore being explored. Ataluren promotes readthrough of a nonsense mutation to produce full-length functional dystrophin protein.[4–7] About 10–15% of patients with

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Research in context

Evidence before this study

In May, 2017, we searched CENTRAL, MEDLINE, Embase, CINAHL Plus, and LILACS for available literature published from Jan 1, 1990, to May 1, 2017, with the search-terms "nonsense mutation or stop codon mutation, AND Duchenne, muscular dystrophy, dystrophin or clinical trials". Results from a phase 2a trial showed that ataluren improved dystrophin expression in the skeletal muscle of patients with nonsense mutation Duchenne muscular dystrophy (DMD) after 28 days of treatment. Results from the 6-minute walk test (6MWT) and other timed function tests from a 48 week, phase 2b trial showed a clinical benefit of ataluren (40 mg/kg per day) versus placebo in patients with nonsense mutation DMD. In this phase 2b trial, a post-hoc subgroup analysis showed that the treatment effect was more evident in patients predicted to be in the decline phase of disease (ie, those aged 7–16 years with a baseline 6-minute walk distance [6MWD] ≥150 m and ≤80% of the predicted normal value for age and height). Furthermore, findings from natural history studies show that patients with a baseline 6MWD of more than 400 m have fewer declines across multiple measures of physical function; by contrast, patients with a baseline 6MWD of less than 300 m are at higher risk of precipitous declines in 6MWD and loss of ambulation in the subsequent year.

Added value of this study

In the present phase 3 trial, ataluren-treated boys (aged 7–16 years) in the intention-to-treat population had a 13·0 m (SE 10·4, 95% CI −7·4 to 33·4) least-squares mean difference in change in 6MWD after 48 weeks of treatment compared with placebo-treated boys, which, although numerically in favour of ataluren, did not reach statistical significance (p=0·213). In a prespecified subgroup of patients with a baseline 6MWD of 300 m or more to less than 400 m, treatment with ataluren led to a statistically significant least-squares mean difference of 42·9 m (SE 15·9, 95% CI 11·8–74·0; p=0·007) in change in 6MWD after 48 weeks versus placebo. This subgroup is believed to represent a stage of the disease at which a response to dystrophin restoration therapy, as measured by the 6MWT, is more likely to be observed over 48 weeks. Change in 6MWD did not differ significantly between groups in patients in the other two prespecified subgroups—ie, those with a baseline 6MWD of less than 300 m and 400 m or more. Within this 1 year treatment duration, the 6MWT has restricted sensitivity both in patients with higher baseline function (baseline 6MWD ≥400 m) due to their stability, and likewise in patients with lower baseline function (baseline 6MWD <300 m), on the basis of high interpatient variability and increased risk of loss of ambulation. Other efficacy endpoints showed a similar pattern of encouraging results in the prespecified subgroup of patients with a baseline 6MWD of 300 m or more to less than 400 m, attributable to more predictable declines over 1 year in untreated patients in this subgroup. Ataluren-treated patients in the intention-to-treat population had less deterioration numerically, as measured by the timed function tests, versus placebo; this treatment effect was also more evident in patients with a baseline 6MWD of 300 m or more to less than 400 m. The other prespecified subgroups did not have a consistent treatment benefit with ataluren. Ataluren-treated patients in the subgroup with a baseline 6MWD of 300 m or more to less than 400 m also had benefits in function versus placebo, as measured by the North Star Ambulatory Assessment (NSAA). Furthermore, a post-hoc analysis using data from the NSAA showed that patients in the intention-to-treat population and in the subgroup with a baseline 6MWD of 300 m or more to less than 400 m had statistically significant reductions in the relative risk of loss of clinically meaningful milestones versus placebo (31% reduction in risk of lost function for intention-to-treat patients, and 46% reduction in risk of lost function for the ≥300 m to <400 m subgroup; p=0·010 for both).

Implications of all the available evidence

Our results support the clinical benefit of ataluren in a subgroup of patients with nonsense mutation DMD with a baseline 6MWD of 300 m or more to less than 400 m, in whom the 6MWT is most likely to show a treatment benefit over 48 weeks on the basis of the increased sensitivity of this outcome measure in this subgroup experiencing a transition to ambulatory deterioration. Patients in the two additional prespecified subgroups did not have a statistically significant 48 week benefit of ataluren. Additional study of ataluren in a targeted patient population is warranted to confirm these findings. It is likely that multiple clinical endpoints and longer-term duration assessment over several years might help to define the potential benefits of ataluren for targeting of nonsense mutation readthrough in patient populations spanning the wide range of severity in dystrophinopathy.

DMD have a nonsense mutation,[8] which introduces a premature stop codon into the dystrophin mRNA, leading to the translation of a truncated, non-functional protein. The readthrough mechanism of ataluren targets this mutation to treat the underlying cause of disease.[4]

Results from an open-label, dose-ranging, phase 2a trial[6] showed an increase from baseline in dystrophin expression in 23 (61%) of 38 patients with nonsense mutation DMD after 28 days of treatment with ataluren (16, 40, or 80 mg/kg per day). A randomised, double-blind, placebo-controlled, phase 2b, trial showed a slowing of disease progression in patients given ataluren (40 mg/kg per day) versus those given placebo, as measured by the primary endpoint of change in 6-minute walk distance (6MWD) after 48 weeks (corrected intention-to-treat population: observed mean difference 31·3 m;[7] least squares mean difference 31·7 m; unadjusted p=0·0197; adjusted p=0·0367),[9] although a more conservative permutation test analysis[7] rendered an adjusted p value of 0·0561. In a subgroup of patients in

ambulatory decline (aged 7–16 years, with a baseline 6MWD ≥150 m and ≤80% predicted for age, height, and use of corticosteroids), the observed mean difference in 6MWD between ataluren-treated and placebo-treated patients was 49·9 m[7,9,10] (least squares mean difference 45·6 m, unadjusted p=0·0096; adjusted p=0·0182; unpublished). In 2014, ataluren was conditionally approved by the European Medicines Agency for the treatment of ambulatory nonsense mutation DMD in patients aged 5 years and older.[11,12]

