FDA Briefing Document

Peripheral and Central Nervous System Drugs Advisory Committee Meeting

September 28, 2017

NDA 200896
Ataluren

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Memorandum to the Committee

MEMORANDUM

DATE: August 30, 2017

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TO: Members and Invited Guests of the Peripheral and Central Nervous System Drug Advisory Committee (PCNS AC)

SUBJECT: Memorandum for New Drug Application (NDA) 200896, for the use of Translarna (ataluren) for the treatment of dystrophinopathies resulting from nonsense mutations in the dystrophin gene.

1) Introduction

The Peripheral and Central Nervous System Drugs Advisory Committee will meet on September 28, 2017, to discuss a New Drug Application (NDA) for Translarna (ataluren), submitted by PTC Therapeutics Inc., for the treatment of dystrophinopathies [most notably Duchenne muscular dystrophy (DMD)] resulting from nonsense mutations in the dystrophin gene. For simplicity, this memo will refer to the proposed indicated population as nmDMD.

DMD can be caused by a number of different mutations in the dystrophin gene. Approximately 10-15% of patients with DMD have what are referred to as nonsense mutations in the dystrophin gene. Nonsense mutations in the dystrophin deoxyribonucleic acid (DNA) result in a premature stop codon in the protein-coding region of the corresponding messenger ribonucleic acid (mRNA). When this occurs, ribosomal translation of the mRNA is terminated before a full-length, functional dystrophin protein can be produced. The applicant believes that ataluren should allow ribosomes to read through these premature stop codons, which would theoretically result in the production of a functional dystrophin protein.

This advisory committee is in the unusual position of being asked to provide input on an application that has been filed-over-protest. In very rare circumstances, an applicant has insisted that the Agency conduct a further review of data that were determined upon submission to be incapable of supporting approval (in this case, incapable of supporting a conclusion of effectiveness), resulting in the Agency refusing-to-file a marketing application. The Agency has refused-to-file applications for ataluren for the treatment of nmDMD on this basis on two occasions, once in 2011 and again in 2016. The applicant twice formally appealed the decision to refuse-to-file these applications, one appeal for each refusal decision, and each time the applicant's appeal was denied. In addition to the letters the sponsor received outlining the concerns leading to the refuse-to-file decisions and the letters outlining the basis for rejecting each of the appeals, the applicant has had multiple meetings with the Agency discussing these same issues. The applicant has chosen to insist that this most recent application be filed over protest. This memo will provide the regulatory context for these decisions and will also discuss the extensive history of interactions between the Agency and the applicant.

As recent FDA drug approvals indicate, the Agency is highly sensitive to the need to exercise regulatory flexibility in the setting of serious diseases like DMD. However, the critical requirement remains that substantial evidence of effectiveness be provided in order to support approval of a new drug[1].

This memo will summarize the review team's concerns regarding the interpretability of the data intended by the applicant to establish effectiveness that have been submitted with this application, including:

- Study 007, which evaluated 2 doses of ataluren compared to placebo, was negative.
- The fact that the high-dose of ataluren performed worse than the low-dose in Study 007 was attributed by the applicant to a "predictable inverted-U shaped dose-response". Such assertions

[1] Substantial evidence is defined as "…evidence consisting of adequate and well-controlled investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could be fairly and responsibly concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof."

are frequently made by applicants in an attempt to explain a lack of effectiveness with higher doses. In practice, this pattern of dose-response is extremely rare, and the review team finds that the sponsor's speculative explanation is not supported by the data. In addition, this explanation was only proposed after the data from Study 007 were unblinded.

- Multiple simultaneous exploratory post hoc manipulations were then made to the analysis methods and population based on the unblinded data to derive a post hoc subgroup (the so-called "ambulatory decline phase" [ADP] subgroup) that nominally favored the low-dose of ataluren compared to placebo.
- The results of these unblinded analyses of Study 007 were the basis of the 2011 NDA submission where the applicant claimed that the effectiveness of ataluren for the treatment of nmDMD had been established.
- Study 020 evaluated only the low-dose of ataluren from Study 007, compared to placebo, and was explicitly enriched based on the exploratory unblinded post hoc manipulations that resulted in the ADP population described above from Study 007. Study 020 was clearly negative. The observed nominal effect size was also less than 1/3rd of that of the post hoc analysis of the ADP population from Study 007, despite enrolling over 3 times as many subjects (N=228 versus N=63). This finding is a direct illustration of the frequently misleading nature of conclusions that are based on exploratory analyses of negative trials.
- After the data from Study 020 were unblinded, the applicant stated that the trial was not appropriately enriched based on 6-minute walk distance (6MWD). Analyses conducted by the Agency suggest that it was.
- The applicant then conducted exploratory analyses in 9 subgroups in Study 020, 5 of which were based on baseline 6MWD alone. There was no planned hierarchical ordering of these analyses (which would have been invalid, regardless, in the setting of a negative primary analysis), i.e., there was no prospective plan to control for multiplicity. Only 1 of these 9 exploratory subgroups (subjects with a baseline 6MWD between 300-400m) nominally favored ataluren (with complementary groups numerically favoring placebo in some analyses), again noting that this was in the setting of a negative primary analysis.
- The applicant then claimed to retrospectively support this exploratory finding with post hoc analyses of the unblinded data from Study 007 as well as post hoc pooled analyses of these negative trials. The approach of attempting to retrospectively support an exploratory result in a negative trial with a post hoc analysis of unblinded data from an earlier negative trial substantially lacks scientific rigor.

The application contains a large number of exploratory analyses that lack interpretability and are often entirely based on unblinded data. The presentation of the data in the application is often unclear as to which analyses were used by the applicant. Ultimately, no positive results from any prospectively planned analyses that are persuasive have been provided with this application. In the one instance where an exploratory analysis (the unblinded post hoc analysis of Study 007) was prospectively tested (in Study 020), the results were clearly negative.

We believe that it is important to discuss with the committee findings from the review team related to these issues.

2) Regulatory History

Before considering a detailed analysis of the data, it is critical to first provide an overview of the regulatory history of this development program as a necessary framework for understanding the data that you are being asked to consider. We strongly encourage the committee to review the complete appended letters, memoranda, and meeting minutes that reflect the extensive interactions that have occurred between the Agency and the applicant. The most important conclusions from these communications/discussions are summarized below. As these documents demonstrate, the Agency has had persistent concerns regarding the applicant's interpretation of its data. Specifically, the applicant has repeatedly attempted to explain away negative results on pre-specified analyses with novel theories developed with data in-hand. Such conclusions are often very tempting, but are well-known to be highly prone to both known and unknown biases when generated with the full knowledge of a trial's results. As will be discussed below, in the one instance in this development program where such a post hoc theory was prospectively tested in a well-designed trial, the results were clearly negative.

Upon receipt of an NDA, the Agency conducts a review of the application to determine if it contains the required components according to the appropriate regulations (21 CFR 314.101). If during that process the review team determines that there are substantive deficiencies or concerns that cannot be rectified readily, including a clear failure to include evidence of effectiveness compatible with statute and regulations, the Agency can refuse-to-file (RTF) an application.

The applicant first submitted an NDA for ataluren for the treatment of nmDMD on March 31, 2011. That application primarily included data from Study PTC1124-GD-007-DMD (Study 007), which is summarized in the following table.

Table 1: Overview of Study 007

Protocol	Design	Population	Duration	Sample Size	Primary Endpoint	Dose
Study 007	Randomized, double-blind, placebo-controlled.	Ambulatory male nmDMD subjects ≥5 years old, baseline 6-minute walk distance (6WMD) ≥75m Subjects were not required to be on corticosteroids at baseline.	48 weeks	174	Change from baseline on the 6-minute walk test (6MWT)	10, 10, 20 mg/kg TID; 20, 20, 40 mg/kg TID; or placebo

The data from this trial will be discussed in greater detail later in this memo. Most notably, however, the study failed to meet any of its statistically pre-specified endpoints. As the May 26, 2011, RTF Letter (see Appendix A) notes, by the usual statistical standards, Study 007 was "clearly and convincingly negative." The applicant made numerous post hoc adjustments to both the analysis methods and populations in order to identify what it believed was a signal of effectiveness in a narrow subset of subjects including (1) narrowing the age to ≥7 to ≤16 years (2) restricting the baseline 6MWD to ≥150m and less than 80%-predicted, and (3) only including subjects who were taking corticosteroids at baseline

[a population that the applicant defined as the "Ambulatory Decline Phase (ADP)" subgroup]. After the data were unblinded, the applicant also disregarded the consistent failure of the high-dose in any population based on the theory that ataluren had a predictable inverse dose-response ("inverted-U") relationship. The RTF Letter went on to note that these additional analyses "beyond being post hoc and not obviously more appropriate than the protocol-specified analyses, clearly do not reach statistical significance for any dose-placebo comparison, when taking into account any reasonable adjustment for multiple comparisons." Further weakening the ability of these data to support approval was that the applicant was proposing an approval based on the results of a single clinical trial – a circumstance where data are expected to be highly compelling. These results led the Division of Neurology Products (DNP) to RTF the NDA on the basis that it was "clear that the application cannot be approved based on the data submitted."

In a July 19, 2011, meeting with the Agency in response to the RTF decision (see Appendix B), the Agency reiterated that the applicant's many post hoc analyses of Study 007 could only be considered exploratory and encouraged the applicant to test its theories in a second adequately designed trial. The Agency indicated that such a trial, if robustly positive, in conjunction with the first study might be the basis of an approval.

The applicant elected to appeal DNP's decision to the Office of Drug Evaluation I (ODEI) on December 23, 2011. In a memo issued on January 20, 2012, Robert Temple, MD, the ODEI Director, agreed with DNP's determination that the application could not be filed (see Appendix C). Dr. Temple's memo noted that the primary and secondary efficacy endpoints and statistical analysis plan (SAP) for Study 007 had been discussed extensively with DNP, including at a November 12, 2009, pre-NDA meeting, and that no alternative analyses that were obviously more appropriate than those ultimately used for the protocol-specified analyses were identified. The memo further commented that the applicant proposed "applying simultaneously no less than three essentially unrelated post hoc adjustments, again with full knowledge of the data, to generate p-values for the primary endpoint that turn out to be just within the range of those normally considered to provide weak statistical support for efficacy, not a level of support suitable for a single study, and a level of support generally only high enough to warrant the conduct of additional studies." Dr. Temple further observed that all but one of the applicant's post hoc analyses of four timed function tests (TFTs) remained negative and that "given the known potential for introduction of bias through post hoc adjustments to statistical analyses, these results do not appear, on face, to be persuasive." Finally, the memo noted that the applicant attributed the fact that the high-dose arm remained negative, despite post hoc adjustments to the analyses, to a "fourth post hoc conclusion, plainly not recognized when the study was designed, that the high dose arm could have been predicted to be ineffective based on preclinical studies, and that the resulting 'umbrella-shaped' dose-response curve was clearly to be expected." Dr. Temple ultimately concluded that "even if accepted individually, the series of post hoc adjustments simultaneously necessary to explain the negative findings of Study 007 are, on face, difficult to accept as a basis for concluding that Study 007 is a positive study, i.e., [that it] provides any support at all for effectiveness."

Following the negative results from Study 007, the applicant went on to conduct Study PTC124-GD-020-DMD (Study 020), summarized in the following table.

Table 2: Overview of Study 020

Protocol	Design	Population	Duration	Sample Size	Dose
Study 020	Randomized, double-blind, placebo-controlled.	Ambulatory male nmDMD subjects ≥7 to ≤16 years old, on corticosteroid treatment, baseline 6-minute walk distance (6MWD) ≥150m but ≤80%-predicted.	48 weeks	230	10, 10, 20 mg/kg TID; or placebo

Study 020 was powered and enriched explicitly based upon the post hoc subgroup findings from Study 007. In addition, only the low-dose of ataluren from Study 007 was included. On December 23, 2015, the applicant submitted an NDA that included the previous results of Study 007, the new findings from Study 020, and a meta-analysis of both trials.

The applicant had previously described a nominal post hoc treatment effect of 46m on the 6MWT at Week 48 in the post hoc ADP population from Study 007. Therefore, it is particularly troublesome that despite this enrichment, the pre-specified efficacy analysis of Study 020 was clearly negative (p=0.21), with less than 1/3rd the observed effect size of Study 007 at Week 48 (13m), despite enrolling more than three times the number of subjects (N=228) that were part of the post hoc ADP population in Study 007 (N=63 for the low-dose versus placebo comparison). Additionally, only one of the trial's multiple secondary endpoints was nominally positive in the intent-to-treat (ITT) population. The application also presented a number of analyses that either lacked interpretability (e.g., subgroup analyses that were uncontrolled for multiple comparisons) or were entirely post hoc in an attempt to explain the failure of the pre-specified primary analysis.

In a letter issued on February 22, 2016, DNP refused-to-file the NDA (see Appendix D), primarily on the basis that the data from Study 020 were "clearly and convincingly negative" and that "most of the secondary endpoints (again, in the setting of a failed primary endpoint) in Study 020 are also nominally negative." DNP also found that the applicant's analyses of numerous additional subgroups that were not statistically controlled for multiple comparisons were incapable of providing any support for effectiveness.

The applicant met with DNP to discuss the RTF decision on April 19, 2016 (see Appendix E). On July 13, 2016, the applicant elected to again appeal the RTF decision to ODEI. The applicant also met with the Agency on August 29, 2016, to discuss its appeal (see Appendix F). In a memo issued on October 13, 2016, Dr. Temple again upheld the decision to RTF the application (see Appendix G). This memo agreed with DNPs conclusion that "Studies 007 and 020 are negative and clearly cannot provide substantial evidence of effectiveness." The application had attempted to highlight a nominally positive treatment effect in subjects with a 6MWD between 300 and 400m at baseline. Dr. Temple agreed that the findings in this subgroup were nominally suggestive of benefit, but emphasized that looking within a study for subsets that lack Type I error control has the potential to be misleading, as was directly illustrated by the enrichment of Study 020 based on the post hoc ADP population from Study 007. The memo states that the analysis of the 300-400m 6MWD subgroup cannot be considered to be pre-specified as it was "clearly not identified as a planned effectiveness analysis, with planned control of the Type I error rate, in the SAP." Additionally, it notes that any of the evidence that the applicant cites with respect to the

likelihood of the 300-400m 6MWD population to deteriorate during the course of the trial could have led the applicant to enrich Study 020 for these subjects or identify them as a primary endpoint right up until unblinding. Therefore, Dr. Temple notes that "what [the applicant] now find obvious after examining the Study 020 results was plainly not recognized [the applicant] prior to the study." The memo goes on to conclude that "when analysis plans are developed with data in hand, without a prospective plan for controlling the Type I error rate, [a] study lacks the statistical rigor needed to consider it an adequate and well-controlled trial" and that Studies 007 and 020 "analyzed as prospectively planned, clearly cannot provide the basis for a finding of substantial evidence of effectiveness." Finally, Dr. Temple cautioned that an RTF decision represents, in part, "an effort to advise applicants on the most efficient way forward, which in this case is the prompt conduct of another trial, perhaps enriching for the 300-400m 6MWD population."

In the appeal of the RTF decision, the applicant also attempted to make an argument for approval largely based on dystrophin results from a non-quantitative dystrophin analysis that was conducted in Study PTC-GD-004-DMD (Study 004) which was a 28-day open-label trial in 38 male nmDMD subjects that evaluated doses of 4, 4, 8mg/kg TID; 10, 10, 20mg/kg TID, and 20, 20, 40 mg/kg TID. The October 13, 2016, Appeal Denied Letter summarizes the reasons that interpretable evidence of dystrophin production had not been provided. The deficiencies of these dystrophin analyses, as they relate to the applicant's assertion of an "inverted-U" shaped dose-response relationship, will also be discussed later in this memo as well as in Dr. Ashutosh Rao's review summary.

3) Additional Considerations

Two additional considerations that have occurred outside the context of the current review cast additional doubt on the interpretability of the data that have been submitted.

a. Development of Ataluren in Nonsense Cystic Fibrosis (nmCF)

The applicant has indicated that ataluren is capable of reading through all nonsense mutations, irrespective of the specific clinical disease. Therefore, the recently publically available information with respect to the development of ataluren for the treatment of nmCF is relevant for consideration.

In 2014, the applicant released negative results (see Appendix H) from a Phase 3 trial of ataluren in 232 subjects with nmCF. The applicant argued that the data from this trial suggested trends towards effectiveness and stated that the collective data from the trial, including retrospective and subgroup analyses, supported the conclusion that ataluren was active and showed clinically meaningful improvements over placebo. To explain the trial's negative findings, the applicant argued that a post hoc population of subjects who were not treated with aminoglycoside antibiotics appeared to benefit the most, and postulated that these drugs interfered with ataluren's activity.

Based on the post hoc theory about aminoglycoside interference from the negative trial, the applicant went on to conduct a subsequent large Phase 3 trial in 279 subjects with nmCF that excluded all subjects who were taking chronic inhaled aminoglycosides. However, in March 2017 (see Appendix I), the applicant announced that this enriched trial did not achieve its primary or secondary endpoints and that it planned to discontinue further development of ataluren for nmCF.

The unfortunate failure of ataluren to demonstrate effectiveness in nmCF is directly relevant to the current application for two important reasons. First, the applicant states that ataluren should read-

through all nonsense mutations. Therefore, the lack of clinical benefit in nmCF is consistent with the negative results from Studies 007 and 020 in nmDMD based on what should be a shared mechanism of action. In addition, almost identically analogous to the nmDMD program, the applicant identified a post hoc subgroup from an initial trial that was explained with a seemingly plausible theory that when prospectively tested failed to demonstrate any signs of effectiveness. These findings should strongly reinforce the pitfalls of viewing tempting post hoc theories to explain negative data as anything more than hypothesis-generating for further investigation.

b. 2016 Oncologic Drugs Advisory Committee (ODAC) Meeting

On September 14, 2016, the ODAC met to consider an application from a different applicant for apaziquone for immediate intravesical instillation post-transurethral resection of bladder tumors in patients with non-muscle invasive bladder cancer (NMIBC). That application included data from two randomized and well-controlled trials that both failed to demonstrate a statistically significant effect on their primary endpoints (reduction in disease recurrence at 2 years). That applicant then subsequently identified a post hoc analysis that it believed suggested that the timing of therapy could enhance the clinical benefit of treatment. When asked to vote on whether substantial evidence of a treatment effect for apaziquone over placebo had been demonstrated, the committee unanimously voted 14-0 that it had not. The official minutes from that meeting importantly reflect a comment from a statistician on the committee that the applicant's subgroup analysis was "ad hoc and could lead to potentially biased estimates of treatment effect in the subgroups of interest" (see Appendix J). The committee also concluded that a post hoc pooled analysis of the two negative trials did not provide the same level of statistical certainty or robustness as the two separate trials would have.