The 6-minute walk test (6MWT) and timed function tests are recommended in guidelines from the European Medicines Agency[13] and the US Food and Drug Administration for use in clinical trials of DMD.[14] These guidelines recommend stratification of patients according to disease status, functional status, or developmental stage.[13,14] Natural history data show that patients with a baseline 6MWD of greater than 400 m have fewer declines in physical functioning than do those with a distance of 400 m or less.[15–17] Moreover, emerging MRI data show that, as DMD progresses, fibrotic tissue and fat replace muscle fibres,[18] contributing to patients' physical decline. Magnetic resonance spectroscopy data show that patients with more than an 80% fat fraction in the vastus lateralis muscle are likely to have a 6MWD of less than 300 m and are at increased risk of losing ambulation compared with those with a 6MWD of 300 m or more.[19] Treatment effects using the 6MWT are therefore more likely to be observed in patients in the mid-range (declining) stage of disease (baseline 6MWD ≥300 m to <400 m). This outcome is attributable to the stability of patients with DMD with high baseline function (6MWD >400 m) and, consequently, the restricted sensitivity of the 6MWT (over 48 weeks) in these patients. Furthermore, interpatient variability is greater in patients with lower baseline ambulatory function (ie, those at risk of loss of ambulation [6MWD <300 m]).

We did the ACT DMD trial to assess the ability of ataluren to stabilise ambulation in patients with nonsense mutation DMD, and to identify the effect of ataluren on other measures of physical function. On the basis of an evolving understanding of the 6MWT,[15,20] we also did a prespecified analysis of patients with a baseline 6MWD of 300 m or more to less than 400 m.

Methods

Study design and participants

We did this multicentre, randomised, double-blind, placebo-controlled, phase 3 trial at 54 sites in 18 countries in North America, Europe, the Asia-Pacific region, and Latin America. The trial comprised a 2 week screening period, followed by a 48 week treatment period. Subsequently, patients were eligible to enter an open-label extension study (NCT02090959).

We enrolled ambulatory boys aged 7–16 years with phenotypic evidence of dystrophinopathy (onset of characteristic clinical symptoms or signs by age 6 years, elevated serum creatine kinase, and difficulty with ambulation); nonsense mutation DMD, confirmed by gene sequencing; systemic corticosteroid use for at least 6 months before recruitment into the trial, with no substantial change in dosage or dosing regimen (not related to change in bodyweight) for at least 3 months before the start of treatment and an expectation that this would not change during the study; and a 6MWD of 150 m or more and 80% or less of the predicted normal value for age and height during screening. Subsequently, patients were required to perform two valid (as determined by the clinical evaluator at each study site) 6MWTs on 2 separate days (with the second value plus or minus 20% of the first value). The mean of these two tests was taken as the baseline 6MWD, and was to be within 20% (plus or minus) of the screening 6MWD. Patients' laboratory results during screening were required to be within normal ranges (with the exception of tests indicative of muscle breakdown). The appendix (p 1) provides a full list of exclusion criteria. Parents or guardians provided written informed consent, and patients provided written assent when appropriate.

See Online for appendix

The trial and any changes to the protocol were approved by the local regulatory authorities and the institutional review board of each site. The trial was done in accordance with the Declaration of Helsinki (2000) and the principles of Good Clinical Practice, according to the International Conference on Harmonisation harmonised tripartite guideline.

Randomisation and masking

Patients were randomly assigned (1:1), via permuted block randomisation (block size of four) using, with an interactive voice-response or web-response system, to receive placebo or ataluren. Randomisation was stratified by age (<9 years *vs* ≥9 years), duration of previous corticosteroid use (6 months to <12 months *vs* ≥12 months), and baseline 6MWD (<350 m *vs* ≥350 m). We included age as a stratification variable because it is simultaneously predictive for increased disease severity and developmental capacity.[21] A study site representative provided patient information to the interactive response systems for randomisation; patients, parents and caregivers, investigational site personnel, PTC Therapeutics employees, and all other study personnel were masked to group allocation until after database lock. The identity of the study treatment was concealed by use of a matched placebo that was identical to the active drug in appearance, taste, odour, packaging, and labelling.

Procedures

Placebo and ataluren (PTC Therapeutics International, Dublin, Ireland) were provided in sachets to parents and caregivers, and patients received doses orally three times daily (10, 10, and 20 mg/kg of bodyweight for morning,