The conclusions from this meeting are relevant to the consideration of the current application where many of the applicant's analyses of two similarly negative trials are either entirely post hoc or among a number of analyses that had no pre-specified statistical control for Type I error among numerous comparisons. In addition, the pooled analyses contained in the current application were also either designed with the unblinded data from Study 007 in-hand or when both Studies 007 and 020 were unblinded.

4) Clinical Efficacy Evidence

This section of the memo will discuss the review team's findings with respect to the results of Study 007, Study 020, and the applicant's meta-analyses based on pooled data from these trials. The applicant's numerous post hoc analyses and/or post hoc theories as to why subgroup analyses that were not controlled for Type I error should be considered interpretable will be addressed. However, it is well-established that both known and unknown sources of bias can contribute to misleading results in such analyses. Therefore, as the details of the trial results are considered, it is important that they are viewed in the context of the fact that no positive pre-specified results that could be considered interpretable by usual standards have been submitted with this application.

Study 007

Study 007 was a 48-week randomized, double-blind, placebo-controlled trial. 174 subjects with nmDMD were randomized in a 1:1:1 ratio to receive either ataluren 10,10,20 mg/kg TID (low-dose); ataluren 20,20,40 mg/kg TID (high-dose); or placebo. Subjects were required to be ambulatory, ≥5 years of age at enrollment, and have a baseline 6-minute walk distance (6MWD) ≥75m. Dynamic randomization was

utilized with 3 stratification factors: age (<9 years or ≥9 years), corticosteroid use (yes/no), and baseline 6MWD (<350m and ≥350m).

The primary endpoint was the difference between treatment and placebo on the change from baseline in 6MWD at Week 48. Over 50 secondary endpoints were included in the protocol, including timed function tests (TFTs), with no hierarchical ordering of importance in the SAP.

The protocol-defined ITT population consisted of all randomized subjects who had a valid 6-minute walk test (6MWT) from the baseline visit and from at least 1 post-baseline visit.

As the FDA Biometrics review details, the primary analysis specified in the SAP was a mixed model repeated measures (MMRM) on rank-transformed data as Shapiro-Wilks tests indicated departure from normality for the untransformed data and log-transformed data. Holm's method was applied to adjust for multiplicity and an unstructured covariance matrix was used as it provided the best fit.

Results in the ITT Population

The following table presents the results of the pre-specified analyses of the primary endpoint [as noted, the rank-transformed MMRM analysis was primary (p=0.15 and p=0.48 for the low-dose and high-dose comparisons versus placebo, respectively – yellow highlights)]. Statistical significance was set at an alpha of 0.025 for the comparison of each dose of ataluren to placebo.

Table 3: Pre-specified Analyses of the Primary Endpoint in the ITT Population

Analysis method / Source	Transformation	Low Dose vs Placebo		High Dose vs Placebo	
		Δ (SE)	p-value nominal(adjusted*)	Δ (SE)	p-value nominal(adjusted*)
Primary Analysis					
MMRM					
CSR1 Table 14.2.1.14B	Ranks (primary)	--	0.15 (0.30)	--	0.48 (0.48)
CSR1 Table 14.2.1.8.5B	None	26.4 (15.5)	0.09 (0.16)	-0.1 (15.3)	1.0 (1.00)
Pre-specified Sensitivity Analyses					
Permutation Test					
S0025 Table 14.2.2.12.30	None	--	0.08 (0.15)	--	1.0 (1.00)
ANCOVA with LOCF					
CSR1 Table 14.2.2.16	Ranks	--	0.16 (0.27)	--	0.42 (0.63)
CSR1 Table 14.2.2.15	None	28.4 (14.0)	0.05 (0.08)	-0.7 (13.8)	0.96 (1.0)

*The adjusted p-values for the primary analysis on rank-transformed data were based on Holm's method; all other adjusted p-values were based on Dunnett's test.
Results were confirmed by FDA reviewer.

As the preceding table indicates, there were no statistically significant results on the pre-specified primary analyses of the primary endpoint. Only one sensitivity analysis (untransformed ANCOVA with LOCF) nominally favored ataluren (discussed below).

Post Hoc Covariate Adjustment

The applicant makes an argument that "a marked discrepancy was observed between the p-value for the difference between low-dose ataluren and placebo of 0.05 obtained with this ANCOVA versus the p-value of 0.09 obtained with the pre-specified MMRM on untransformed 6MWD; because missing data at Week 48 were few, this observation suggested an inadequacy in the pre-specified MMRM model." To address this issue, the applicant added a baseline-by-visit interaction term to the model, referred to as augmented MMRM or refined MMRM. The applicant stated that the interaction term was nominally significant, and the resulting nominal p-value of 0.05 was close to the nominal p-value of ANCOVA with LOCF, as expected when there are only a few missing data.

The Agency statistical reviewer notes, however, that a model could undergo such post hoc refinement in many ways when the data are unblinded and that the pre-specified analysis should therefore carry the most credibility. For example, if the baseline Time to Rise from Supine, or Rise Time (RT), a known prognostic factor in DMD, is added to the model, the resulting nominal p-value for the low-dose versus ataluren comparison becomes 0.1.

The following table presents the analyses of the secondary endpoints assessing physical function.

Table 4: Protocol-Defined Analyses of Secondary Endpoints Assessing Physical Function

	Baseline			Low Dose vs Placebo		High Dose vs Placebo	
	P	L	H	Δ	p-value	Δ	p-value
Timed Function Test Times, seconds (negative deltas indicate improvement relative to placebo)[a]							
Stair ascend	6.04	6.94	7.63	-2.40	0.10	-1.28	0.34
Stair descend	5.52	6.08	6.75	-1.62	0.43	-1.08	0.67
10-meter run/walk	6.86	7.45	7.80	-1.35	0.70	-0.66	0.73
Supine to stand	11.5	10.8	12.3	-0.01	0.42	-0.24	0.74
Timed Function Test Method Grading, scores (positive deltas indicate improvement relative to placebo)[b]							
Stair ascend	4.02	3.56	3.85	0.45	0.91	0.04	0.75
Stair descend	3.65	3.28	3.63	0.23	0.64	-0.10	0.72
10-meter run/walk	4.81	4.72	4.57	0.24	0.96	0.23	0.19
Supine to stand	3.60	3.65	3.58	0.11	0.60	0.05	0.84

[a] Comparisons were based upon analyses of rank-transformed data using the original MMRM model. Differences in observed mean changes from baseline to Week 48 were shown.
[b] Timed function test method grading was analyzed using generalized estimating equation models.
Source: CSR1 table 26

As the table indicates, the analyses of these endpoints uniformly failed to reach nominal significance when analyzed according to the SAP (i.e., MMRM on rank-transformed data). In a post hoc analysis of untransformed data, only the 4-stair climb (4SC) was nominally positive for the comparison of the low-dose and placebo (nominal p=0.04), with no correction for multiple comparisons. These findings are consistent with the lack of an effect on the primary endpoint.

In the applicant's analyses, the high-dose of ataluren performed numerically worse than the low-dose. The applicant has argued that this was a predictable outcome based on what it believes is an "inverted-

U" dose-response relationship. The limitations of the available data to support this assertion will be discussed later in this memo. In addition, the applicant only suggested the predictability of the failure of the high-dose after the trial results were available.

When analyzed as prospectively planned, the results from Study 007 were clearly negative. The applicant then went on to conduct numerous post hoc analyses and adjustments to the unblinded trial data.

Corrected ITT (cITT) Population

The protocol specified a set of rules to determine the validity of the 6MWTs as well as to allow for repeat 6MWTs, if necessary. However, only after the data were unblinded, the applicant determined that two subjects [a high-dose subject (501-0120) and placebo subject (501-014)] at the same site had suffered lower-limb injuries within 1-2 days prior to baseline that appeared to have impaired walking at baseline. The applicant then suggested that the baseline 6MWT values for these subjects should have been declared invalid and the screening values should be used. This is a substantial change, as it impacts all of the applicant's further post hoc subgroup analyses that will be discussed below. The applicant also identified another low-dose subject with a knee injury 9 days prior to the Week 48 visit, but determined that this result should remain valid. The following table depicts the findings from these 3 subjects that were identified by the applicant:

Table 5: Applicant's List of Lower Limb Injuries Identified in 6MWD Listings

Treatment arm	Subject	Injury	Study Visit	6MWD Status	6MWD prior visit	6MWD at Visit	6MWD at next Visit	Time of Injury in relation to test
Placebo	501-014	Knee	Baseline	Valid	395	309	418	1-2 days
Ataluren 20, 20, 40	501-012	Ankle	Baseline	Valid	303	125	309	1-2 days
Ataluren 10, 10, 20	034-001	Knee	Week 48	Valid	357	298	350	9 days prior to visit

Ref: Adapted from Table 26 CSR for Study 007.

The applicant termed the post hoc study population where the baseline 6MWD was replaced by the screening 6MWD in these 2 subjects as the "cITT" population. The following table summarizes the applicant's post hoc analyses of the primary endpoint based on this population.

Table 6: Applicant's Post-Hoc Analyses of the Primary Endpoint in the cITT Population

Analysis method Source	Analysis Set	Transformation	Low Dose vs Placebo		High Dose vs Placebo	
			Δ (SE)	Nominal p-value*	Δ (SE)	Nominal p-value*
MMRM						
FDA reviewer	cITT	Ranks	--	0.10	--	0.48
FDA reviewer	cITT	None	28.6 (14.7)	0.05	-1.6 (14.5)	0.91
Augmented MMRM						
CSR1 Table 14.2.1.24B	ITT	None	29.0 (14.3)	0.05	0.4 (14.2)	0.98
CSR2 Table 14.2.1.24.2S	cITT	None	31.7 (13.5)	0.02	-1.6 (13.3)	0.90
Permutation Test based on Augmented MMRM						
CSR1 Table 25	ITT	None	--	0.06	--	0.98
CSR2 Table 28	cITT	None	--	0.03	--	0.91

*P-values were not adjusted for multiple comparisons of the two doses against the placebo.

The rank-transformed MMRM for the low-dose versus placebo comparison remained negative (nominal p=0.10). These post hoc results illustrate the sensitivity of the data to changes in even 2 data points. The review team has expressed several concerns regarding the reliability of this post hoc change to the analysis population. Most fundamentally, the protocol did not prespecify conditions under which subjects should not take the 6MWT based on concerns about a potential impact on the test results. Many other conditions (e.g., low back pain) may also impact a subject's 6MWD, so the completeness of this post hoc dataset is likely to be limited and subject to obvious selection bias. In addition, the review team identified a number of subjects with lower limb injures within days of testing where the 6MWD was not affected. Finally, many other subjects had similar fluctuations in 6MWD between trial visits without apparent injury.

Ultimately, a plausible argument can be made that the changes in 6MWD in subjects 501-014 and 501-012 may have been a result of lower limb injuries. However, judgment-based post hoc changes to the unblinded dataset based on rules that were not defined in the protocol, applied with data in-hand, and that ultimately favored ataluren are subject to obvious bias and therefore of questionable reliability.

Post Hoc Ambulatory Decline Phase (ADP) Population

The applicant conducted a post hoc analysis in a group of subjects who were defined by multiple simultaneous adjustments to the unblinded data including 1) restricting the age-range to ≥7 to ≤16 years at baseline, 2) restricting the baseline 6MWD ≥150m and ≤80%-predicted, and 3) requiring a stable dose of corticosteroid (CS) therapy at baseline based on the theory that these subjects were most likely to decline during the course of the trial. The applicant reports a treatment difference in the low-dose ataluren versus placebo comparison of 46m (nominal unadjusted p-value of 0.01). The high-dose versus placebo comparison yielded a treatment difference of 4.5m (nominal unadjusted p-value of 0.8). However, these analyses were based on the already post hoc cITT population. When the protocol-defined ITT population is used, the treatment difference in the low-dose versus placebo comparison is 44m (nominal unadjusted p-value of 0.05). The high-dose versus placebo comparison in the ITT population yielded a treatment difference of 16.8m (nominal unadjusted p-value of 0.45).

In its 2011 NDA submission, the applicant had claimed the effectiveness of the low-dose of ataluren had been established based on the analyses of the ADP population. However, when this population was prospectively evaluated in Study 020, the results were clearly negative. This finding directly illustrates the often misleading nature of conclusions based on exploratory analyses of negative trials.

Post Hoc Baseline 300-400m 6MWD

The applicant retrospectively conducted another post hoc analysis based on baseline 6MWD only after the results of Study 020 were available (discussed later). The following table summarizes the results from these post hoc subgroups based on the protocol-defined ITT population:

Table 7: Change in 6MWD at Week 48 by Baseline 6MWD (ITT Population)

Population	N High/Low/Placebo	Low Dose vs Placebo		High Dose vs Placebo	
		Δ (m)	p-value	Δ (m)	p-value
ITT	59/57/57	26.4	0.09	-0.1	1.0
<300m	16/15/13	20.8	0.59	5.4	0.89
≥300 to <400m	20/22/22	51.0	0.06	0.8	0.98
≥400m	23/20/22	18.0	0.19	10.1	0.45

Analysis method: MMRM on untransformed data
Source: FDA Biometrics reviewer

As the table indicates, none of these analyses are nominally positive, with the high-dose of ataluren consistently performing worse than the low-dose. The following table presents the timed function tests (TFT) results by baseline 6MWD subgroup for the comparison of low-dose ataluren versus placebo, all of which are all also nominally negative. The high-dose of ataluren also performed numerically worse than the low-dose on the TFT analyses. The interpretation of these analyses in the context of the results of the analyses of the baseline 6MWD subgroups from Study 020 will be discussed along with those findings.

Table 8: Change in Timed Function Tests at Week 48 by Baseline 6MWD

Endpoint	BL 6MWD <300m		BL 6MWD ≥300 to <400m		BL 6MWD ≥400m	
	Δ, s	p-value	Δ, s	p-value	Δ, s	p-value
Time to walk/run 10 m	-1.1	0.75	-2.8	0.08	-0.2	0.43
Time to climb 4 stairs	-4.0	0.17	-3.2	0.15	-0.4	0.53
Time to descend 4 stairs	-0.7	0.82	-3.9	0.09	-0.1	0.73

Analysis method: MMRM on untransformed data
Deltas: LS mean difference between low-dose ataluren and placebo; negative deltas indicate improvement relative to placebo.
Source: FDA Biometrics reviewer

Inverse Dose-Response Relationship

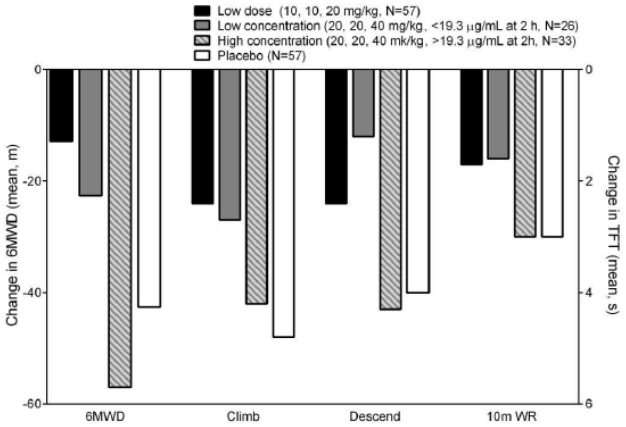
Before discussing the clinical results from Study 020, it is important to consider the applicant's position that there was a predictable "inverted-U" shaped dose-response for ataluren. This is an important consideration, as this is the basis for the applicant's assertion that the failure of the high-dose from

Study 007 should be ignored. The applicant's position is based, in large part, on the dystrophin findings from Studies 004 and 007. Dr. Ashutosh Rao from the Office of Biotechnology Products (OBP) has reviewed these data and does not find them to be persuasive for the following reasons:

- Although the in vitro data suggests an "inverted-U" shaped dose-response, this finding is not supported by the in vivo data from Study 004.
- There did not appear to be a correlation in dystrophin expression between in vivo data and in vitro data generated from the same set of patient-derived myotube cultures. No method validation or method development information is provided to explain the discrepancy. Possible reasons for the differences between cultured myotubes and in vivo data could be due to the pro-inflammatory neuromuscular tissue environment in tissue versus the homogeneous and nutrient rich culture of myotubes. Therefore, it may not be relevant to rely solely on the in vitro data to determine dose-response.
- The immunohistochemistry (IHC) results of dystrophin production were not confirmed with a quantitative western blot analysis. The restored dystrophin gene expression was also not verified using Quantitative-PCR (Q-PCR). The current IHC method appears to have several methodological issues with sample processing, staining, and dystrophin quantification, which could also explain differences in the cultured myotubes and in vivo data.
- The immunofluorescence data from Study 007 were uninterpretable due to problems with sample quality and freezing related artifacts in a significant number of samples (an assertion the applicant also makes in the clinical study report for that trial).

In addition, the application included post hoc exposure-response analyses using the data from Study 007 in support of an "inverted-U" shaped dose-response. Specifically, the applicant identified a post hoc concentration threshold of 19 µg/mL at 2-hours post-dose after which effectiveness reportedly decreases, as depicted in the following table copied from the application:

Figure 1: Mean change in 6MWD and timed function tests (TFTs) in ataluren groups by mean C2h ≤19.3 µg/mL vs >19.3 µg/mL in Study 007



Source: Page 132 in clinical study report for Study 007

The Office of Clinical Pharmacology (OCP) does not consider these data supportive. Most importantly, the OCP review notes that information on potential imbalances that could have contributed to the effects observed on the clinical endpoints was not described. As depicted in the following table, multiple key prognostic baseline factors (i.e., all TFTs including 6MWD) were markedly worse in the subjects with concentrations ≥19 µg/mL, which is almost certainly responsible for the misleading appearance of an "inverted-U" shaped dose-response.