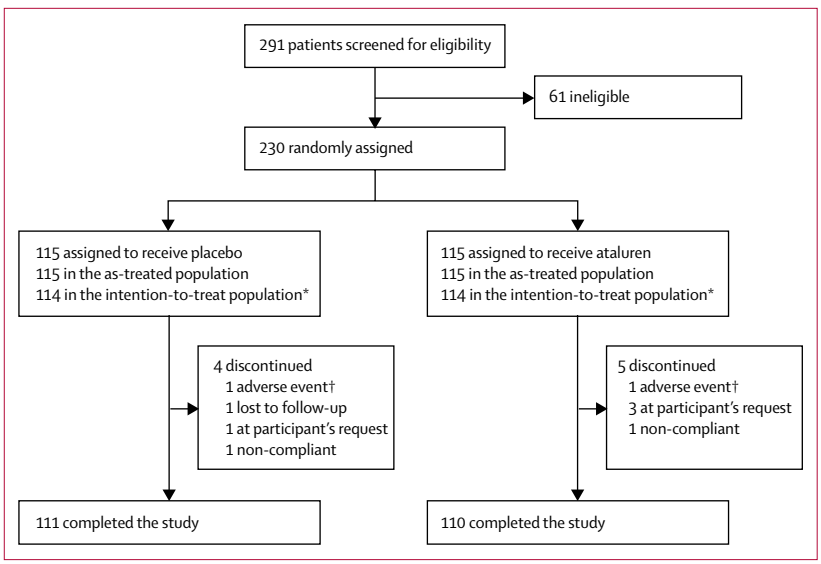

Figure 1: **Trial profile**
*Two patients from the as-treated population (n=1 per group) were prematurely discontinued when dystrophin gene sequencing did not confirm the presence of a nonsense mutation in the dystrophin gene; these patients therefore did not have at least one valid post-baseline 6-minute walk distance value—a requirement for the intention-to-treat population. †Adverse events leading to discontinuation were constipation, possibly related to the study drug (n=1 in the ataluren group) and disease progression (n=1 in the placebo group).

midday, and evening doses, respectively) for 48 weeks. Doses were to be given 6 h apart on the same day, with a 12 h interval between evening and morning doses on the next day. Patients' clinical and medical histories were recorded during screening. Vital signs, height and weight measurements, and concomitant medications were recorded, and laboratory assessments were done during screening, at baseline, and every 8 weeks until the end of treatment. A physical examination was done during screening, at baseline, at 24 weeks, and at the end of treatment. Additionally, patients' physical function was assessed with the 6MWT,[16,22,23] timed function tests,[10,23] and the North Star Ambulatory Assessment (NSAA)[24–27] during screening, at baseline, and every 8 weeks until the end of treatment. A second 6MWT was done at baseline and at week 48, and the average of the two tests was used.

Outcomes

The primary efficacy endpoint was the ability of ataluren to slow disease progression, as assessed by the change in 6MWD from baseline to week 48. The secondary efficacy endpoint was the effect of ataluren on proximal muscle function, as assessed by timed function tests (10 m run or walk, four-stair climb, four-stair descend). Rise from supine and time to 10% persistent worsening in 6MWD were also included in the protocol as secondary efficacy endpoints. Rise from supine was included originally for prognostic purposes and the data are included here as part of the NSAA; data for the time to 10% persistent worsening are included in the appendix (p 3). Exploratory efficacy endpoints were change in physical function, as assessed by change in the NSAA (total score);[24] parent-reported health-related quality of life, as assessed by the Pediatric Outcomes Data Collection Instrument (PODCI);[28] and the activities of daily living (ADL) and disease status survey. Endpoints were also evaluated in a prespecified subgroup of patients who had a baseline 6MWD of 300 m or more to less than 400 m.

We did a prespecified meta-analysis with data from the intention-to-treat population of this trial and a subgroup of patients from the intention-to-treat population of the phase 2b trial[7] (who met the ACT DMD entry criteria). Post-hoc analyses included a sensitivity analysis for the 6MWT, including intervals of baseline distance; the proportion of patients who lost ambulation; a composite timed function test endpoint (linear combination of 10 m run or walk, four-stair climb and four-stair descend); time to loss of ability to perform the four-stair climb and four-stair descend; and the proportion of patients who lost function across each of the individual 17 items in the NSAA. The appendix (p 1) provides full details of PODCI, ADL, and post-hoc analyses. Adverse events were recorded throughout the 48 week treatment period.

Statistical analyses

The as-treated population comprised all randomly assigned patients who received any study treatment, with treatment assignments designated according to actual study treatment received. This population was used to analyse safety and treatment administration. The intention-to-treat population comprised all patients who were randomly assigned, with study drug assignment designated according to initial randomisation. Patients in this population were required to have a valid baseline 6MWD value and at least one valid post-baseline 6MWD value. This population was used to analyse all efficacy measures. Both the intention-to-treat population and the subgroup with a baseline 6MWD of 300 m or more to less than 400 m were prespecified in the statistical analysis plan.

We hypothesised that there would be a difference of at least 30 m in change from baseline to week 48 between ataluren-treated and placebo-treated patients in the decline phase of disease. In the phase 2b study,[7] the SD of the change in observed 6MWD from baseline to week 48 was 72 m in patients receiving ataluren 40 mg/kg per day. With 1:1 randomisation, 210 patients (n=105 per group) would be required to detect a difference of 30 m in 6MWD with at least 85% power (α=0·05). With the assumption that roughly 5% of patients would discontinue prematurely, a total of 220 patients (n=110 per group) would need to be enrolled.

We used an ANCOVA model for the primary analysis. This model included treatment group and the stratification factors for age, duration of corticosteroid use at baseline, and baseline 6MWD category, as well as baseline 6MWD as a covariate. If patients were unable to perform the 6MWT due to disease progression, a value of zero was used. Within-group multiple imputations on the actual

scale were applied to handle missing values via the Markov chain Monte Carlo method; 100 imputations were done, which we expected to be adequate in view of the anticipated amount of missing data. The MIANALYZE procedure (SAS version 9.3) combined the results from the respective invocations of multiple imputations, producing a final estimate of treatment effect and corresponding SE.