Table 9: Summary of Baseline Clinical Endpoints by Treatment and/or Concentration Groups in Study 007

	Baseline Time(s) to Descend 4 Stairs		Baseline Time(s) to Climb 4 Stairs	Baseline Time(s) Taken to Walk/Run 10m	Baseline Time(s) to Rise from Supine	6 Minute walk Distance at Baseline (m)	Age at Baseline
	N	Mean	Mean	Mean	Mean	Mean	Mean
High Dose (20/20/40 mg/kg) High Concentration =>19.3 ng/mL	30	8.53	10.25	9.66	15.63	332.91	9.23
High Dose (20/20/40 mg/kg) Low Concentration <19.3 ng/mL	29	4.97	5.05	5.94	9.04	391.09	7.53
Low Dose 10,10,20 mg/kg	57	6.08	6.94	7.45	10.80	355.59	8.77
Placebo	56	5.53	6.02	6.81	11.36	361.52	8.32
All	172	6.14	6.90	7.37	11.53	359.59	8.49

Source: FDA OCP Review

Ultimately, the review team has concluded that both the applicant's dystrophin analyses and the post hoc exposure-response analyses do not provide persuasive evidence to support the presence of an "inverted U" shaped dose-response relationship for the reasons described above. It is also important to note that the applicant's claim that the pattern of response observed in Study 007 could have been predicted was only made after the results of the trial were available.

Study 020

Study 020 was a 48-week, randomized, double-blind, placebo-controlled trial. Importantly, the enrollment of Study 020 was enriched based on the post hoc ADP population from Study 007, as follows:

- Ambulatory male nmDMD subjects
- 7 to 16 years of age (inclusive)
- Taking corticosteroids at baseline
- Baseline 6MWD ≥ 150m but ≤ 80%-predicted

In addition, only the low dose (10, 10, 20mg TID) of ataluren from Study 007 was evaluated in Study 020, based on the applicant's belief regarding the presence of an inverse dose-response relationship in that trial. Dynamic randomization was utilized and was stratified based on age (<9 or ≥9 years), duration of corticosteroid use (approximately ≥6 to <12 months versus ≥12 months), and baseline 6MWD (<350 meters or ≥350 meters).

Results in the ITT Population

The analysis of the primary efficacy endpoint in Study 020 was the difference between treatment arms in the change from baseline in 6MWD at Week 48 in the ITT population. The primary analysis was based on an ANCOVA with multiple imputations (MI). The ANCOVA model stratified by age, duration of CS use, baseline 6MWD category, and baseline 6MWD. The results of the primary analysis were negative, as indicated in the following table.

Table 10: Analyses of the Primary Endpoint in Study 20

	LS Means	Difference	95% Confidence Interval	p-value
Ataluren (n=114)	-47.7		(-65.82, -29.57)	
Placebo (n=114)	-60.7		(-78.94, -42.40)	
Ataluren vs Placebo		13.0	(-7.44, 33.39)	0.21

Source: CSR Table 14.2.1.3.1, confirmed by FDA Biometrics reviewer

Sensitivity analyses yielded similar results to the primary analysis.

The review team's concerns regarding the lack of interpretability of the post hoc ADP population from Study 007 have already been discussed. In that context, it is very informative that the effect size in Study 020 was less than 1/3rd (13m versus 46m) of that seen for the post hoc ADP population for the low-dose ataluren arm from Study 007, despite actively enriching for this population and enrolling more than 3.5 times more subjects (N=228 versus N=63 [ADP for the low-dose ataluren arm and placebo in Study 007]). This result is a direct illustration of the frequently misleading nature of what are often tempting post hoc analyses of fully unblinded data or exploratory analyses of subgroups that lack any statistical control for Type I error in the setting of a negative trial.

The Agency Biometrics review notes that applicant has indicated that "despite efforts to enrich for patients in the ambulatory decline phase of the disease, the Study 020 population remained heterogeneous. The range of baseline 6MWD in Study 020 (142 to 521 meters) was broad…" and that "the mean baseline 6MWD was 23 meters higher in Study 020 ITT than in the Study 007 ambulatory decline phase subgroup. Collectively, these observations demonstrate that Study 020 failed to enrich for patients in the ambulatory decline phase of DMD." To assess the impact of the higher mean baseline 6MWD in Study 020, the Agency Biometrics reviewer conducted an analysis on a subgroup of subjects with baseline 6MWD <433 meters. The cutoff of 433 meters was chosen so that the mean baseline 6MWD for this subgroup was the same as the Study 007 ADP subgroup. The results from this analysis are shown in the following table:

Table 11: Change in 6MWD at Week 48 for Subgroup of Baseline 6MWD <433 meters in Study 20

	LS Means	Δ (SE)	95% Confidence Interval	p-value
Ataluren (n=92)	-54.7		(-75.32)	
Placebo (n=91)	-69.5		(-90.18)	
Ataluren vs Placebo		14.8	(-9.51)	0.23

Source: FDA Biometrics reviewer

As the table indicates, the treatment effect increased only slightly (i.e., the estimate is 15 meters, nominal p-value = 0.23), which is still much smaller than the treatment effect observed in the ADP population in Study 007. The Agency Biometrics reviewer concludes that this finding suggests that the discrepancy in the treatment effects between the two trials cannot be explained by differences in mean baseline 6MWD.

Post Hoc Analyses of the Primary Endpoint

The applicant has also submitted the results of two post hoc analyses of the primary endpoint using a non-linear two-part model and a slope-based analysis. These analyses are intended to assess the treatment effect in the context of subjects who remain ambulatory throughout the trial and those who lose the ability to ambulate.

The Agency Biometrics review contains a detailed discussion of several concerns regarding these analyses. The main potential deficiencies can be summarized, as follows:

- The non-linear two-part model resulted in a nominally positive treatment difference favoring ataluren of 13.9m (nominal p=0.04). However, the Agency statistical reviewer notes that predicted values were not independent because the same model parameter estimates were used to predict the change in 6MWD for all of the subjects in the ataluren group. Such correlation or dependence as well as the statistical uncertainty of the model parameter estimates were not properly incorporated into the analysis. The standard error may have been underestimated as to co-variances of the predicted values were not properly accounted for.
- The slope-based analysis was nominally negative (p=0.1). In addition, the Agency statistical reviewer used a residual plot to check if the linear model fit the data well. However, it appeared that the residuals from the slope-based model were not randomly scattered around the horizontal zero line, suggesting that the linear model had a lack of fit, limiting the interpretability of this post hoc analysis.

Timed Function Tests

TFTs were evaluated in the ITT population. In the setting of a negative primary endpoint analysis, these analyses could only be considered exploratory (there was also no planned statistical control for Type I error). If the time taken to perform a test exceeded 30 seconds, or if a subject could not perform the test due to disease progression, a value of 30 seconds was used. Only the 4SD was nominally positive in favor of ataluren, as indicated in Table 12. These results are consistent with the negative results of the primary analysis.

Two protocol-defined sensitivity analyses were performed for the TFTs: (1) using an upper limit of 45 seconds, and (2) using the highest value observed for a given endpoint. The Agency statistical reviewer

concludes that the results of TFT analyses seemed sensitive to the handling of the maximum value. The nominally positive result on the 4SD was lost when the highest observed value was used if a subject cannot perform the test due to disease progression. The following table summarizes the protocol-defined primary and sensitivity analyses of the TFTs.

Table 12: Analyses of Change in Timed Function Tests

Endpoint	Maximum = 30 Seconds		Maximum = 45 Seconds		Maximum = Highest Observed Value	
	Δ, s	p-value	Δ, s	p-value	Δ, s	p-value
Time to walk/run 10 m	-1.2	0.12	-1.9	0.16	-2.7	0.20
Time to climb 4 stairs	-1.8	0.06	-2.5	0.10	-4.7	0.33
Time to descend 4 stairs	-1.8	0.01	-2.3	0.04	-2.6	0.14

Source: CSR Table 17

Subgroup Analyses

Study 020 evaluated the efficacy of ataluren in 9 subgroups, including 5 based on baseline 6MWD alone. In the setting of the negative results of the primary efficacy analysis, these results can only be viewed as exploratory. There was no pre-specified ordering of the relative importance of any of these subgroups in the analysis plan. The following tables, copied from the application, summarize the results of the analysis of the primary endpoint in these various groups.

Table 13: Applicant's Subgroup Analyses in Study 020

Subgroup	n (%)		Ataluren vs Placebo[a]	
	Placebo	Ataluren	Difference, m	p-value
Baseline 6MWD				
≥350 m	73	73	9.5	0.540
<350 m	41	41	23.6	0.210
Age group				
<9 y	53	57	20.1	0.279
≥9 y	61	57	7.6	0.494
Duration of prior corticosteroid use				
<12 to 6 months	18	19	-17.3	0.903
≥12 months	96	95	21.7	0.159

[a] The table presents observed differences between ataluren and placebo. P-values obtained from analysis of covariance (ANCOVA) with multiple imputation for missing data. The relevant stratification factor-by-treatment interaction term was added to the ANCOVA model for each stratification factor.

Abbreviation: 6MWD = 6-minute walk distance

Subgroup	n (%)		Ataluren vs Placebo[a]	
	Placebo	Ataluren	Difference, m	p-value
Baseline 6MWD				
<300 m	21 (18.4)	24 (21.1)	-1.0	0.749
≥300 to <400 m	52 (45.6)	47 (41.2)	47.2	0.007
≥400 m	41 (36.0)	43 (37.7)	-9.6	0.580

[a] The table presents observed differences between ataluren and placebo. P-values obtained from analysis of covariance (ANCOVA) with multiple imputation for missing data. The relevant stratification factor-by-treatment interaction term was added to the ANCOVA model for each stratification factor.
Abbreviation: 6MWD = 6-minute walk distance

Out of 9 subgroups that were evaluated, only 1, the subjects with a baseline 6MWD of 300-400m, demonstrated a nominally positive result favoring ataluren on the change from baseline in 6MWD. However, the results in the complementary <300m and ≥400m subgroups numerically favored placebo, suggesting that this exploratory result could be a function of chance (or the result of excluding subjects with negative results).

The following table summarizes the results of the TFTs by baseline 6MWD subgroup.

Table 14: Change in Timed Function Tests at Week 48 by Subgroups in Study 020

Endpoint	6MWD <300m		6MWD ≥300 to <400m		6MWD ≥400m	
	Δ	p-value	Δ	p-value	Δ	p-value
Time to walk/run 10 m*	-2.75	0.07	-1.84	0.07	0.21	0.85
Time to climb 4 stairs*	-0.47	0.80	-3.46	0.003	0.17	0.89
Time to descend 4 stairs*	-0.97	0.60	-4.36	<0.001	-0.13	0.92

* *Negative deltas indicate improvement relative to placebo.*
+ *Positive deltas indicate improvement relative to placebo.*
Source: CSR Table 14.2.2.2.8, 14.2.2.3.8, 14.2.2.4.8, 14.2.3.6 & 14.2.3.8

Numerical trends favoring ataluren were observed in the TFTs in the baseline 300-400m 6MWD subgroup with the 4SC and 4SD being nominally positive. However, the 10MWR and 4SC numerically favored placebo in the complementary ≥400m subgroup which is consistent with the results of the primary endpoint analyses.

Most importantly, the scientific understanding of how specific baseline 6MWD cut-offs can be best used to predict decline during a clinical trial in DMD has not been established. Other known and unknown factors also impact progression and there is substantial variability in decline even within the 300-400m subgroup. This subgroup represented 43% of the subjects in Study 020. However, the applicant did not place any unique emphasis on the analysis of this specific subgroup until after the data from Study 020 were unblinded, further weakening the strength of any conclusions that can be made based upon this exploratory analysis.

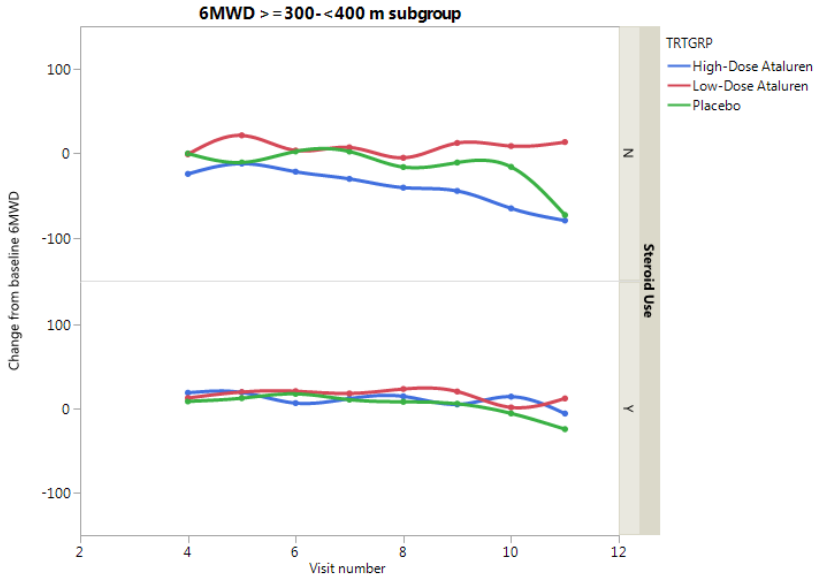
300-400m 6MWD Subgroup from Study 007

The applicant suggests that the nominal results in the exploratory 300-400m 6MWD subgroup in Study 020 have been retrospectively replicated in Study 007 (The LS mean difference of 51m in Study 007 and 47m in Study 020). Fundamentally, this sort of retrospective attempt to validate an exploratory finding from a negative trial with post hoc analyses of unblinded data from an earlier negative trial lacks scientific rigor. In addition, none of the results of the 6MWT or TFTs in Study 007 were nominally

positive in favor of ataluren for the 300-400m 6MWD subgroup in Study 007 for both doses of ataluren when analyzed according to the protocol's analysis plan (as presented earlier).

Critically, these subgroups were also drawn from different populations with respect to age and corticosteroid use, limiting their comparability. As the following figure indicates, any exploratory trends in the 300-400m subgroup in Study 007 were observed in subjects not taking corticosteroids, who are not representative of Study 020 where all subjects were taking corticosteroids. This finding illustrates that this pattern of results could likely be the result of chance.

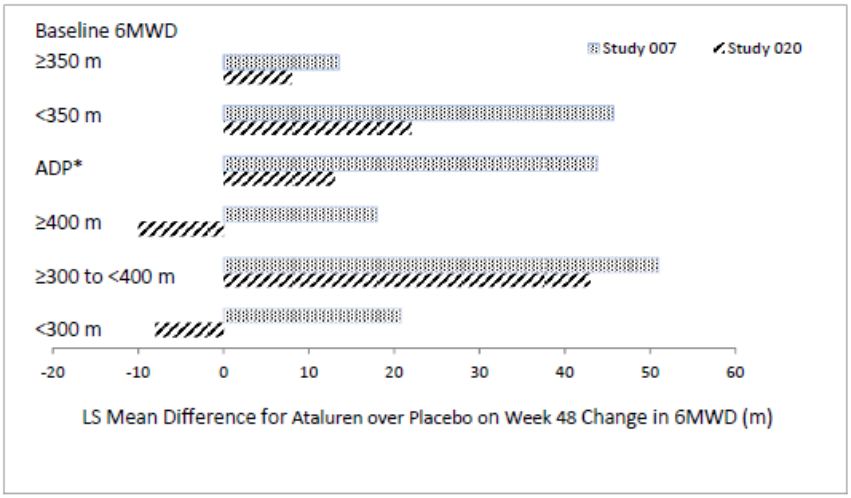
Figure 2: Change from Baseline in 6MWD in Study 007 by CS Use (Yes/No)



Source: FDA Clinical Reviewer

The following figure illustrates that the only apparent consistent effect that was observed between the two trials was in the 300-400m 6MWD group. However, as indicated above, potentially important differences exist between these groups with respect to corticosteroid use and age. In other baseline 6MWD subgroups, the treatment effects were much larger in Study 007, despite the study itself being substantially smaller (for the low-dose versus placebo comparison). Further, a very troublesome observation is that opposite numerical trends were observed in both trials for the complementary 6MWD subgroups <300m and ≥400m. These findings reinforce the possibility that the results in the 300-400m 6MWD subgroup could likely be explained by chance alone.

Figure 3: Comparison of Week 48 Change in 6MWD by Baseline 6MWD Category



** ADP (ambulatory decline phase) included patients who were ≥7 to ≤16 years old and had 6MWD ≥150 meters but ≤80%-predicted at baseline while receiving a stable dose of corticosteroid therapy.*
Positive differences indicate ataluren is better than placebo
Source: FDA reviewer

North Star Ambulatory Assessment (NSAA)

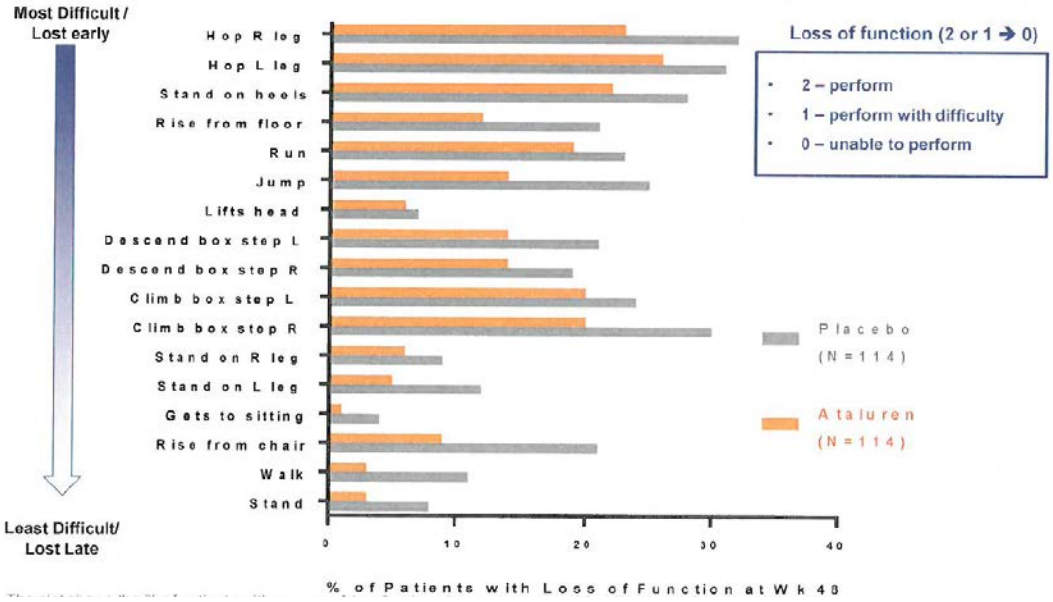
The NSAA consists of 17 items that focus on various aspects of ambulation in DMD (e.g., ability to rise from the floor, ability to transition from lying to sitting or sitting to standing, hopping, etc.). Each item is scored as either a 2 (normal – no obvious modification of activity), 1 (modified method but achieves goal independent of physical assistance from another), or 0 (unable to achieve independently). The NSAA total score ranges from 0-34, with higher scores representing greater abilities.