We analysed the secondary efficacy endpoints in a similar manner to the primary endpoint; however, if the time taken to perform a timed function test exceeded 30 s, or if a patient could not do the test because of disease progression, a value of 30 s was used. For the NSAA,[24] the study investigator rated patients on a scale of 0–2 for each of the 17 items; 0 indicated the patient was unable to perform function; 1 indicated the patient performed function with difficulty, independent of physical assistance from another person, using a modified method; and 2 indicated the patient performed function, without modification or assistance. The sum of the 17 activity scores was used to form an ordinal total score (maximum score 34). If 13–16 functions were performed, the total score was calculated as ([sum of the scores]×[17/number of activities completed]). If fewer than 13 activities were performed, the total score was considered missing. Ordinal scores were transformed to a linear total score (0–100) for further analysis.[26,27] We did a post-hoc analysis of loss of individual functions on the NSAA by examining the proportion of patients who shifted from a score of 1–2 at baseline to a score of 0 after 48 weeks of treatment. A p value was obtained by use of a permutation test with 1000 permutations of treatment assignments within the original eight strata combinations to account for the correlation between the 17 items on the NSAA. The appendix provides details of methods for the PODCI and ADL and disease status survey. No adjustment for multiple comparisons with respect to subgroups was made;[29] all p values for this study can be considered nominal. This study is registered with ClinicalTrials.gov, number NCT01826487.

Role of the funding source

The funder of the study had a role in study design, data collection, data analysis, data interpretation, and writing of the report, and reviewed the manuscript for medical accuracy. CMM and EM had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between March 26, 2013, and Aug 26, 2014, we randomly assigned 230 patients to receive ataluren (n=115) or placebo (n=115); 228 patients comprised the intention-to-treat population (figure 1). Baseline demographic and clinical characteristics, including type of concomitant corticosteroid use, were similar between groups (table 1).

	Ataluren group (n=115)	Placebo group (n=115)
Age (years)	9·0 (7–10)	9·0 (8–10)
Male sex	115 (100%)	115 (100%)
Race		
Caucasian	89 (77%)	86 (75%)
Black	1 (1%)	1 (1%)
Asian	7 (6%)	6 (5%)
Hispanic	4 (4%)	8 (7%)
Other	7 (6%)	4 (4%)
Not reported	7 (6%)	10 (9%)
Height (cm)	125·6 (118–132)	126·0 (118–133)
Weight (kg)	29·3 (23–37)	27·0 (24–34)
Body-mass index (kg/m²)	18·4 (16–22)	17·9 (16–20)
Age at diagnosis (years)	4·0 (3·3–6·8)	4·0 (2·3–6·9)
Time from diagnosis to randomisation (years)	4·8 (2·2–5·5)	4·7 (2·1–5·9)
Phenotype diagnosis		
Waddling gait	83 (72%)	76 (66%)
Gowers' manoeuvre	83 (72%)	91 (79%)
Calf hypertrophy	91 (79%)	92 (80%)
6MWD (m)	375·2 (314–421)	370·5 (314–422)
6MWD <300 m	25 (22%)	22 (19%)
6MWD ≥300 m to <400 m	47 (41%)	52 (45%)
6MWD ≥400 m	43 (37%)	41 (36%)
Concomitant corticosteroid use		
Deflazacort	50 (44%)	54 (47%)
Prednisone	38 (33%)	37 (32%)
Prednisolone	29 (25%)	28 (24%)

Data are median (IQR) or n (%). 6MWD=6-minute walk distance.

Table 1: **Baseline demographic and clinical characteristics (as-treated population)**

For the primary efficacy endpoint, the least-squares mean change in 6MWD from baseline to 48 weeks was –47·7 m (SE 9·3) for ataluren-treated patients and –60·7 m (9·3) for placebo-treated patients (difference 13·0 m [SE 10·4], 95% CI –7·4 to 33·4; p=0·213; figure 2). The observed difference was 15·4 m. This effect was more evident in the prespecified subgroup of patients with a baseline 6MWD of 300 m or more to less than 400 m, with a least-squares mean change of –27·0 m (SE 12·6) in ataluren-treated patients and –69·9 m (12·1) in placebo-treated patients at week 48 (difference 42·9 m [SE 15·9], 95% CI 11·8–74·0; p=0·007; figure 2). The observed difference was 47·2 m. The observed mean change in 6MWD from baseline to 48 weeks in the two other prespecified subgroups was –1·0 m (least-squares mean –7·7 m [SE 24·1], 95% CI –54·9 to 39·5; p=0·749) in the subgroup with a baseline 6MWD of less than 300 m, and –9·6 m (–9·5 m [17·2] –43·2 to 24·2; p=0·580) in the subgroup with a baseline 6MWD of 400 m or more (figure 2).

Patients in the ataluren group had less of a decline in physical function than did those in the placebo group, as measured by the timed function tests after 48 weeks of