The NSAA was not evaluated in Study 007 and was included as an exploratory endpoint in Study 020, with no statistical control for Type I error. The protocol planned to explore the NSAA results using both an ordinal total score (0-34) and after transforming the ordinal data to a linear total score ranging from 0 (worst) to 100 (best). The latter approach omits the "lifts head" item based on a Rasch analysis. Neither approach to the analysis of the NSAA in the ITT population was nominally positive (ordinal score nominal p-value=0.13 and linear score nominal p-value=0.27), consistent with the negative results on the primary endpoint analysis and the all but one nominally negative results on the secondary endpoint analyses.

The application also presents nominally positive results of the NSAA in subjects with a baseline 6MWD 300-400m (ordinal score nominal p-value=0.04 and linear score nominal p-value=0.04). However, these results are subject to the same concerns and potential biases for this subgroup that have already been discussed, including the fact that the results of these analyses in the >400m subgroup numerically favored placebo.

The applicant further conducted a post hoc analysis that evaluated subjects who declined from a 2 or 1 to 0 during the course of the trial. The following graphic is copied from the application and was intended by the applicant to demonstrate that more placebo subjects declined from 2 or 1 to 0 in each of the 17 items of the NSAA:

Figure 4: Applicant's Analysis of NSAA Decline from a Category of 2 or 1 to 0



These data are the result of a post hoc analysis of an exploratory endpoint that itself failed to demonstrate even nominal significance in two methods of analysis. Additionally, subjects who decline from a 2 to 1, an equally valid clinical change, were not presented. In that analysis, more subjects on ataluren declined in 10 categories, while more subjects on placebo declined in only 2. This critical result highlights the inherent limitations in the selective presentation of post hoc data.

Meta-Analyses

The only pre-specified meta-analysis that was included in the protocol for Study 020 combined the post hoc ADP population from Study 007 (low-dose only) and the ITT population from Study 020, as indicated in the following table.

Table 15: Applicant's Meta-Analyses of the ADP Population from Study 007 and the ITT Population from Study 020

Endpoint	Study 007		Study 020		Between-Study Δ	Meta-Analysis		
	Mean Δ	SE	Mean Δ	SE	p	Mean Δ	SE	p
Pre-specified (Study 007 ADP subgroup and Study 020 ITT)								
N (ataluren, placebo)	32, 31		114, 114			146, 145		
Change in 6MWD	45.6	18.069	13.0	10.415	0.1174	**21.1**	**9.023**	**0.0193**
Time to 10% worsening in 6MWD[a]	0.42	--	0.75	--	0.1877	**0.66**	--	**0.0232**
Change in time to run/walk 10 m	-2.5	1.359	-1.1	0.680	0.3325	**-1.4**	**0.608**	**0.0251**
Change in time to climb 4 stairs	-2.3	1.521	-1.4	0.754	0.6234	**-1.6**	**0.675**	**0.0184**
Change in time to descend 4 stairs	-2.3	1.667	-2.0	0.787	0.8721	**-2.0**	**0.712**	**0.0044**

Source: Section 2.7.3. Summary of Clinical Efficacy (page 64)

The ADP population from Study 007 was generated based on multiple simultaneous post hoc adjustments to the data to find a subgroup with low nominal p-values. This population was then prospectively tested in a well-designed clinical trial that was clearly negative. It is clearly inappropriate to then take the results of that negative trial and combine them with the post hoc results from another negative trial (Study 007) in order to generate a pooled analysis with nominal p-values.

The application also presents the results of a post hoc meta-analysis that combines the already post hoc cITT population from Study 007 (low-dose only) with the ITT population from Study 020. This situation is analogous to the application for apaziquone that was discussed earlier in this submission. Combining the unblinded data from two negative trials in a post hoc manner to generate nominally positive findings with data in hand should not be capable of overcoming the clearly negative results of the individual trials when analyzed according to their pre-specified analysis plans. In addition, this analysis combines two very different populations from the trials with respect to steroid use (ranging from none to >12 months), age (≥5 versus ≥ 7 years), and baseline 6MWD (≥75m versus ≥150m).

Conclusion

Ultimately, no positive results from any prospectively planned analyses that are persuasive have been provided with this application. The applicant has presented only the results from numerous post hoc and exploratory analyses that are intended to mitigate two negative clinical trials. In 2011, the applicant claimed that the effectiveness of ataluren had been established based on the post hoc analyses of the ADP population in Study 007. However, when this conclusion was prospectively evaluated in Study 020, the results were clearly negative. This finding directly highlights the frequently misleading nature of exploratory analyses of negative trials. It is arguable that some trends observed in the applicant's data may warrant further prospective investigation, which the Agency has consistently encouraged the applicant to consider. Even so, for the reasons discussed above, it seems quite possible that any future study designed based on exploratory analyses of Study 020 will also turn out to be negative, just as Study 020, which was based on exploratory post hoc analyses from Study 007, was negative. The analogous results from the applicant's development of ataluren for the treatment of nmCF offer a similar cautionary tale. Overall, the data intended by the applicant to establish the effectiveness of ataluren for the treatment of nmDMD are not persuasive.

Draft Points to Consider

FOOD AND DRUG ADMINISTRATION (FDA)

Center for Drug Evaluation and Research (CDER)

Peripheral and Central Nervous System Drugs Advisory Committee Meeting

DRAFT POINTS TO CONSIDER

September 28, 2017

Discuss the interpretability and persuasiveness of the exploratory data from the clinical trials intended by the applicant to establish the effectiveness of ataluren for the treatment of dystrophinopathies resulting from nonsense mutations in the dystrophin gene.

Consult Memorandum of Review:
Dystrophin Immunohistochemistry Bioassay

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Office of Biotechnology Products
Division of Biotechnology Review & Research III
Silver Spring, MD 20993

Consult Memorandum of Review

NDA:	200896
Subject:	Review of *in vitro* and *in vivo* dystrophin bioassay methods to specifically assess the interpretability of the "inverted U" shaped (bell-shaped) dose response of PTC124 (Ataluren)
Review/Revision Date:	8/14/2017
Primary Reviewer:	Baikuntha Aryal, Ph.D.
Secondary Reviewer:	Ashutosh Rao, Ph.D.
RPM:	Fannie Choy
Applicant:	PTC Therapeutics Inc.
Product:	Translarna™ (Ataluren)
Indication:	Treatment of Duchenne muscular dystrophy resulting from a nonsense mutation in dystrophin gene
Clinical Division:	CDER/ODEI/DNP

Executive summary

Overall, the Sponsor did not provide sufficient bioassay validation information to reliably interpret the inverted U-shaped dose response for dystrophin production. While the *in vitro* data suggests an inverted U-shaped dose response with PTC124 treatment, this is not supported by the *in vivo* data in study 004. There did not appear to be a correlation in dystrophin expression between *in vivo* data and *in vitro* data generated from the same set of patient-derived myotubes cultures. No method validation or method development information is provided to explain the discrepancy. Possible reasons for the differences between cultured myotubes and in vivo data could be due to the proinflammatory neuromuscular tissue environment in tissue versus the homogeneous and nutrient rich culture of myotubes. Therefore, it may not be relevant to rely solely on the *in vitro* data to determine dose response. The Sponsor did not confirm immunohistochemistry (IHC) results of dystrophin production with western blot. The restored dystrophin gene expression was also not verified using Q-PCR. The current IHC method appears to have several methodological issues with the samples processing, staining and dystrophin quantification as detailed in this memo, which could also explain differences in the cultured myotubes and *in vivo* data. Study 007 was designed for relatively longer exposure of atalurin (48 weeks) using a larger patient population but the immunofluorescence data were uninterpretable due to problems with sample quality and freezing related artifacts in a significant number of samples.

Background

Ataluren (PTC124) is a small molecule that promotes ribosomal readthrough of nonsense mutation. Ataluren is formulated for oral administration. In this NDA application, the Sponsor proposed to use ataluren for the treatment of nonsense mutation Duchenne muscular dystrophy (nmDMD) patients resulting from a nonsense mutation in the dystrophin gene. In this application, the Sponsor (PTC Therapeutics Inc.) claims that ataluren has an "inverted U" shaped dose response for the expression of dystrophin. Division of Neurology Products (DNP) requested a consult to the Office of Biotechnology Products (OBP) to assess if methodological differences can address the "inverted U" shaped ataluren dose response to dystrophin expression. In this review memo, we cover the bioassay methodological information in support of the *in vitro* and *in vivo* dystrophin expression data from study PTC124-GD-004-DMD and study PTC124-GD-007-DMD. Very limited method validation or bioassay development information was submitted as part of the NDA. This review memo covers both approaches taken by PTC in study 004 to measure dystrophin by using either cultured nmDMD patient-derived myotubes (*in vitro*) or in patient tissue samples (*in vivo*). It also covers technical issues with the *in vivo* dystrophin measurement in patient tissue samples from study 007.

Assessment of *in vitro* data generated in study PTC124-GD-004-DMD from cultured nmDMD patient-derived myotubes PTC124-10027

The Sponsor determined the effect of PTC124 on dystrophin expression in primary myotubes derived from biopsies of the extensor digitorum brevis (EDB) muscles from nmDMD patients from clinical study PTC124-GD-004-DMD. One set of muscle biopsies of the EDB from participating patients prior to exposure to PTC124 were collected for the *in vitro* study. Myotubes were allowed to differentiation for 3 days before PTC124 treatment. Cells were treated with different concentrations of PTC124 for 9 days with a change of differentiation medium and PTC124 every 3 days. Two sets of concentrations were used; 0, 0.5, 1, 2.5, 5, 10 and 20 µg/mL for the first experiment and 0, 7.5, 10, 15, 20, 30 and 40 µg/mL in the second experiment. After the treatment, myotubes were fixed and permeabilized for immunofluorescence staining. Monoclonal anti-dystrophin antibody (DYS2 from Biogenix), and polyclonal anti-spectrin antibody (ab11182 from Abcam) were used as primary antibodies. Alexa Fluor 488 goat anti-mouse IgG1 and Alexa Fluor 568 goat anti-rabbit IgG1 were used as secondary antibodies. For each patient's cultures, the Sponsor used same confocal parameters across all doses; however, between patient's cultures, different PMT gain settings were used while keeping all other parameters the same. The Sponsor states that since each patient was imaged at different PMT gain settings, all patient data were then calibrated to the same gain based on a "PMT gain calibration curve" before they were grouped for statistical analysis; however, no justification or details on the PMT calibration curve are provided.

The Sponsor provided the following dose-response relationship curve for the mean change in dystrophin expression.

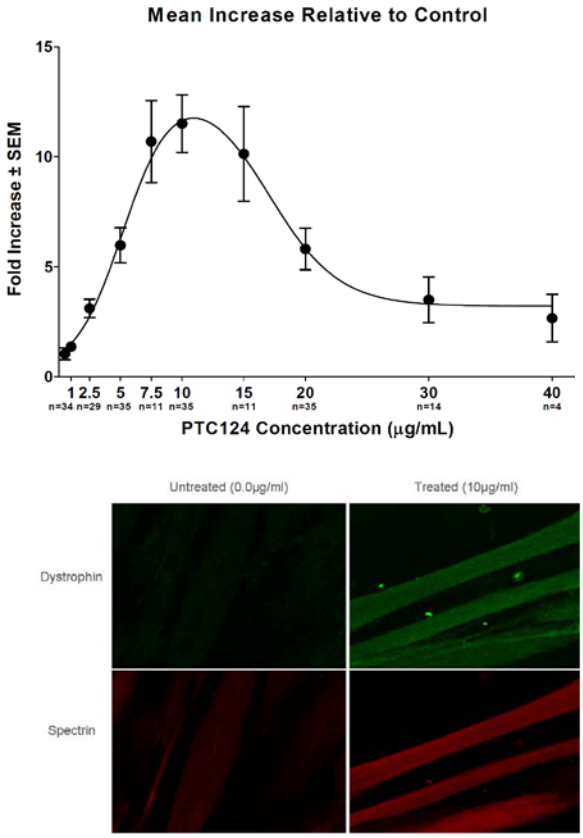


Figure 22. PTC124 produces full-length dystrophin in cultured myotubes from DMD patient 002-004. Dystrophin expression in primary cell cultures from muscle treated with PTC124. Primary myoblasts were treated with varying concentrations of PTC124. After 9 days of treatment, dystrophin expression was evaluated by the quantification of immunofluorescence profiles of PTC124-treated and untreated myotubes. Graphical representation of immunofluorescence profiles. Images below graph correspond to untreated myotubes and myotubes treated with 10 µg/mL PTC124.

***Reviewer's comments**: The immunofluorescence data provided by the Sponsor suggests an inverted U-shaped dose response with PTC124. Immunofluorescence has been widely used to assess level of protein expression in cells and tissue; however, it is considered a semi-quantitative and is subject to variability in sensitivity, specificity, and staining related artifacts. In the absence of a standardized procedure, the method can have high inter- and intra-analyst variability. As observed in the representative immunofluorescence images, spectrin staining shows variability between untreated and treated samples (figure 22 above provided by the Sponsor). This may suggest that the assay has not been appropriately optimized or validated because spectrin, the counter-stain used to normalize dystrophin, itself shows high variability. The Sponsor also collected images of each patient sample at different PMT gain settings but calculated to the same gain based on the PMT gain calibration curve. The Sponsor didn't provide details of their calculation to the same PMT gain or a scientific justification why the adjustment of data to a same PMT gain has no impact in the overall results. The appropriateness of recalibrating for different PMT gains is not clear because using different PMT gains between patient samples not only changes the signal but also the noise in each image, and recalibration would require systematic and standardized compensation for two opposing attributes (signal/noise) if all images were recalibrated after acquisition. Such re-calibration of images*

after acquisition is not a standard practice in well-controlled and standardized immunohistochemistry assays.

Overall, based on the deficiencies in image acquisition, analyses and the lack of a consistent and validated procedure, there may be inconsistencies in the signal to noise ratio across the samples that obscure a reliable interpretation of the quantitative immunohistochemistry data.

Assessment of *in vivo* data for Dystrophin expression in nmDMD patients-PTC124-GD-004 DMD

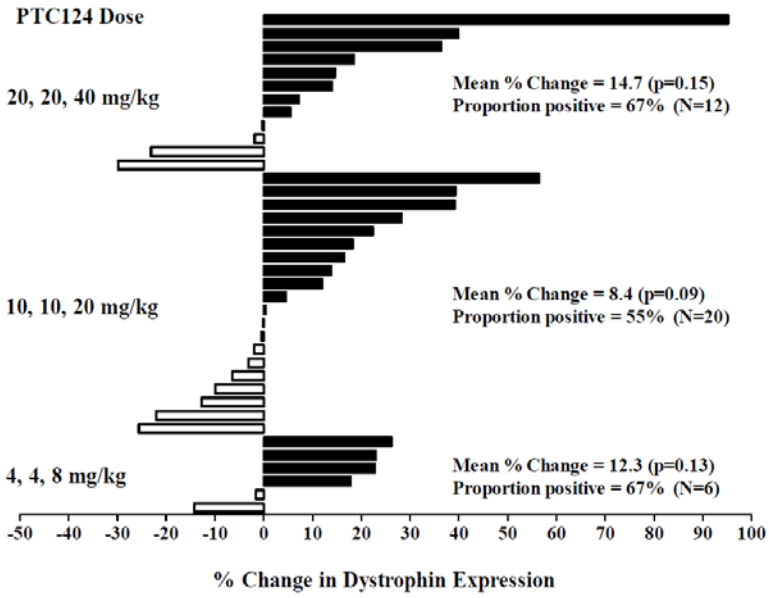
A total of 38 patients were enrolled in study PTC124-GD-004 DMD. The study was not blinded. All DMD patients were male with some variability in race in each treatment group. Patients were assigned to three dosing group: 4/4/8 mg/kg group (4mg/kg in the morning, 4 mg/kg at midday, and 8 mg/kg in the evening for a total daily dose of 16 mg/kg), 10/10/20 mg/kg group, and 20/20/40 mg/kg group. Each patient received 28 days of oral treatment with PTC124 at one of the three doses level. According to the Sponsor, all patients completed the single 56-day cycle therapy (28 days of treatment with PTC124, followed by 28 days follow-up). The EDB muscle biopsy was taken from one foot during the screening period and biopsy from other foot was taken on day 28 of treatment to assess the dystrophin expression after PTC124 therapy. The Sponsor used immunofluorescence to analyze dystrophin expression but it was not confirmed by a more quantitative method such as western blot. The Sponsor did not provide details of their immunofluorescence method validation approach. The Sponsor also did not confirm underlying mechanism of action by providing Q-PCR data on the mRNA levels of restored dystrophin. Additionally, there were different mutations per treatment group that could respond differently, have different levels of basal revertant dystrophin, and be differentially amenable to probing with the same antibody for IHC analysis. Specifically, certain mutations prevent reliable staining with antibodies generated against an antigenic epitope that contained the mutant site. Given these caveats, it does not appear that the sponsor carried out a comprehensive method optimization and validation prior to their study to address these technical aspects.

For *in vivo* immunostaining, the Sponsor used the same antibodies that were used for *in vitro* immunostaining. According to the Sponsor, four or five fields per patient samples were randomly selected for fluorescence imaging. Single confocal images were captured instead of a stack or epifluorescence images to quantify dystrophin. This may have limited the sponsor's ability to capture a realistic level of dystrophin expression because a single slice of a confocal image does not always represent the entire 3-dimensional fiber's dystrophin expression. Hence, quantitation can vary significantly between images depending on where the confocal image was "sliced".

The regions of interest (ROI) in the spectrin image were selected using an intensity threshold chosen by the user. There are no details in the NDA description that suggest that efforts were made to automate or standardize this approach or to reduce the potential for bias. The dystrophin intensity was evaluated only at the spectrin-positive regions but no quantitative

threshold was provided. The intensity of dystrophin in the spectrin positive area was scored to an arbitrary scale from 0 to 4096. The sponsor states that the presumed mechanism of action of PTC124 would be expected to result in a general increase in dystrophin expression but not an increase in the number of dystrophin-positive revertant fibers. The Sponsor excluded revertant fibers from the analysis assuming that all revertant fibers have dystrophin signal intensity > 30% of the maximum intensity.

The Sponsor reported an increase of 11.0% in dystrophin expression after treatment. The percent change in dystrophin expression for each patient after 28 days of treatment with PTC124 by dose group is given in the following figure provided by the Sponsor. Among 38 patients, 23 (61%) showed positive change in dystrophin expression and 15 (39%) showed negative change in dystrophin expression after 28 days of treatment. Analysis of mean percent change in dystrophin expression in each treatment groups was 12.3% for 4/4/8 mg/kg group (n=6), 8.4% for 10/10/20 mg/kg group (n=20) and 14.7% for 20/20/40 mg/kg group (n=12). The Sponsor did not calculate outlier but analysis of % change in dystrophin expression using GraphPad Prism's Grubbs test indicates one outlier (subject 001-016, % dystrophin expression 95.14) with a z value of 2.411 within the 20/20/40 mg/kg treatment group that may be driving the mean % change data.



Reviewer's comment

The Sponsor used variable number of patients in each treatment group and there is high variability in the dystrophin expression (-29.85% to +95.14 %) with 39% of patients showing a negative dystrophin expression. Although there is no significant difference in the mean % change in dystrophin expression in the treatment groups overall, in vivo data indicates a steady or U-shaped dose response trend (12.3% for 4/4/8 mg/kg group, 8.4% for 10/10/20 mg/kg group, and 14.7% for 20/20/40 mg/kg group) instead of inverted U-shaped dose response

reported in the in vitro study using the same set of nmDMD patient-derived myotube cultures. There does not appear to be an obvious correlation between the in vivo and in vitro data for dystrophin expression. The Sponsor did not provide details of their immunofluorescence method validation approach and, similar to the in vitro method described earlier, there are several technical issues with the staining and quantitation that obscure reliable interpretation. Some of these issues are highlighted below.

i. *The EDB muscle biopsy was taken from one foot during the screening period and biopsy from other foot was taken on day 28 of treatment with PTC124 to assess the dystrophin expression after PTC124 therapy. Expression of revertant fibers can be muscle specific (Pigozzo et al PLoS ONE 2013, 8(8): e72147); therefore, the Sponsor may have to verify the consistency of trace dystrophin expression and revertant fibers in EDB muscle from either feet. This may be particularly important when the Sponsor is looking for small changes in dystrophin expression after the treatment.*
ii. *The in vivo immunofluorescence results are based on the randomly selected 4-5 fields in each tissue section. No standardized or automated steps were incorporated that may provide confidence in the objectivity of the data. Additionally, ROI and threshold intensity were determined by user which may introduce some bias in the overall results.*
iii. *The Sponsor excluded revertant fibers from the analysis assuming that all revertant fibers have dystrophin signal intensity > 30% of the maximum intensity. Exclusion of revertant fibers with dystrophin intensity > 30% of maximum intensity may bias the overall results because DMD patients may contain dystrophin in high intensity in revertant fibers and traces of dystrophion with low intensity (Arechavala-Gomeza et al, Neuromuscul Disord. 2010 May;20(5):295-301). With this cutoff any fibers expressing high dystrophin with intensity >30 of maximum intensity after the treatment will also be excluded from the calculation. Current literature suggests that trace dystrophin or revertant fiber dystrophin are not expected to change over time (Arechavala-Gomeza et al, Neuromuscul Disord. 2010 May; 20(5):295-301). However, there is no data or literature to support a 30% threshold. It is also not possible to visually distinguish a dystrophin-positive fiber derived from a revertant fiber versus a drug-induced dystrophin*-positive non-revertant fiber.
iv. *The reported negative change in dystrophin expression in 15 of 38 patients (39%) may indicate the assay variability, improper selection of threshold intensity value (based on 30% revertant), or staining artifacts. In the absence of a systematic approach to method validation, it is not possible to attribute this finding to a true biological responses versus methodological issue.*
v. *The study was not blinded*.
vi. *The Sponsor did not confirm the dystrophin levels with western blotting or verify the underlying mRNA expression using RT-PCR.*

Assessment of *in vivo* data for Dystrophin expression in nmDMD patients-PTC124-GD-007 DMD

Study 007 was a Phase 2b, international, multicenter, randomized, double-blind, placebo-controlled dose-ranging study to evaluate the efficacy and safety of ataluren. The study was conducted in 11 countries using 37 different sites. The study was designed for a 6-week screening period, a 48-week blinded study drug treatment period, and a 6-week posttreatment follow-up period. Patients were assigned to two dosing group: 10/10/20 mg/kg group (N = 57) and 20/20/40 mg/kg group (N = 60), and a Placebo control group (N = 57).

Biopsy from biceps brachii from one arm at baseline (pre-treatment) and biopsy from other arm at week 36±14 days (post-treatment) were taken to assess the effect of ataluren in dystrophin production. The Sponsor chose biceps brachii because it was not expected to affect the patients' performance in 6MWT. Sample tissue of approximately 5 mm^3 was removed from patients' biceps.

The biopsy was flash-frozen in isopentane surrounded by liquid nitrogen. The frozen sample was wrapped in pre-cooled foil, labeled, transferred to a 4-oz sterile container, and stored at –70°C until shipment to a regional Covance Laboratory site for long-term storage. The samples were shipped from Covance laboratory to Dr. Moor's laboratory at the University of Iowa for sectioning, staining and analysis. Samples were cut into 10 µm cryosections for H&E staining and dual-label immunostaining. H&E staining was used to examine the fiber orientation, presence of freezing artifacts, and severity of dystrophic pathology.

The primary antibodies for spectrin (mouse monoclonal NCL-SPEC1, Leica) and dystrophin (rabbit polyclonal ab15277, Abcam) were used for immunostaining. Images were acquired on a Zeiss 710 confocal microscope. All images were photographed under the same laser intensity, aperture, and photomultiplier tube sensitivity setting. Dystrophin intensity was measured with and without inclusion of the signals from presumed revertant fibers. For analysis, revertant fibers were defined as those having dystrophin intensity greater than 30% of maximum intensity. The regions of interest (ROI) in the spectrin image were selected using an intensity threshold chosen by the user. The dystrophin intensity was evaluated only at the spectrin-positive regions. The intensity of dystrophin in the spectrin-positive area was scored to an arbitrary scale from 0 to 4096.

According to the Sponsor, the dystrophin measurements in study 007 were uninterpretable to provide reliable conclusion about the dystrophin production. The main technical challenge associated with study 007 was processing a large number of muscle samples associated with a multi-national clinical trial for immunostaining to assess dystrophin. According to report from Dr. Steven Moor at the University of Iowa, there were only 21.6% samples (74/342) without freezing artifacts but 36% (123/342) samples had mild to moderate freezing artifact and 42.4% (145/342) samples had severe freezing artifacts.

Reviewer's comment*: There were some differences between study 004 and study 007 for the assessment of dystrophin expression using immunofluorescence such as selection of biopsy*

muscle sub-type, patient population, treatment periods, dystrophin and co-staining antibodies used in immunostaining, and PMT gain setting to collect data. Overall, study 007 appears to be relatively better designed for the assessment of dystrophin compared to study 004 because;

i. *Study 007 was blinded but study 004 was not*
ii. *All images in study 007 were photographed under the same laser intensity, aperture, and photomultiplier tube sensitivity setting but different photomultiplier tube gain settings were used for each patient samples in study 004.*
iii. *The treatment period for study 007 was relatively longer (48 weeks) than the study 004 (4 weeks). A 48 week treatment may be better than a 4 week treatment for the assessment of dystrophin expression (Mendell et. al., Annals of Neurology 2013, 74 (5), 637-647).*
iv. *Study 007 includes relatively larger patient population from 11 different countries compared to study 004*

Despite slight improvement in the overall study design for the assessment of dystrophin expression in study 007, no reliable conclusion can be drawn for dystrophin production from the immunofluorescence data because of freezing-related artifacts in significant number of samples. Additional problems with biopsy such as poor orientation, lack of muscle fibers in some of the biopsy samples, and proteolysis of biopsy samples were also reported in study 007. Therefore, as acknowledged by the sponsor, immunofluorescence data from study 007 would not be recommended to reliably interpret a dose response by ataluren.

Statistical Review

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	200,896
Drug Name:	Ataluren (PTC124)
Indication(s):	Nonsense-mutation-mediated Duchenne muscular dystrophy (nmDMD)
Applicant:	PTC Therapeutics, Inc.
Date(s):	Submission date: 2/24/17
	PDUFA Date: 10/24/17
Review Priority:	Standard Review
Biometrics Division:	Division of Biometrics I
Statistical Reviewer:	Xiang Ling, Ph.D.
Concurring Reviewers:	Kun Jin, Ph.D., Team Leader
	Jim Hung, Ph.D., Director
Medical Division:	Division of Neuropharm
Clinical Team:	Veneeta Tandon, Ph.D.
	Nicholas Kozauer, M.D., Team Leader
Project Manager:	Fannie Choy, R.Ph

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1 EXECUTIVE SUMMARY

Both pivotal studies failed to conclude that ataluren has a treatment effect on the primary endpoint, change in 6MWD at Week 48. For Study 007, the primary endpoint failed to achieve statistical significance. The p-value based on the pre-specified primary analysis was 0.15 for the low-dose ataluren (adjusted p-value = 0.30 based on pre-specified Holm's procedure). The estimated difference in least-squares (LS) mean change in 6MWD at Week 48 was 26 meters. The permutation test, a pre-specified sensitivity analysis to incorporate the distinct feature of dynamic randomization, yielded a nominal p-value of 0.08 (adjusted p-value = 0.15 based on Dunnett's test). The permutation test does not rely on normality assumption and therefore does not require rank transformation. All analyses of secondary endpoints for physical functions failed to achieve nominal statistical significance, although most showed a numerical trend in favor of the low-dose ataluren. The high-dose ataluren had little effect on the primary endpoint and the secondary endpoints.

Study 020 was enriched to enroll patients in ambulatory decline phase, based upon the results of a post-hoc subset in Study 007, and was twice the size of Study 007. However, the primary endpoint also failed in Study 020; the observed treatment effect of 13 meters on 6MWD was not statistically significant (p-value = 0.21). Secondary endpoints for physical functions showed a numerical trend in favor of ataluren, and one of them (time to descend 4 steps) reached nominal statistical significance (nominal p-value = 0.01). The exploratory endpoint of NSAA total score showed a non-significant treatment effect of 0.8 in favor of ataluren (nominal p-value = 0.13). A post-hoc analysis examining the shift of score for each NSAA item from "1" or "2" (able to perform function) to "0" (unable to perform function) suggested that fewer patients in the ataluren arm lost the ability to perform NSAA functions. A post-hoc subgroup of baseline 6MWD ≥300 to <400 meters, showed nominal statistical significance on the primary endpoint of change in 6MWD and most of the secondary endpoints of function tests.

A similar treatment effect in the patients with baseline 6MWD ≥300 to <400 meters range was observed in Study 007. The LS mean differences in the subgroup of baseline 6MWD ≥300 to <400 meters were 51 meters in Study 007 and 47 meters in Study 020. Within the baseline 6MWD ≥300 to <400-meter range, none of the ataluren patients lost ambulation in either study, while 4 placebo patients in Study 020 and 2 in Study 007 lost ambulation. Based on these results in the subgroup of baseline 6MWD ≥300 to <400 meters, there appeared to be a possible signal of treatment effect of ataluren at the dose regimen of 10/10/20 mg/kg on 6MWD and most of the secondary endpoints. However, these results were very difficult to interpret based on the observations below.

- For Study 007, the nominal p-value of the low dose was in the range of 0.04 to 0.15 without multiplicity adjustment. The high dose did not even have a numerical trend in favor of ataluren.

- The treatment effect on 6MWD was inconsistent, 44 meters in Study 007 versus 13 meters in Study 020, in ambulatory decline phase patients. Of the five subgroups based on baseline 6MWD category, the ≥300 to <400-meter subgroup was the only one giving a numerically consistent ataluren effect on 6MWD in the two studies. In all other baseline 6MWD subgroups, the treatment effect was seen much larger in Study 007 than in Study 020. See Figure 6.
- Multiplicity adjustment was not pre-specified for testing the ≥300 to <400-meter subgroup. This subgroup was the only one of the 9 pre-specified subgroups reaching nominal significance for the treatment difference in the change from baseline to Week 48 in 6MWD.
- Opposite trends were observed in the complementary subgroup of patients (i.e., baseline 6MWD <300 or ≥400 meters) in Study 020, suggesting that the treatment effect observed in the baseline ≥300 to <400 meters group might have resulted from excluding subsets of patients with negative results.

In summary, there appeared to be numerical trends in favor of ataluren in the ITT population and nominally significant treatment effects on 6MWD in the ≥300 to <400-meter subgroup of both studies. However, the suggestion of the treatment effect in this subgroup was not a confirmation of an ataluren treatment effect on 6MWD. Whether this could be sufficient evidence to support approval of ataluren for the treatment of nonsense-mutation-mediated Duchenne Muscular Dystrophy is up for discussion.

2 INTRODUCTION

2.1 Overview

The submission included two pivotal studies (Table 1). Study 007, a Phase 2b, randomized, double-blind, placebo controlled, dose-ranging study, was conducted in patients with nonsense-mutation-mediated Duchenne Muscular Dystrophy (nmDMD), ≥5 years of age and baseline 6-Minute Walk Distance (6MWD) ≥75 meters. A stable regimen of concomitant corticosteroid therapy was allowed but not required. A total of 174 patients were randomized 1:1:1 to receive placebo, ataluren 10/10/20 mg/kg, or ataluren 20/20/40 mg/kg for 48 weeks. The primary endpoint was change in 6MWD at Week 48.

Study 020, a Phase 3, randomized, double-blind, placebo-controlled study, was enriched based on Study 007 results to enroll patients with nmDMD ≥7 to <16 years of age and baseline 6MWD ≥150 meters to <80%-predicted. A stable regimen of concomitant corticosteroid therapy was required. A total of 230 patients were randomized 1:1 to receive placebo or ataluren 10/10/20 mg/kg for 48 weeks. The primary endpoint was change in 6MWD at Week 48.

Table 1: **Summary of Studies**

Study	Study Design	Population	Ataluren Dosage	Number of Subjects
Study 007	Double-blind, randomized, Placebo-controlled, parallel- group	Boys with nmDMD aged 5-20 years and baseline 6MWD ≥ 75 meters	10/10/20 mg/kg 20/20/40 mg/kg	174 from 37 sites in North America, Europe, Israel, Australia
Study 020	Double-blind, randomized, placebo-controlled, parallel- group	Boys with nmDMD aged 7-16 years and baseline 6MWD ≥ 150 meters to <80%-predicted	10/10/20 mg/kg	230 from 54 sites in North America, South America, Europe, Israel, Asia, Australia

nmDMD: nonsense-mutation-mediated Duchenne muscular dystrophy

2.2 Data Sources

Materials reviewed for this application include the clinical study reports, summary of clinical efficacy, raw and derived datasets, SAS codes used to generate the derived datasets and tables, protocols, statistical analysis plans, which are located in the following directories.

Clinical study reports
\\cdsesub1\evsprod\NDA200896\0014\m5\53-clin-stud-rep\535-rep-effic-safety-stud\nonsense-mutation-dystrophinopathy\5351-stud-rep-contr
\\cdsesub1\evsprod\NDA200896\0010\m5\53-clin-stud-rep\535-rep-effic-safety-stud\nonsense-mutation-dystrophinopathy\5351-stud-rep-contr\ptc124-gd-007-dmd
Study 007 data
\\CDSESUB1\evsprod\NDA200896\0002\m5\datasets\ptc124-gd-007-dmd
\\CDSESUB1\evsprod\NDA200896\0025\m5\datasets\ptc124-gd-007-dmd\analysis\adam
Study 020 data
\\CDSESUB1\evsprod\NDA200896\0014\m5\datasets\ptc124-gd-020-dmd
Study 020 SAS program
\\CDSESUB1\evsprod\NDA200896\0022\m5\datasets\ptc124-gd-020-dmd\analysis\adam\programs
Module 2.7.3 summary of clinical efficacy
\\CDSESUB1\evsprod\NDA200896\0018\m2
Additional-efficacy-analysis-outputs
\\CDSESUB1\evsprod\NDA200896\0018\m5\53-clin-stud-rep\535-rep-effic-safety-stud\nonsense-mutation-dystrophinopathy\5353-rep-analys-data-more-one-stud\ise
Responses to FDA information requests
\\CDSESUB1\evsprod\NDA200896\0022
\\CDSESUB1\evsprod\NDA200896\0034
\\CDSESUB1\evsprod\NDA200896\0036

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3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

This reviewer was able to trace how the primary endpoint was derived and reproduce the key analysis results.