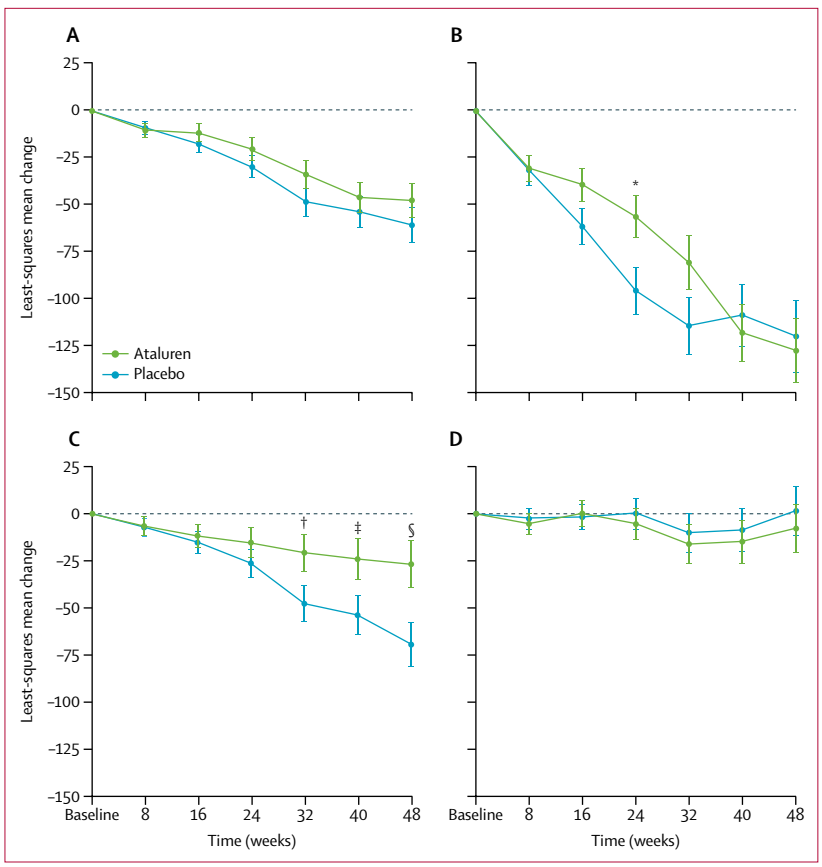

***Figure 2*: Least-squares mean change in 6-minute walk distance from baseline to week 48**
(A) For patients in the ataluren (n=114) and placebo (n=114) groups of the intention-to-treat population. (B) For patients in the ataluren (n=24) and placebo (n=21) subgroup of patients with a baseline 6-minute walk distance of less than 300 m. (C) For patients in the ataluren (n=47) and placebo (n=52) subgroup of patients with a baseline 6-minute walk distance of 300 m or more to less than 400 m. (D) For patients in the ataluren (n=43) and placebo (n=41) subgroup of patients with a baseline 6-minute walk distance of 400 m or more. Error bars show SEs. ANCOVA model based on change from baseline as the dependent variable; independent variables included stratification for age (<9 years *vs* ≥9 years), duration of previous corticosteroid use (6 months to <12 months *vs* ≥12 months), and baseline 6-minute walk distance (<350 m *vs* ≥350 m), treatment, and baseline 6-minute walk distance as a covariate. p values were obtained via ANCOVA applying multiple imputation. *p=0·012. †p=0·032. ‡p=0·030. §p=0·007.

treatment; however, only the four-stair descend was statistically significant in the intention-to-treat population (appendix p 7). This treatment effect was more evident in the subgroup of patients with a baseline 6MWD of 300 m or more to less than 400 m (appendix p 7).

We recorded a least-squares mean treatment difference of 0·8 points (SE 0·5, 95% CI –0·2 to 1·8; p=0·128; ordinal scale) in the prespecified total NSAA score, which numerically, albeit not significantly, favoured ataluren treatment. The treatment benefit remained non-significant when the score was linear transformed (least-squares mean difference 1·5 points [SE 1·4], 95% CI –1·2 to 4·2; p=0·268). This treatment effect was more evident in individuals with a baseline 6MWD of 300 m or more to less than 400 m, based on both observed total score (least-squares mean difference 1·7 points [SE 0·8], 95% CI 0·1–3·3; p=0·037) and linear-transformed score (4·3 points [2·1], 0·2–8·4; p=0·041).

A prespecified meta-analysis of data from this phase 3 trial and from patients in the earlier phase 2b trial who met ACT DMD entry criteria[7] showed that when these 6MWD data were combined, a 21·1 m (SE 9·0, 95% CI 3·4–38·8) treatment benefit was observed for ataluren-treated versus placebo-treated patients over 48 weeks (appendix p 14). Similarly, when data for timed function tests were combined, patients in the ataluren group had less of a decline than did those in the placebo group (–1·4 to –2·0 across the three tests, SE 0·6–0·7; 95% CI –3·4 to –0·2; appendix p 14).

The mean duration of drug exposure was 332·3 days (SD 39·6) for patients in the ataluren group and 333·3 days (39·7) for patients in the placebo group. Ataluren was generally well tolerated, with high compliance in dosing, as determined by return of unused study drug. At least one treatment-emergent adverse event was reported for most patients and most treatment-emergent adverse events were mild to moderate in severity (table 2). Treatment-related (possible or probable) adverse events were more common in patients in the ataluren group than in those in the placebo group (table 2). The appendix (p 9) summarises severe treatment-emergent adverse events. Serious adverse events were reported in eight (3%) patients (n=4 per group); four of these patients reported more than one serious adverse event. All serious adverse events, except one in the placebo group (abnormal hepatic function deemed possibly related to treatment), were deemed unrelated to treatment. No new safety signals were identified. The appendix (pp 3–4) provides additional safety information.

We did a post-hoc sensitivity analysis to assess the change in 6MWD from baseline in other patient subgroups. The largest change between groups was for patients with a baseline 6MWD of 300 m or more to less than 400 m (appendix p 5). An additional post-hoc analysis showed that loss of ambulation was reduced in ataluren-treated versus placebo-treated patients in both the phase 2b and the ACT DMD trials. In the intention-to-treat population of ACT DMD, nine (8%) patients in the ataluren group lost ambulation compared with 14 (12%) patients in the placebo group (appendix p 6). Most of these patients had severely impaired ambulation at baseline (6MWD <300 m; appendix). For patients with a baseline 6MWD of 300 m or more to less than 400 m, none of 47 patients in the ataluren group lost ambulation after 48 weeks versus four (8%) of 52 patients in the placebo group (appendix p 6).

A post-hoc composite analysis of timed function tests showed that patients receiving ataluren had less deterioration than those receiving placebo (difference least-squares mean change –1·6 s [SE 0·7], 95% CI –3·1 to –0·2; p=0·023; appendix p 10). This effect was more evident in patients with a baseline 6MWD of 300 m or more to less than 400 m (least-squares mean change –3·5 s [SE 1·0], 95% CI –5·6 to –1·5; p=0·0007; appendix

p 10). Time to loss of ability to climb and descend four stairs numerically favoured ataluren-treated patients, but did not differ significantly between groups (appendix p 11).