Numerous post-hoc analyses were performed for Study 007 and Study 020. In addition to the original Clinical Study Reports (CSR), an updated CSR for Study 007 was submitted and post-hoc analyses for Study 020 were included in Module 2.7.3 Summary of Clinical Efficacy and Module 5.3.5.3 Integrated Summary of Efficacy. The study reports did not always clearly indicate whether and how the presented analyses deviated from the protocol-specified analyses, posing a challenge for the statistical review.

3.2 Evaluation of Efficacy

3.2.1 Study 007

3.2.1.1 Study Design and Endpoints

Study 007 was conducted at 37 sites in the US, Canada, Israel, Australia, and Europe. The first patient was enrolled on 2/28/08, and the last patient visit was on 12/17/09. The study protocol had four amendments, with major changes in the final Amendment 3.0 dated 3/4/09. The major changes included: (1) baseline 6MWD stratification was updated from "<270 meters and ≥270 meters" to "<350 meters and ≥350 meters"; and (2) baseline 6MWD was to be included as a continuous variable in the primary analysis, instead of a categorical variable for stratification of 6MWD. Those changes were discussed with the Division of Neurology at a meeting on 8/13/2008. The statistical analysis plan (SAP) was finalized on 1/14/10 and the database lock was on 2/5/2010.

Two CSRs were submitted for Study 007. The original version (CSR1) was dated 1/14/10. The updated version (CSR2) was released on 2/26/11 and subsequently revised on 8/31/2012 and 11/14 2014. The report was revised to include efficacy results in subgroups and change the baseline values of 6MWD for 2 patients.

Study Design

Study 007 was a Phase 2b, randomized, double-blind, placebo-controlled study in ambulatory males ≥5 years old with nmDMD. Eligible patients were randomized 1:1:1 to orally receive placebo, ataluren 10/10/20 mg/kg, or ataluren 20/20/40 mg/kg three times daily for 48 weeks. If a subject had a sibling who was previously randomized into the study, the subject was assigned to the same treatment arm as the first randomized sibling. Dynamic randomization was utilized with three stratification factors: age (<9 years or ≥9 years), corticosteroid (CST) use (yes or no), and baseline 6MWD (<350 meters or ≥350 meters).

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Evaluations of 6MWD were performed twice during the pre-treatment period (i.e., at screening and at baseline) and every 6 weeks during the treatment period. A 6-Minute Walk Test (6MWT) was considered valid if the subject completed the test as intended or discontinues the test solely due to exhaustion. A subject may rest against the wall during a valid test. A test was to be considered invalid if the subject:

- failed to follow instructions;
- did not remain on the course for the duration of the test;
- moved in a reverse direction for any part of the test; or
- discontinued the test prior to 6 minutes due to noncompliance or reasons other than exhaustion (e.g., injury due to fall, sitting down).

The sites had been instructed that if the subject did not have a valid test on the initial attempt or was too exhausted to complete the initial test, repeat testing was to be attempted to obtain a valid test for each clinic visit. Subjects who became unable to perform a valid 6MWT due to loss of ambulation were to be assigned a 6MWD of zero from the visit at which the subject was no longer able to perform the test. For ambulatory subjects who did not perform a valid test, the 6MWD was to be entered as missing.

Efficacy Endpoints

The primary endpoint was change from baseline to Week 48 in 6MWD.

Over 50 secondary endpoints were listed, including timed function tests (standing from supine position, walking/running 10 meters, and climbing/descending 4 stairs). The protocol did not identify key secondary endpoints.

3.2.1.2 Statistical Methodologies

The efficacy analysis set was the Intent-to-Treat (ITT) population, consisting of all randomized patients who had a valid 6MWT from the baseline visit and from at least 1 post-baseline visit. All siblings were included in the ITT population.

The protocol specified that the primary analysis was based on a mixed-model repeated-measures (MMRM) model with treatment, visit, treatment-by-visit interaction, baseline 6MWD as a covariate, and the stratification factors of age group and corticosteroids use at baseline. Data from the best valid 6MWT at each scheduled visit were used. The covariance matrix for the MMRM analysis was selected from compound symmetry, autoregressive, or unstructured, whichever provided the smallest Akaike Information Criterion value. Shapiro-Wilks test was performed to test normality and, if necessary, transformed data (log- or rank-based) would be analyzed. If a rank transformation was required, all observations were to be ranked together.

If original or log-transformed 6MWD data were analyzed, Dunnett's method was to be used to adjust for the comparisons of the two dose groups against the placebo arm. If rank-transformed

data were analyzed, Holm's procedure was to be applied to control for multiplicity. The analyses of the secondary endpoints were not under control for multiplicity.

To check the effect of missing values on the robustness of the primary analysis, the primary analysis was repeated using a multiple imputation (MI) method for missing 6MWDs. An analysis of covariance (ANCOVA) with the last observation carried forward (LOCF), which used the last available post-randomization value, was to be performed.

Sensitivity of the primary results to dynamic randomization was evaluated using permutation test that re-sequenced subject treatment assignment. Permutation testing was to be performed, employing the final model that was used in the primary analysis on 10,000 permuted data sets.

To check the effect of allocation of siblings to the same treatment group on the primary analysis, a sensitivity analysis was performed. All subpopulations derived by selecting 1 sibling from each of the sibling pairs (a total of 64 subpopulations were derived as there were 6 sibling pairs in Study 007) were analyzed using the same methods as used for the primary analysis. The average of the resulting model parameters was used in the hypothesis testing.

As a further analysis of the primary outcome variable, the proportions of subjects with a ≥10% improvement in 6MWD at Week 48 (responders) and with a ≥10% worsening in 6MWD at Week 48 (progressors) were assessed. Cochran-Mantel-Haenszel Chi-square tests were to be used to compare the proportions of responders and the proportions of progressors between the treatment arms.

Blinded interim analyses were conducted for sample size re-estimation and safety monitoring. The Independent Data Monitoring Committee (DMC) recommended no changes to the study. One interim efficacy analysis was planned but not carried out per the DMC recommendation because there was not an agreement with the FDA on the analysis plan at that time.

3.2.1.3 Patient Disposition, Demographic and Baseline Characteristics

A total of 174 patients were randomized to the 3 treatment groups. Patients were enrolled at 37 study sites in 11 countries. About half of the patients were enrolled in the United States. One patient in the ataluren 20/20/40 mg/kg group discontinued at approximately Week 6 due to protocol noncompliance. All 174 patients were included in the ITT population.

Patients were all male, predominantly Caucasian (90%), ranging in age from 5 to 20 years with a median age of 8 years. About 70% of the patients were on corticosteroid. There were 4 sibling-pairs in the placebo group and 1 in each ataluren group. Of note, a change of the baseline 6MWD stratification from a cutoff of 270 to 350 meters was made after 42 subjects had been enrolled. Of these 42 patients, 13 had baseline 6MWD values ≥270 meters and <350 meters, including 4 in the placebo, 4 in the low-dose group, and 5 in the high-dose group. The treatment groups appeared to be balanced at baseline (Table 2).

Table 2: Study 007: Demographic and Baseline Disease Characteristics

	Placebo N=57	Low Dose N=57	High Dose N=60
Age, years			
Mean (SD)	8.3 (2.3)	8.8 (2.9)	8.4 (2.5)
Median	8.0	8.0	8.0
Range	5-15	5-20	5-16
Age group, n (%)			
<9 y	32 (56)	32 (56)	34 (57)
≥9 y	25 (44)	25 (44)	26 (43)
Race, n (%)			
Caucasian	54 (94.7)	53 (93.0)	50 (83.3)
Black	0 (0.0)	1 (1.8)	1 (1.7)
Asian	1 (1.8)	1 (1.8)	4 (6.7)
Hispanic	1 (1.8)	1 (1.8)	2 (3.3)
Other	1 (1.8)	1 (1.8)	3 (5.0)
Body weight, kg			
Mean (SD)	28.6 (9.1)	31.2 (12.1)	31.9 (12.8)
Median	25.6	27.0	27.6
Range	16-55	16-76	17-84
6MWD, m			
Mean (SD)	359.6 (87.7)	350.0 (97.6)	358.2 (104.0)
Range	159-533	75-525	90-554
6MWD, n (%)			
≥350 m	34 (60)	32 (56)	33 (55)
<350 m	23 (40)	25 (44)	27 (45)
Corticosteroid use, n (%)			
Yes	40 (70)	41 (72)	43 (72)
No	17 (30)	16 (28)	17 (28)
Age at diagnosis, years			
Mean (SD)	3.9 (2.3)	3.3 (1.8)	3.8 (2.0)
Range	0-10	0-9	0-8

Source: CSR2 table 11, 12, & 13

3.2.1.4 Results and Conclusions

Analyses of the Primary Endpoint

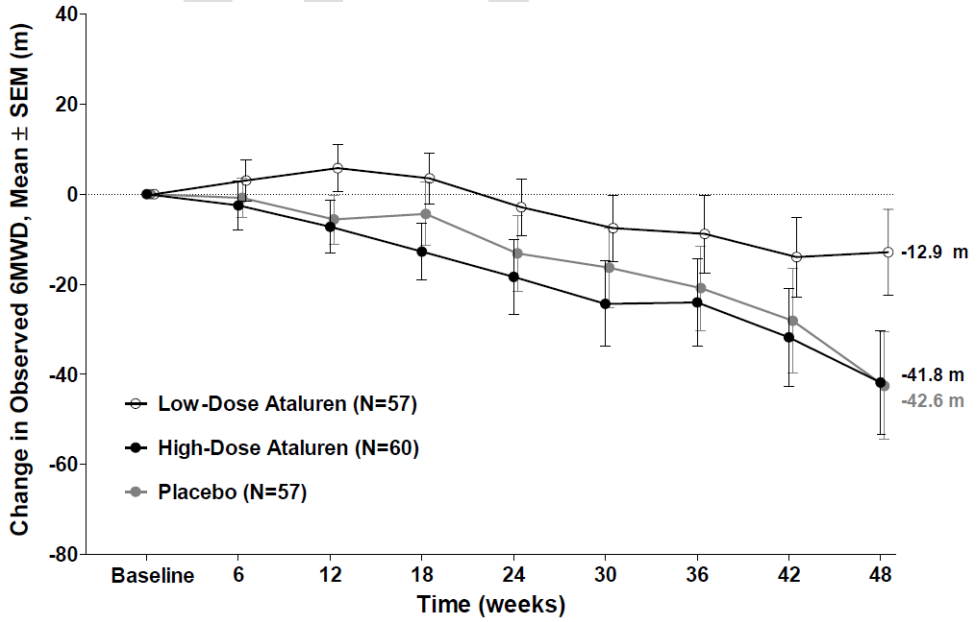
The primary endpoint was change from baseline to Week 48 in 6MWD. The primary analysis specified in the SAP was MMRM on rank-transformed data as Shapiro-Wilks tests indicated departure from normality for the untransformed data and log-transformed data. Holm's method was applied for multiplicity adjustment. An unstructured covariance matrix was used as it provided the best fit. The resulting unadjusted p-value was 0.149 for the low-dose ataluren and 0.476 for the high dose (Table 3). All 3 groups showed deterioration from baseline during the 48-week treatment period (Figure 1). Differences in mean ranks are not clinically interpretable and thus were not shown. Based on the MMRM analysis of untransformed data, the low-dose group had 26.4 meters less decline in 6MWD at Week 48 compared to placebo. The high-dose ataluren had little treatment effect on 6MWD, relative to the placebo (Table 3).

Table 3: Study 007: Pre-specified Analyses of the Primary Endpoint

Analysis method Source	Analysis Set	Transformation	Low Dose vs Placebo		High Dose vs Placebo	
			Δ (SE)	p-value nominal(adjusted*)	Δ (SE)	p-value nominal(adjusted*)
Primary Analysis						
MMRM						
CSR1 Table 14.2.1.14B	ITT	Ranks (primary)	--	0.149 (0.298)	--	0.476 (0.476)
CSR1 Table 14.2.1.8.5B	ITT	None	26.4 (15.5)	0.091 (0.159)	-0.1 (15.3)	0.996 (1.000)
Pre-specified Sensitivity Analyses						
Permutation Test						
S0025 Table 14.2.2.12.30	ITT	None	--	0.079 (0.150)	--	0.997 (1.000)
ANCOVA with LOCF						
CSR1 Table 14.2.2.16	ITT	Ranks	--	0.158 (0.268)	--	0.415 (0.625)
CSR1 Table 14.2.2.15	ITT	None	28.4 (14.0)	0.045 (0.081)	-0.7 (13.8)	0.958 (0.998)

*The adjusted p-values for the primary analysis on rank-transformed data were based on Holm's method; all other adjusted p-values were based on Dunnett's test.
Delta (Δ): LS mean difference; SE: standard error
Results were confirmed by FDA reviewer.

Figure 1. Study 007: Mean Change in Observed 6MWD by Visit (ITT)



Note: 1 patient dropped out.
Source: CSR1 Figure 3

Effect of Dynamic Randomization

A permutation test of 10,000 re-randomizations was specified to address the possible effect of dynamic randomization. As permutation test is a non-parametric test and therefore does not rely on normality assumption, MMRM analyses were performed on the permuted data sets without rank transformation. The result of the permutation test was similar to that of the MMRM analysis on untransformed data. The nominal p-value was 0.079 for the low-dose group compared to placebo (Table 3).

Effect of Missing Data

A sensitivity analysis using ANCOVA on last available data was pre-specified to check the effect of missing data. Although the SAP did not specify whether transformed data would be used for this analysis, this reviewer assumed that the same data used for the primary analysis would be used. The ANCOVA of rank-transformed data showed nominal p-values of 0.158 for low-dose ataluren versus placebo and 0.415 for high-dose ataluren versus placebo (Table 3). The results were similar to those from the pre-specified MMRM on rank-transformed data. A mean difference of 28.4 meters favoring low-dose ataluren was reported based on ANCOVA of untransformed data (nominal p-value = 0.045, Table 3).

Two patients in the low-dose group and 2 patients in the placebo group did not have a valid 6MWD at the primary time point of Week 48.

- Subject 515-002 and 516-003 were in the placebo group and had the last 6MWD of 331 and 406 meters respectively at Week 42. The 6MWDs at Week 48 were missing for both subjects.
- Subject 103-003 in the low-dose group had baseline 6MWD of 246 and the last valid 6MWD of 150 meters at Week 36. This subject only walked 50 meters for the first 4 minutes at Week 42, and walked 40 meters for the first 3 minutes at Week 48. He could not walk for the entire 6 minutes "due to fear of falling" and the tests were noted as "invalid".
- Subject 091-004 in the low-dose group had baseline 6MWD of 160 and the last observed valid 6MWD was 119 meters at Week 18. Tests were "not done due to foot fracture" for the next visits and the patient was "non-ambulant due to foot fracture" at Week 42.

The partial information on 6MWD at Week 48 suggested that subjects 103-003 and 091-004 had no or marginal ambulatory capacity, and the assumption of missing completely at random for the "last available value" approach was unlikely to hold. As a worst-case type of analysis, a value of 40 for subject 103-003 and 0 for subject 091-004 were assumed for 6MWD at Week 48. For subjects 515-002 and 516-003, who were relatively stable, the missing values at Week 48 were imputed with the last observations at Week 42. Compared to LOCF, the only differences were the 6MWDs for the two subjects in the low-dose group. With the worst-case type of imputation, ANCOVA on untransformed data yielded a p-value of 0.084 for the low dose ataluren (Table 4), similar to other analyses on untransformed data. This suggested that missing data had only minimal impact on the efficacy results.

Table 4: Study 007: Reviewer's Worst-Case Analyses of the Primary Endpoint

Analysis Set	Transformation	Low Dose vs Placebo		High Dose vs Placebo	
		Δ (SE)	p-value nominal (adjusted)	Δ (SE)	p-value nominal (adjusted)
ITT	None	24.6 (14.1)	0.084 (0.149)	-0.7 (13.9)	0.961 (0.998)

Adjusted p-values were based on Dunnett's test.
Source: FDA reviewer

Effect of Invalid 6MWTs

The study protocol specified rules to determine the validity of 6MWTs and to allow for repeat 6MWTs if necessary. Most patients were able to perform a valid 6MWT on their first and only attempt. A valid baseline 6MWD was required for randomization. After the data were unblinded, it was recognized that two patients at the same site (501-012 in the high-dose group and 501-014 in the placebo group) had suffered lower-limb injuries prior to baseline and had impaired their walking ability at baseline. The applicant stated that "baseline 6MWTs that should have been classified as invalid were incorrectly classified as valid" for these two patients and proposed to replace the two baseline values with screening values. The dataset with the two screening values of 6MWD was referred to as the corrected ITT population (cITT). Using the same primary analysis method on cITT, the resulting p-value was 0.095 for the low-dose ataluren (Table 5).

According to the protocol description (see section 3.2.1.1 above), only certain events occurred during the course of the test would invalidate the test. The protocol did not specify conditions under which patients should not take the test as those conditions might affect efficacy assessments. "Prior lower-limb injury" was identified post hoc to be one such condition. However, there might be other conditions such as "lower back pain" that could limit patients' ability to perform at their optimal level. In addition, as the protocol did not define those conditions, the collection of such information might not be complete. For these reasons, the reliability of the cITT analysis might not be complete.

Table 5: Study 007: Post-Hoc Analyses of the Primary Endpoint

Analysis method Source	Analysis Set	Transformation	Low Dose vs Placebo		High Dose vs Placebo	
			Δ (SE)	Nominal p-value*	Δ (SE)	Nominal p-value*
MMRM						
FDA reviewer	cITT	Ranks	--	0.095	--	0.480
FDA reviewer	cITT	None	28.6 (14.7)	0.053	-1.6 (14.5)	0.914
Augmented MMRM						
CSR1 Table 14.2.1.24B	ITT	None	29.0 (14.3)	0.045	0.4 (14.2)	0.980
CSR2 Table 14.2.1.24.2S	cITT	None	31.7 (13.5)	0.020	-1.6 (13.3)	0.903

Analysis method Source	Analysis Set	Transforma-tion	Low Dose vs Placebo		High Dose vs Placebo	
			Δ (SE)	Nominal p-value*	Δ (SE)	Nominal p-value*
Permutation Test based on Augmented MMRM						
CSR1 Table 25	ITT	None	--	0.058	--	0.980
CSR2 Table 28	cITT	None	--	0.028	--	0.912

*P-values were not adjusted for multiple comparisons of the two doses against the placebo.

Effect of Covariate Adjustment

The applicant stated on page 97 of CSR1 that "a marked discrepancy was observed between the p-value for the difference between low-dose ataluren and placebo of 0.0445 obtained with this ANCOVA versus the p-value of 0.0905 obtained with the pre-specified MMRM on untransformed 6MWD; because missing data at Week 48 were few, this observation suggested an inadequacy in the pre-specified MMRM model." To address this issue, the applicant added a baseline-by-visit interaction term to the model, referred to as augmented MMRM or refined MMRM. The applicant stated that the interaction term was statistically significant, and the resulting p-value of 0.053 (Table 5) was close to the p-value of ANCOVA with LOCF, as expected when there are only a few missing data.

As shown previously, changing only one or two data points (ITT vs. cITT, LOCF vs. worst-case imputation) could result in 1-fold change of the p-value for low-dose ataluren. In this reviewer's view, given the small sample size and relatively large variation of the data, the p-values of MMRM and ANCOVA may not be very close even though the amount of missing data was limited.

A model could be "refined" in various ways, and the p-value could change in either direction. Thus, the pre-specified analysis should carry the most credibility. For example, "baseline time to stand from supine was also an independent prognostic factor for 12-month change in 6MWD" (Mazzone 2016; module 2.7.3 page 102). With the addition of "baseline time to rise from supine" and its interaction with study visit, the resulting p-value for the difference between low-dose ataluren and placebo was 0.096.

Effect of Siblings

The result of the pre-specified sensitivity analysis based on siblings was similar to that of the primary analysis, indicating that the allocation of sibling pairs to the same treatment arm had little effect on the primary analysis results.

Proportions of responders and the proportions of progressors

As a further analysis of the primary outcome variable, the proportion of subjects with a ≥10% improvement in 6MWD at Week 48 (responders) and the proportion of subjects with a ≥10% worsening in 6MWD at Week 48 (progressors) were assessed using Cochran-Mantel-Haenszel

Chi-square tests. At Week 48, 44% and 26% of patients were progressors in the placebo and low-dose ataluren arms, respectively. The odds ratio was 0.4 (nominal p-value = 0.04). More patients in the low-dose ataluren (21%) than in the placebo arm (11%) were responders; the difference did not reach nominal statistical significance (odds ratio = 2.3, nominal p-value = 0.30).

Analyses of the Secondary Endpoints

The time function tests (TFT) were analyzed similarly as the primary endpoint (i.e., MMRM on rank-transformed data), as pre-specified in the SAP. All analyses of the secondary endpoints for physical functions failed to reach nominal statistical significance (Table 6). Using untransformed data, one of the TFTs, Time to Ascend 4 Stairs, was nominally significant in favor of the low-dose group (p-value = 0.04, not adjusted for multiple doses, not the pre-specified analysis).

Table 6: Study 007: Pre-Specified Analyses of Secondary Endpoints for Physical Functions

	Baseline			Low Dose vs Placebo		High Dose vs Placebo	
	P	**L**	**H**	**Δ**	**p-value**	**Δ**	**p-value**
Timed Function Test Times, seconds (negative deltas indicate improvement relative to placebo)[a]							
Stair ascend	6.04	6.94	7.63	-2.40	0.0981	-1.28	0.3425
Stair descend	5.52	6.08	6.75	-1.62	0.4307	-1.08	0.6722
10-meter run/walk	6.86	7.45	7.80	-1.35	0.7025	-0.66	0.7276
Supine to stand	11.5	10.8	12.3	-0.01	0.4153	-0.24	0.7368
Timed Function Test Method Grading, scores (positive deltas indicate improvement relative to placebo)[b]							
Stair ascend	4.02	3.56	3.85	0.45	0.9070	0.04	0.7511
Stair descend	3.65	3.28	3.63	0.23	0.6390	-0.10	0.7224
10-meter run/walk	4.81	4.72	4.57	0.24	0.9577	0.23	0.1927
Supine to stand	3.60	3.65	3.58	0.11	0.5937	0.05	0.8431

[a] Analysis method: original MMRM on rank-transformed data. Differences in observed mean changes at Week 48 were shown.
[b] Analysis method: generalized estimating equation models.
Source: CSR1 table 26

Subgroup Analyses

The applicant identified an Ambulatory Decline Phase (ADP) subgroup that showed a larger treatment difference of 44 meters in Study 007 (Table 7). The ADP subgroup included patients with:

- age ≥7 and ≤16 years; and
- screening 6MWD ≥150 meters and ≤80% of predicted for age and height; and
- on stable CST use (for a minimum of 6 months and no significant change for at least 3 months prior to start of study treatment).

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According to the sponsor, Study 020 was designed based on the results of the ADP subgroup. The results for subgroups by Baseline 6MWD (<300 meters, ≥300 to <400 meters, ≥400 meters) were also presented as they were pre-specified in Study 020 to explore the effect of the relevant subgroups on 6MWD. The comparison of the low-dose ataluren versus placebo yielded a nominal p-value of 0.055 in the subgroup of ≥300 to <400 meters (Table 7). None of the subgroups reached nominal statistical significance on the secondary endpoints for function tests, although there appeared to be numerical trends in favor of the low-dose ataluren (Table 8), especially for the subgroup of baseline 6MWD ≥300 to <400 meters.

Table 7: Study 007: Change in 6MWD at Week 48 by Subgroups

Population	n			Low Dose vs Placebo		High Dose vs Placebo	
	H	L	P	Δ	p-value	Δ	p-value
ITT	59	57	57	26.4	0.091	-0.1	0.996
<300m	16	15	13	20.8	0.590	5.4	0.887
≥300 to <400m	20	22	22	51.0	0.055	0.8	0.976
≥400m	23	20	22	18.0	0.190	10.1	0.448
Ambulatory Decline Subgroup	33	32	31	43.8	0.051	16.8	0.446
<300m	10	8	9	6.1	0.904	-0.3	0.995
≥300 to <400m	7	14	12	69.9	0.050	22.7	0.584
≥400m	16	10	10	24.6	0.220	12.1	0.503

Analysis method: MMRM on untransformed data
Source: FDA reviewer

Table 8: Study 007: Change in Function Tests at Week 48 by Subgroups

Endpoint	6MWD <300m		6MWD ≥300 to <400m		6MWD ≥400m	
	Δ	p-value	Δ	p-value	Δ	p-value
Time to walk/run 10 m, *s*	-1.1	0.748	-2.8	0.084	-0.2	0.431
Time to climb 4 stairs, *s*	-4.0	0.166	-3.2	0.145	-0.4	0.526
Time to descend 4 stairs, *s*	-0.7	0.823	-3.9	0.092	-0.1	0.726

Analysis method: MMRM on untransformed data
Deltas: LS mean difference between low-dose ataluren and placebo; negative deltas indicate improvement relative to placebo.
Source: FDA reviewer

3.2.2 Study 020

3.2.2.1 Study Design and Endpoints

The pivotal Study 020 was conducted at 54 sites in North America, South America, Europe, Israel, Asia, and Australia. The first patient visit took place on 3/26/13, and the last patient visit was on 8/20/15. The final protocol was dated 3/14/2014. There was no major change to the protocol after the study was initiated. The SAP was finalized on 8/19/ 2015. The final SAP

incorporated the following major changes from the initial plan: (1) changed the primary analysis of continuous longitudinal endpoints (eg, 6MWD, timed function tests) from a non-parametric ANCOVA to a traditional ANCOVA after multiple imputation for missing values; and (2) added subgroup analyses of patients with baseline 6MWD <300 meters, ≥300 to <400 meters, or ≥400 meters.

Study Design

This was a Phase 3, randomized, placebo-controlled, 48-week study in ambulatory males ≥7 and ≤16 years old with nmDMD. Eligible patients were randomized in a 1:1 ratio to receive placebo or 10/10/20 mg/kg ataluren 3 times per day. If a patient had a sibling who was previously randomized into the study, the patient was assigned to the same treatment arm as the first randomized sibling. Dynamic randomization was utilized and was stratified based on age (<9 or ≥9 years), duration of corticosteroid use (approximately ≥6 to <12 months vs. ≥12 months), and baseline 6MWD (<350 meters or ≥350 meters).

The study was enriched for patients in the ambulatory decline phase of the disease, based upon the results of prior Study 007. Furthermore, patients were only to receive either the low dose of ataluren or placebo.

Efficacy Endpoints

The primary efficacy endpoint was change from baseline to Week 48 in 6MWD.

Key secondary efficacy endpoints were

- Time to persistent 10% worsening in 6MWD; and
- Changes in proximal muscle function as assessed by timed function tests, including time to climb 4 stairs, and time to descend 4 stairs, time to walk/run 10 meters.

Change from Baseline to Week 48 in the North Star Ambulatory Assessment (NSAA) score was included as an exploratory endpoint.

3.2.2.2 Statistical Methodologies

The efficacy analyses were based on the ITT population, consisting of all patients who were randomized and who had a valid baseline 6MWD value and at least one valid, post-baseline 6MWD value.

<u>Analyses of Change in 6MWD</u>

The primary analysis of change in 6MWD was ANCOVA with multiple imputation (MI). The ANCOVA model included the stratification factors for age, duration of corticosteroids use, baseline 6MWD category, and baseline 6MWD as a covariate. A total of 100 imputations were conducted to impute missing values and the MIANALYZE procedure was used to combine the results from the imputed datasets.

DRAFT

A sensitivity analysis was specified using MMRM with an unstructured variance-covariance matrix. The model included the stratification factors for age, duration of corticosteroids use, baseline 6MWD category, baseline 6MWD as a covariate, treatment, visit, the interaction of treatment by visit, the interaction of visit by baseline 6MWD and the interaction of each of the stratification factors with visit.

Analyses of Time to Persistent Worsening

Time to 10% persistent worsening in 6MWD was assessed using a Cox proportional hazards model with baseline 6MWD, treatment and the three stratification factors included in the model. The imputed values obtained for the analysis of the primary endpoint were used in the determination of 10% persistent worsening. Patients who become non-ambulatory were considered to have 10% worsening.

Analyses of Timed Function Tests (TFTs)

The TFTs (10-meter run/walk, 4-stair climb, and 4-stair descend) were analyzed using the same analysis as specified for the primary endpoint. If the time taken to perform a TFT exceeded 30 seconds or if a subject was not able to perform the test due to disease progression, a value of 30 seconds was used.

Analyses of NSAA score

The NSAA consists of 17 activities. If fewer than 13 of the 17 activities were performed, the total score was considered missing. If from 13 to 16 activities are performed, the total score was calculated by multiplying the sum of the scores in the x activities that were performed by 17/x. If a patient was unable to perform an activity due to disease progression or to loss of ambulation, then a score of zero was assigned. The total score was analyzed by the same method for the primary endpoint.

Adjustment for Multiplicity

If the primary endpoint was declared positive, the first secondary endpoint of time to 10% persistent worsening in 6MWD was to be tested at a two-sided 0.05 significance level. If the first secondary endpoint was statistically significant, a Hochberg procedure was to be applied to control multiplicity at the 0.05 level for the following timed function tests: 4-stair climb, 4-stair descend, and 10-meter run/walk.

Subgroup Analyses

An ANCOVA model with an additional treatment-by-subgroup factor interaction was used to explore the effect of the relevant subgroup on 6MWD. The following subgroups were examined:

- Baseline 6MWD stratification factor [>350 meters vs. <350 meters];
- Baseline 6MWD group [<300 meters, ≥300 to <400 meters, ≥400 meters];
- Duration of prior corticosteroid use at baseline [≥6 to <12 months vs. ≥12 months];
- Baseline age group [<9 years vs. ≥9 years].

DRAFT

3.2.2.3 Patient Disposition, Demographic and Baseline Characteristics

The number of randomized patients was 115 in each group. Patients were enrolled at 54 study sites in 18 different countries. The US contributed the highest number of patients (30%). A total of 9 patients discontinued early from the study (5 in ataluren group and 4 in placebo group). Two patients, 1 in each treatment arm, were randomized but prematurely discontinued from the study when dystrophin gene sequencing results did not confirm the presence of a nonsense mutation in the dystrophin gene; these patients did not meet the criteria for inclusion in the ITT population.

Overall, the 2 treatment groups appeared comparable with regard to demographic and baseline characteristics (Table 9). The range of age was from 7 to 14 years with a median age of 9 years. Most are Caucasian (76%) and were on corticosteroid for at least 12 months (84%). There were 2 sibling-pairs in the placebo group and 4 in the ataluren group.

Table 9: Study 020: Demographic and Baseline Disease Characteristics

	Placebo (N= 115)	**Ataluren (N= 115)**
Age, years		
Mean (SD)	9.0 (1.7)	8.9 (1.8)
Age group, n (%)		
<9 y	53 (46.1)	57 (49.6)
≥9 y	62 (53.9)	58 (50.4)
Race, n (%) *		
Caucasian	86 (74.8)	89 (77.4)
Black	1 (0.9)	1 (0.9)
Asian	6 (5.2)	7 (6.1)
Hispanic	8 (7.0)	4 (3.5)
Other	4 (3.5)	7 (6.1)
Body weight, kg		
Mean (SD)	30.6 (10.4)	31.4 (10.8)
Median	27.0	29.3
Range	18.1, 68.0	15.8, 63.0
6MWD, m		
Mean (SD)	362.7 (81.4)	364.0 (73.3)
Range	142.5, 526.0	166.8, 511.0
6MWD, n (%)		
≥350 m	73 (63.5)	73 (63.5)
<350 m	42 (36.5)	42 (36.5)
NSAA		
Mean (SD)	21.9 (8.0)	22.2 (7.8)
Range	4, 34	5, 34
Duration of prior corticosteroid use, n (%)		
<12 to 6 months	19 (16.5)	19 (16.5)
≥12 months	96 (83.5)	96 (83.5)

* Information on race is not allowed to be collected due to government regulations for 17 subjects from France.
Source: CSR Table 9, 10, 11, 14.2.3.1

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3.2.2.4 Results and Conclusions

Analyses of the Primary Endpoint

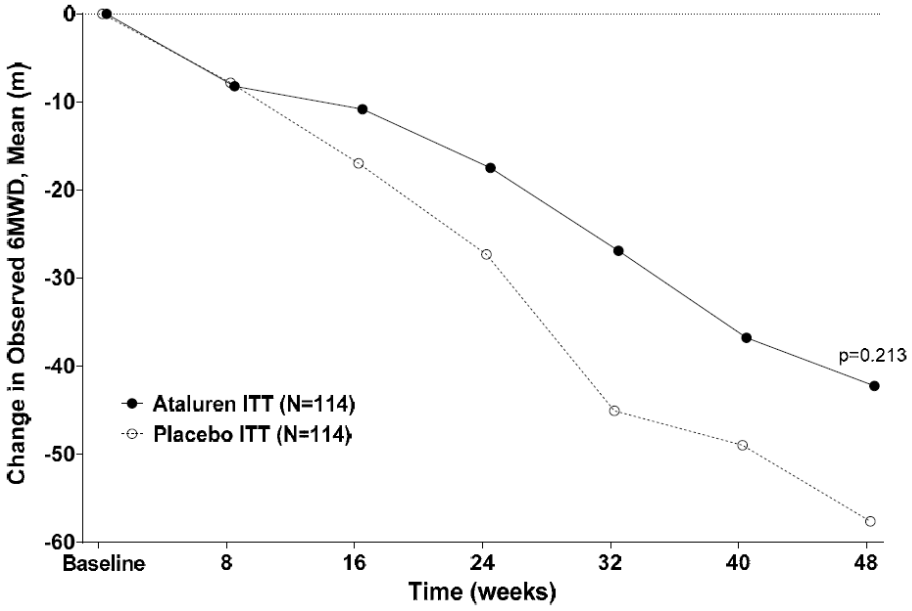
The primary analysis of the 6MWD data using ANCOVA with MI did not reach statistical significance (p-value = 0.213; Table 10). The decline in the mean 6MWD from baseline was numerically less in the ataluren group than in the placebo group starting at Week 16 (Figure 2), and the LS mean difference was 13 meters at Week 48 in favor of ataluren.

Table 10: Study 020: Analyses of the Primary Endpoint

	LS Means	Δ (SE)	95% Confidence Interval	p-value
Ataluren (n=114)	-47.7		(-65.82, -29.57)	
Placebo (n=114)	-60.7		(-78.94, -42.40)	
Ataluren vs Placebo		13.0 (10.4)	(-7.44, 33.39)	0.213

Source: CSR Table 14.2.1.3.1, confirmed by FDA reviewer

Figure 2. Study 020: Mean Change in Observed 6MWD by Visit (ITT)



Note: a total of 9 patients dropped out.
Source: CSR Figure 3

For each group 5 (4%) patients did not have at least one valid 6MWD at Week 48 but the pre-specified sensitivity analysis of MMRM yielded similar results to those of the primary analysis. This reviewer also conducted an additional MMRM model without baseline-by-visit interaction terms and the resulting p-value was similar (Table 11). These analyses suggested that analysis was robust to how missing data were handled.

Table 11: Study 020: Sensitivity Analyses of the primary endpoint

Analyses Method	Difference	SE	p-value
MMRM with pre-specified interaction terms	13.5	10.4	0.195
MMRM without interaction terms	15.2	11.6	0.191

Source: FDA reviewer

The applicant submitted two post-hoc analyses, using a nonlinear two-part model and a slope-based analysis, to assess the treatment effect while considering the two classes of patient profiles: patients who remained ambulatory throughout the entire study, and patients who became non-ambulatory.