We did a post-hoc analysis to assess the loss of ability to perform each of the 17 individual items of the NSAA. The proportion of patients able to perform each function was balanced at baseline (appendix p 8). Every patient (n=114 per group) performed each of the 17 functions (1938 total functions per group). At baseline, 273 (14%) functions were assessed as 0 (inability to perform the activity) in the ataluren group and 282 (15%) functions were assessed as 0 in the placebo group. After 48 weeks, patients given ataluren lost 12·9% (203/1665) of functions compared with 18·8% (294/1656) of functions lost by patients given placebo, equating to a 31% reduced risk (risk ratio 0·687, 95% CI 0·516–0·914; p=0·010) of loss of function for ataluren-treated patients (figure 3). This observation was more evident in patients with a baseline 6MWD of 300 m or more to less than 400 m (functions lost: 14·3% in the ataluren group *vs* 25·3% in the placebo group; reduced risk 46%; risk ratio=0·537, 95% CI 0·335–0·862; p=0·010). Results for the PODCI and ADL and disease status survey did not differ significantly between groups (appendix pp 12–13).

Discussion

Treatments focusing on dystrophin restoration, such as ataluren, are expected to preserve existing muscle function, thereby stabilising or slowing disease progression in patients with DMD. The slowing of disease progression and motor decline is viewed by the DMD physician community as a realistic expectation for the effect of dystrophin restoration therapies,[30] and patients and their caregivers consider this to be a highly valuable benefit of therapy.[31] In the present trial, the change in 6MWD between ataluren-treated and placebo-treated patients in the intention-to-treat population was not significant; however, the treatment effect was more evident in the prespecified subgroup of patients with a baseline 6MWD of 300 m or more to less than 400 m. Furthermore, ataluren had a positive safety profile. Stratification of patients by baseline function is advisable, because of the decreased sensitivity of the 6MWT in patients with higher baseline function and the increased interpatient variability in patients with a baseline 6MWD of less than 300 m (unpublished). The change in the 6MWD in the intention-to-treat group was 43% of the 30 m distance that was prespecified for statistical power. This outcome was mainly because of the little change in 6MWD observed over 48 weeks in treated and untreated patients with a baseline 6MWD of more than 400 m. However, emerging evidence shows that a change in 6MWD of less than 30 m might be clinically meaningful from the viewpoint of patients' self-reported abilities and health-related quality of life, as measured by the PODCI.[32]

	Ataluren group (n=115)	Placebo group (n=115)
Patients with ≥1 TEAE	103 (90%)	101 (88%)
TEAE by severity*		
Mild†	61 (53%)	54 (47%)
Moderate†	35 (30%)	37 (32%)
Severe†	7 (6%)	9 (8%)
TEAEs by relatedness		
Unrelated	44 (38%)	47 (41%)
Unlikely	20 (17%)	30 (26%)
Possible	27 (23%)	18 (16%)
Probable	12 (10%)	6 (5%)
TEAEs reported for ≥5% of patients‡		
Gastrointestinal disorders	52 (45%)	48 (42%)
Vomiting	26 (23%)	21 (18%)
Diarrhoea	20 (17%)	10 (9%)
Abdominal pain upper	9 (8%)	13 (11%)
Nausea	7 (6%)	7 (6%)
Constipation	3 (3%)	10 (9%)
Abdominal pain	7 (6%)	5 (4%)
General disorders and administration-site conditions	29 (25%)	32 (28%)
Pyrexia	16 (14%)	12 (10%)
Disease progression	9 (8%)	14 (12%)
Infections and infestations	63 (55%)	50 (43%)
Nasopharyngitis	24 (21%)	22 (19%)
Upper respiratory tract infection	11 (10%)	6 (5%)
Rhinitis	8 (7%)	4 (3%)
Injury, poisoning, and procedural complications	35 (30%)	34 (30%)
Falls	21 (18%)	20 (17%)
Musculoskeletal and connective tissue disorders	32 (28%)	32 (28%)
Pain in arm or leg, or both	10 (9%)	14 (12%)
Back pain	11 (10%)	8 (7%)
Nervous system disorders	28 (24%)	23 (20%)
Headache	21 (18%)	21 (18%)
Respiratory, thoracic, and mediastinal disorders	34 (30%)	30 (26%)
Cough	19 (17%)	13 (11%)
Oropharyngeal pain	7 (6%)	6 (5%)

Data are n (%). Patients who had the same adverse event more than once were counted only once for that event. TEAE=treatment-emergent adverse event. *No life-threatening or fatal TEAEs were reported. †Mild: sign or symptom not easily tolerated, but not expected to have a clinically significant effect on the patient's overall health and wellbeing; does not interfere with the patient's usual functions; and is not likely to require medical attention; moderate: sign or symptom causes interference with usual activity or affects clinical status and might require medical intervention; severe: sign or symptom is incapacitating or significantly affects clinical status and is likely to require medical intervention or close follow-up. ‡Medical Dictionary for Regulatory Activities system organ class or preferred term.

Table 2: **Reported TEAEs (as-treated population)**

Additionally, fewer patients lost ambulation in the ataluren group than the placebo group, in both the intention-to-treat population and in patients with a

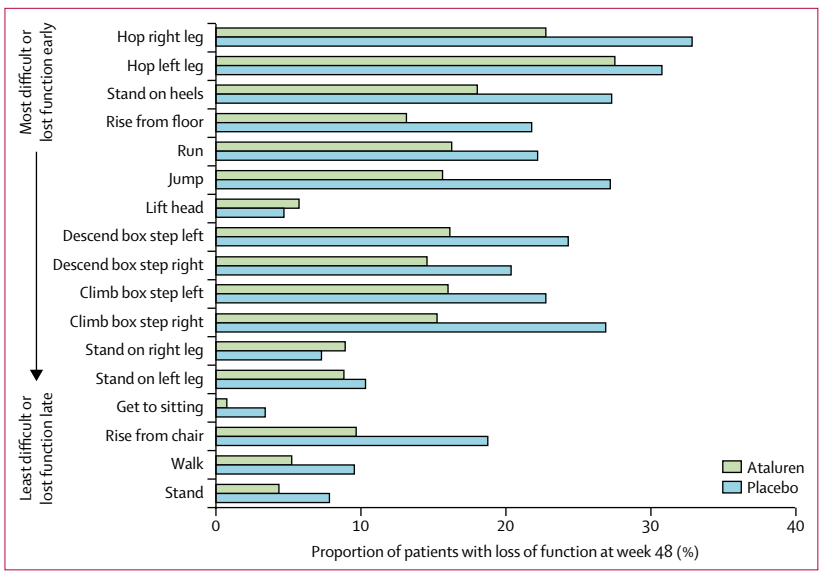

Figure 3: **Proportion of patients who lost the ability to perform each individual item in the North Star Ambulatory Assessment over 48 weeks (intention-to-treat population)**
A score of 0 indicated that the patient was unable to perform the function, a score of 1 indicated that the patient performed the function with difficulty (ie, the patient completed the activity independent of physical assistance from another person using a modified method), and a score of 2 indicated that the patient performed the function (without modification or assistance).

baseline 6MWD of 300 m or more to less than 400 m. Furthermore, a prespecified meta-analysis of 6MWD and timed function test data from a subset of patients from the phase 2b trial[7] and this phase 3 trial showed a significant treatment benefit of ataluren versus placebo.

The timed function tests are key secondary endpoints that are predictive of loss of function, including ambulation.[10,23] Across the tests, a 1·1–2·0 s benefit in ataluren-treated versus placebo-treated patients was observed in the intention-to-treat population. This treatment effect was more evident in patients with a baseline 6MWD of 300 m or more to less than 400 m (1·8–4·4 s). A clinical benefit of ataluren was also shown with the NSAA, a DMD-specific exploratory efficacy endpoint that provides information about a wide range of functions that are important in everyday life.[24] The total observed and linear transformed NSAA scores differed significantly between groups in favour of ataluren-treated patients with a baseline 6MWD of 300 m or more to less than 400 m. Furthermore, a post-hoc analysis of data showed that loss of clinically meaningful milestones across the 17 NSAA functions was significantly reduced in ataluren-treated patients in both populations (intention to treat and the prespecified ≥300 to <400 m subgroup) versus placebo-treated patients. This finding suggests a broader context of benefit in motor function in patients receiving ataluren.

Ataluren was generally well tolerated and no new safety signals were identified. The data showing clinical benefit are particularly important when considering the serious, ultimately fatal nature of this disorder and the high unmet medical need for disease-modifying therapies.

Our trial has some limitations. The entry criteria used were selected to enrich for patients likely to be in ambulatory decline; however, these criteria allowed for inclusion of a subset of study patients with a broad baseline 6MWD (142·5–526·0 m) and ultimately failed to enrich for patients in ambulatory decline. Patients with a higher range of ambulatory ability (baseline 6MWD ≥400 m) accounted for 37% of patients in this study. These patients tend to remain stable in natural history and placebo studies over a 48 week period, and the inclusion of these patients in the intention-to-treat population might have attenuated the treatment effect of ataluren. More stringent entry criteria with regard to baseline 6MWD subgroups would likely have increased the overall effect observed, as noted for patients with a baseline 6MWD of 300 m or more to less than 400 m. Because of the restricted sensitivity of the 6MWT (over 48 weeks) in patients with higher baseline function (6MWD ≥400 m), and because of the increased interpatient variability in patients with lower baseline function (6MWD <300 m), an effect was more likely to be observed in the mid-range subgroup (≥300 m to <400 m). Additionally, because of the slowly progressive nature of the disorder, a longer treatment duration is recommended in current DMD regulatory guidelines,[13,14] which were not available when this study was designed. Moreover, the clinical endpoints in this trial were effort-dependent or susceptible to rater bias; efforts to develop objective, non-invasive measures for DMD studies should continue.

Although the change in 6MWD in the intention-to-treat population was not statistically significant, the benefit observed in patients with a baseline 6MWD of 300 m or more to less than 400 m supports the clinical benefit of ataluren versus placebo in patients with nonsense mutation DMD, especially when considering the totality of supporting evidence. The data presented here confirm the clinical benefit of ataluren in terms of preserving muscle function.

Future and ongoing trials should assess the long-term benefits of ataluren in patients with nonsense mutation DMD. The delay in loss of ambulation reported in patients given ataluren will hopefully extrapolate to longer-term benefits in both upper-limb and pulmonary function in non-ambulatory patients with DMD. Future research should therefore identify whether these and other outcome measures not assessed here, but relevant to non-ambulatory patients, also respond to treatment with ataluren. Ataluren treatment of young boys (<5 years old) would also be of interest, since treatment initiated earlier is likely to result in the greatest long-term benefit.[14] An additional trial (NCT03179631) to examine the long-term efficacy and safety of ataluren is currently planned.

Contributors

CMM, CC, RET, RSF, KMF, NG, PH, AK, JK, FM, ANO, US, TS, PBS, HLS, HT, MT, JJV, TV, BW, GE, HK, XL, JM, TO, PR, MS, RJS, SWP, EM the Clinical Evaluator Training Group, and the ACT DMD Study Group contributed to the conception or design of the work; the acquisition, analysis, or interpretation of data for the work; drafted the report and revised it critically for important intellectual content; and gave final approval of the version that was submitted. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Declaration of interests

CMM has acted as a consultant on clinical trials of Duchenne muscular dystrophy (DMD) for BioMarin, Catabasis, Eli Lilly, Italfarmaco, Mitobridge, Pfizer, PTC Therapeutics, Santhera Pharmaceuticals, and Sarepta Therapeutics, and has received research support for clinical trials from BioMarin, Eli Lilly, PTC Therapeutics, and Sarepta Therapeutics. CC has collaborated on clinical trials with Acceleron, Biogen, BioMarin, Eli Lilly, Ionis Pharmaceuticals, Pfizer, and PTC Therapeutics. RSF has acted as a consultant for AveXis, Biogen, BioMarin, Catabasis, Eli Lilly, Ionis Pharmaceuticals, Mitobridge, Novartis, PTC Therapeutics, Roche, Sarepta Therapeutics, and Summit Therapeutics, and has received research support for clinical trials from Bristol-Myers Squibb, Cytokinetics, PTC Therapeutics, ReveraGen BioPharma, Sarepta Therapeutics, Santhera Pharmaceuticals, and Summit Therapeutics. KMF has acted as a consultant for Audentes Therapeutics, Italfarmaco, Marathon Pharmaceuticals, PTC Therapeutics, Santhera Pharmaceuticals, Sarepta Therapeutics, Tivorsan; has served as a site investigator for Abeona Therapeutics, Akashi Therapeutics, BioMarin, and PTC Therapeutics; and receives research support unrelated to this work from the National Institutes of Health (National Institute of Arthritis and Musculoskeletal and Skin Diseases, and National Institute of Neurological Disorders and Stroke) and CureDuchenne. NG is a site principal investigator for the PTC Therapeutics extension study of ataluren in DMD and has acted as a consultant and/or advisory board member for BioMarin, Biogen, Bristol-Myers Squibb, Eli Lilly, Italfarmaco, PTC Therapeutics, Roche, and Summit Therapeutics. PH has acted as a consultant for Marathon Pharmaceuticals, PTC Therapeutics, and Sarepta Therapeutics. AK has received speaker fees from PTC Therapeutics. JK has acted as a consultant for AveXis, Biogen, Ionis Pharmaceuticals, PTC Therapeutics, and Roche, and has received research support for taking part in clinical research from Biogen, BioMarin, GlaxoSmithKline, Ionis Pharmaceuticals, Novartis, PTC Therapeutics, Roche, Santhera Pharmaceuticals, and Trophos. FM has received consulting fees from Akashi Therapeutics, Biogen, BioMarin, Catabasis, Italfarmaco, Pfizer, PTC Therapeutics, Roche, Sarepta Therapeutics, and Tivorsan, and is supported by the National Institute of Health Research Biomedical Research Centre at Great Ormond Street Hospital for Children NHS Foundation Trust, and University College London. ANO has received speaker and consulting fees from PTC Therapeutics. US is a site principal investigator for the PTC Therapeutics extension study of ataluren in DMD and for the GlaxoSmithKline–Prosensa studies on exon skipping, and has acted as an advisory board member for PTC Therapeutics. TS has received speaking and expert consultancy fees from Biogen, BioMarin, and PTC Therapeutics. PBS has received speaking fees from Catalyst Pharmaceuticals, Grifols, and PTC Therapeutics; has acted as an ad-hoc consultant for Genentech and Ultragenyx; has acted as an advisory board member for AveXis, BioBlast, Biogen, BioMarin, Catabasis, Cytokinetics, Marathon Pharmaceuticals, and Novartis; and has received research support from Biogen, Catabasis Pharmaceuticals, Ionis Pharmaceuticals, Marathon Pharmaceuticals, Novartis, PTC Therapeutics, and Ultragenyx. HLS has acted as a consultant for PTC Therapeutics. MT has received lecture fees from PTC Therapeutics and has acted as a consultant on DMD clinical trials for PTC Therapeutics and BioMarin, and an advisory board member for AveXis. JJV has received consulting fees from BioMarin, Genzyme, Pfizer, and PTC Therapeutics. TV has acted as an advisory board member for Prosensa-BioMarin and Tarix Orphan, and has acted as a consultant for BioMarin, Debiopharm, FibroGen, Laboratoires Servier, Santhera Pharmaceuticals, and Sarepta Therapeutics. BW has acted as an advisory board member for BioMarin, Gilead Sciences, and Sarepta Therapeutics, and has received research support from, Akashi, Eli Lilly, Pfizer, Prosensa-BioMarin, PTC Therapeutics, and Sarepta Therapeutics. EM has acted as an advisory board member for AveXis, Biogen,

BioMarin, Bristol-Myers Squibb, Ionis Pharmaceuticals, Italfarmaco, Prosensa, PTC Therapeutics, Roche, Santhera Pharmaceuticals, Sarepta Therapeutics, and Summit Therapeutics. All other authors declare no competing interests. GE, HK, XL, JM, TO, PR, MS, RJS, and SWP are employees of PTC Therapeutics. The appendix lists declarations of interest for members of the Clinical Evaluator Training Group and the ACT DMD Study Group.

Acknowledgments

This study was sponsored by PTC Therapeutics. We thank the patients and their families for their participation in this study; individuals who were instrumental in the conduct of this study and the collection of data, particularly principal investigators (appendix), supporting investigators, clinical coordinators, clinical evaluators, and study coordinators. We thank Robert Weiss (University of Utah, UT, USA) for dystrophin gene sequencing; the patient advocacy organisations (including Valerie Cwik and the Muscular Dystrophy Association, and Patricia Furlong and the Parent Project Muscular Dystrophy) for the collaboration and support which made this trial possible; and Panayiota Trifillis of PTC Therapeutics for editorial support. Medical writing and editorial support was provided by Luci Witcomb of PharmaGenesis London, London, UK, and was funded by PTC Therapeutics. FM acknowledges the support of Muscular Dystrophy UK to the Dubowitz Neuromuscular Centre.

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