In the analysis based on nonlinear two-part model, a model was first built using the placebo group data and then the changes in 6MWD at Week 48 were predicted for each patient in the ataluren group using this model. The predicted change in 6MWD at Week 48 = probability of loss of ambulation x inverse of baseline 6MWD + probability of maintenance of ambulation x change in 6MWD estimated by the pre-specified ANCOVA/MI on placebo data. The probability of loss of ambulation was determined via a logistic regression using the placebo data in Study 020. Then the observed change in 6MWD at Week 48 was compared to the change in 6MWD predicted by the nonlinear two-part model for each patient in the ataluren arm. The result showed that mean difference between the observed change in 6MWD for ataluren patients versus their predicted change in 6MWD at Week 48 was 13.9 meters (p-value = 0.042, Table 12). This reviewer does not consider this analysis approach performed by the applicant a valid statistical approach in this setting. The predicted values were not independent because the same model parameter estimates were used to predict the change in 6MWD for all the patients in the ataluren group and such correlation or dependence as well as the statistical uncertainty of the model parameter estimates were not properly incorporated in this analysis. The standard error may have been underestimated as the covariances of the predicted values were not properly accounted for.

Table 12: Study 020: Applicant's Nonlinear Two-Part Model of Week 48 Change in 6MWD

Observed Δ - Predicted Δ, mean (meters)T	Standard Error	95% CI	P-value
13.9	6.8	(0.5, 27.3)	0.042

Source: Module 2.7.3 Table 12

In the slope-based analysis, 6MWD data from all time points for a given patient (up to the time at which a patient became non-ambulatory) was used to calculate a slope (meters/week) as a measure of overall disease progression for each patient. The applicant stated: "an analysis of slope of change in 6MWD, as opposed to change in 6MWD, arguably is more robust and relevant because it takes into account time to loss of ambulation (for those patients who lose ambulation during the study) and because it uses data from all available time points (up to the time that a patient became non-ambulatory), not only baseline and end-of-treatment." The

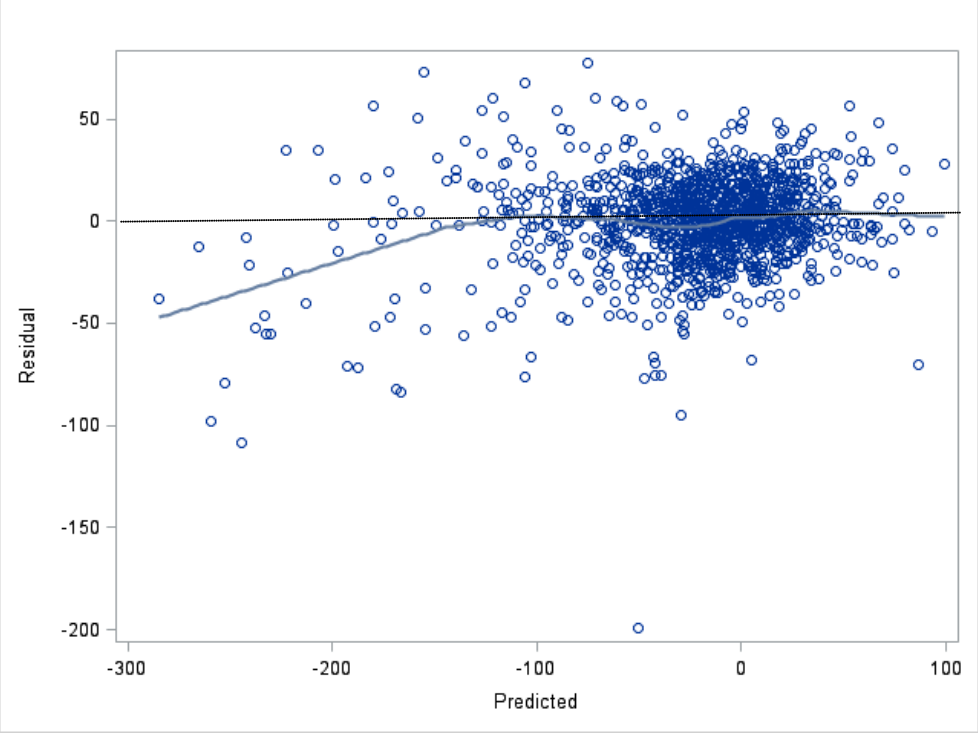
resulting p-value of the slope-based analysis was 0.103 (Table 13), failed to show nominal statistical significance. In addition, this reviewer used a residual plot to check if the linear model fit the data well. From Figure 3, it appeared that the residuals from the slope-based model were not randomly scattered around the horizontal zero line, suggesting that the linear model had lack of fit. Therefore, the slope-based analysis seemed to be limited for interpretation of treatment effect.

Table 13: Study 020: Applicant's Slope Analysis of Week 48 Change in 6MWD

Δ (m/week)	SE (m/week)	P-value	Δ Converted to Δ for Week 48 Change in 6MWD (m)*
0.45	0.27	0.103	18.8

* To facilitate understanding of the slope analysis results, the treatment difference for slope change was converted to a treatment difference in change in 6MWD at Week 48. However, it was recognized that this "back-transformation" involved assigning negative 6MWD values to patients after they lose ambulation, a clinical impossibility.
Source: Module 2.7.3 Table 13

Figure 3. Study 020: Residual Plot for the Slope-Based Analysis with LOESS Fit



Source: FDA reviewer

Analyses of the Secondary Endpoints

The tests for the secondary endpoints were descriptive only as the primary endpoint failed to reach statistical significance. The proportion of patients with at least 10% worsening in 6MWD

at Week 48 was 46% and 43% in the placebo and ataluren group, respectively. The hazard ratio for ataluren versus placebo was 0.75 (nominal p-value = 0.160, Table 14).

Table 14: Study 020: Analysis of Time to 10% Persistent Worsening in 6MWD

	Placebo	Ataluren
Time to 10% Persistent Worsening in 6MWD		
Number of Subjects Assessed	114	114
Number of Subjects with Events	52 (45.6)	49 (43.0)
Hazard Ratio (95% CI)	0.75 (0.51, 1.12)	
p-value	0.160	

Source: CSR Table 14.2.1.5.1

Over 48 weeks, ataluren-treated patients had numerically smaller increase in timed function tests (TFTs), and one of the tests (descend 4 steps) reached nominal statistical significance (nominal p-value = 0.012, Table 15). In these analyses, if the time taken to perform a test exceeded 30 seconds or if a subject could not perform the test due to disease progression, a value of 30 seconds was used. Two pre-specified sensitivity analyses were performed: (1) using an upper limit of 45 seconds, and (2) using the highest value observed for a given endpoint. The results of TFTs seemed sensitive to the handling of the maximum value. The nominal statistical significance for "time to descend 4 stairs" was lost when the highest observed value was used if a subject cannot perform the test due to disease progression (Table 15). As the data were highly skewed, the reviewer conducted the same analyses on log-transformed data. The p-values for the endpoint of "time to descend 4 stairs" ranged from 0.034 to 0.051 (not shown in table), less affected by the handling of the maximum value.

Table 15: Study 020: Primary and Sensitivity Analyses of Change in Timed Function Tests

Endpoint	Maximum = 30 Seconds		Maximum = 45 Seconds		Maximum = Highest Observed Value	
	Δ	p-value	Δ	p-value	Δ	p-value
Time to walk/run 10 m, *s*	-1.2	0.117	-1.9	0.159	-2.7	0.196
Time to climb 4 stairs, *s*	-1.8	0.058	-2.5	0.099	-4.7	0.326
Time to descend 4 stairs, *s*	-1.8	0.012	-2.3	0.040	-2.6	0.144

Source: CSR Table 17

Analyses of Exploratory Endpoints

The NSAA is a composite score of 17 items, each scored as 0, 1, or 2, with 0 = "unable to achieve independently," 1 = "modified method but achieves goal independent of physical assistance from another," or 2 = "normal — achieves goal without any assistance." The sum of these 17 scores was used to form a total score. A linear transformation of the NSAA score to a scale of 0 to 100 was also analyzed. By the pre-specified method of ANCOVA/MI, the

difference between the ataluren and placebo arms was 0.8 point in NSAA total score (nominal p-value = 0.128) and 1.5 in NSAA linear score (nominal p-value = 0.268), numerically favoring ataluren (Table 16).

Table 16: Study 020: Change in NSAA at Week 48

	LS Means (SE)	95% Confidence Interval	p-value
NSAA Total Score			
Ataluren	-2.97 (0.47)		
Placebo	-3.76 (0.47)		
Ataluren vs Placebo	0.80 (0.52)	(-0.23, 1.82)	0.128
NSAA Linear Score			
Ataluren	-6.98 (1.21)		
Placebo	-8.49 (1.21)		
Ataluren vs Placebo	1.51 (1.36)	(-1.16, 4.17)	0.268

Source: CSR Table 14.2.3.2 and Table 14.2.3.4

The applicant performed a post-hoc analysis of percentage of patients who scored either "2" or "1" at baseline and shifted to "0" at Week 48 for each individual item. For 15 of the 17 NSAA items, fewer patients shifted from "1" or "2" (able to perform function) to "0" (unable to perform function) in the ataluren arm, suggesting a trend in favor of ataluren (Table 17). In Study 20, the NSAA loss of function was a post-hoc data-driven endpoint; it was not available in Study 007.

Table 17: Study 020: Applicant's Post-Hoc analysis of NSAA Loss of Function at Week 48

NSAA Items	Ataluren (N=114)	Placebo (N=114)
1 Stand	5/113 (4.4%)	9/114 (7.9%)
2 Walk	6/114 (5.3%)	11/114 (9.6%)
3 Rise from Chair	10/103 (9.7%)	19/101 (18.8%)
4 Stand on R Leg	10/111 (9.0%)	8/108 (7.4%)
5 Stand on L Leg	10/112 (8.9%)	11/106 (10.4%)
6 Climb Box Step R	14/91 (15.4%)	25/93 (26.9%)
7 Climb Box Step L	15/93 (16.1%)	21/92 (22.8%)
8 Descend Box Step R	15/103 (14.6%)	21/103 (20.4%)
9 Descend Box Step L	17/105 (16.2%)	25/103 (24.3%)
10 Gets to Sitting	1/112 (0.9%)	4/114 (3.5%)
11 Rise from Floor	12/91 (13.2%)	19/87 (21.8%)
12 Lifts Head	6/103 (5.8%)	5/105 (4.8%)
13 Stands on Heels	13/72 (18.1%)	20/73 (27.4%)
14 Jump	14/89 (15.7%)	25/92 (27.2%)
15 Hop R Leg	18/79 (22.8%)	26/79 (32.9%)
16 Hop L Leg	21/76 (27.6%)	24/78 (30.8%)
17 Run	16/98 (16.3%)	21/94 (22.3%)
Mean	12.90%	18.80%
Between-Group Difference	-5.80%	
P-value (two-sided)*	0.008	
Risk Ratio	0.687	
Risk Ratio p-value (two-sided)	0.01	

Note: Function loss defined as a shift from non-zero at baseline to zero at Week 48.
Missing data handled by LOCF.
Risk ratio = percent loss of function in the ataluren arm divided by the percent loss of function in the placebo arm.
P-value obtained via 1000 permutations of treatment assignments within strata.
Source: Module 5.3.5.3 ISE Table 92
*The reviewers conducted the same permutation test using 100,000 permutations; the resulting nominal p-value was 0.018.

Subgroup Analyses

A total of 9 subgroups were specified in Study 020 to explore the effect of the relevant subgroups on 6MWD. The subgroups were defined by age stratification factor (results in Table 21), corticosteroid use stratification factor (results not shown as most patients were on stable corticosteroid for at least 12 months), and by baseline 6MWD (Table 18). The subgroup of baseline 6MWD between 300 and 400 meters, comprising 43% of the total population, was the only one of the subgroups to show a nominally significant difference in the change from baseline to Week 48 in 6MWD (43 meters, nominal p-value = 0.007), favoring ataluren. The subgroup analyses were conducted on ITT population with a subgroup-by-treatment interaction term in the model. Using only the ≥300 to <400-meter subgroup data and the primary analysis method, the LS mean difference was 40 meters (nominal p-value = 0.014). Nominal statistical significance was also observed for most of the function tests in this subgroup (Table 19).

Table 18: Study 020: Change in 6MWD at Week 48 by Subgroups

Subgroup	n (%)		Ataluren vs Placebo	
	Placebo	Ataluren	Δ (95%CI)	p-value
Baseline 6MWD				
<300 m	21 (18)	24 (21)	-8 (-55, 40)	0.749
≥300 to <400 m	52 (46)	47 (41)	43 (12, 74)	0.007
≥400 m	41 (36)	43 (38)	-10 (-43, 24)	0.580
Baseline 6MWD				
<350 m	41 (36)	41 (36)	22 (-12, 56)	0.210
≥350 m	73 (64)	73 (64)	8 (-18, 33)	0.540

Analysis method: ANCOVA/MI including a subgroup-by-treatment interaction term
Source: CSR Table 14.2.1.3.3.2 and Table 14.2.1.3.3.1

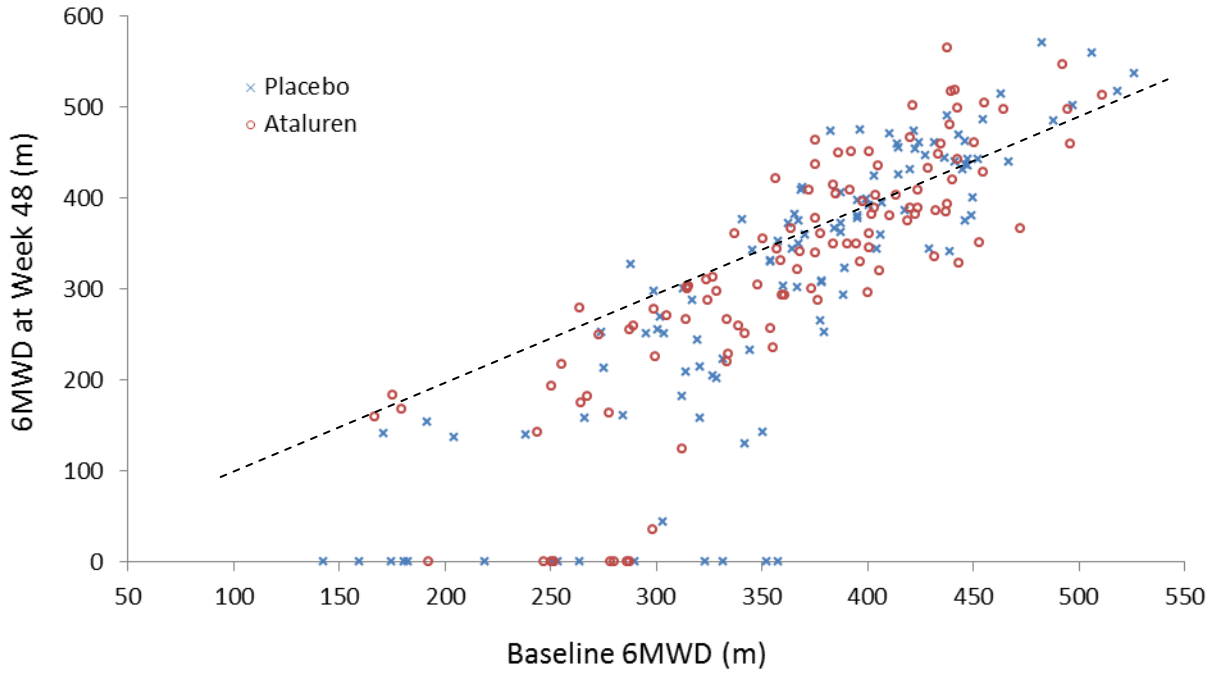
Table 19: Study 020: Change in Function Tests at Week 48 by Subgroups

Endpoint	6MWD <300m		6MWD ≥300 to <400m		6MWD ≥400m	
	Δ	p-value	Δ	p-value	Δ	p-value
Time to walk/run 10 m*	-2.75	0.066	-1.84	0.066	0.21	0.848
Time to climb 4 stairs*	-0.47	0.790	-3.46	0.003	0.17	0.893
Time to descend 4 stairs*	-0.97	0.595	-4.36	<0.001	-0.13	0.917
Total NSAA+	0.37	0.760	1.7	0.037	-0.11	0.896
Linear NSAA+	0.65	0.837	4.26	0.041	-1.06	0.637

* Negative deltas indicate improvement relative to placebo.
+ Positive deltas indicate improvement relative to placebo.
Source: CSR Table 14.2.2.2.8, 14.2.2.3.8, 14.2.2.4.8, 14.2.3.6 & 14.2.3.8

Figure 4 showed the values of 6MWD at Week 48 versus Baseline for Study 020. There was some separation between the two groups in the range of baseline 6MWD ≥300 to <400 meters range. Of note, 4 patients in the placebo group and none in the ataluren group lost ambulation. Nominal statistical significance would be lost, however, if the range was extended to ≥230 to <400 meters to includes those ataluren patients who lost ambulation. Additionally, for the primary endpoint, the numerical trend was opposite in the complementary subgroups, i.e., the subgroup of baseline 6MWD <300 meters and the subgroup of ≥400 meters (Table 18). The subgroup of ≥400 meters also showed an opposite trend on most of the function tests (Table 19). This suggested that the results of the subgroup of ≥300 to <400 meters might be by chance (or resulting from excluding subsets with negative results).

Figure 4. Study 020: 6MWD at Week 48 versus 6MWD at Baseline



Note: 5 patients in each group did not have a valid 6MWD at Week 48 and the last available values were used.
Source: FDA reviewer

Multiplicity adjustment was not pre-specified for testing the ≥300 to <400-meter subgroup (or any of the 9 subgroups). The applicant conducted a post-hoc permutation test to adjust for multiple subgroups, and the result showed that the adjusted p-value for the ≥300 to <400-meter subgroup was 0.036 (module 2.7.3). Without pre-specification, many possible analyses can be done post hoc for multiplicity adjustment. Therefore, the adjusted p-value was difficult to interpret.

Study 020 was enriched to enroll patients in ambulatory decline phase (ADP), defined as patients who were ≥7 to ≤16 years old and had 6MWD ≥150 meters but ≤80%-predicted at baseline while receiving a stable dose of corticosteroid therapy. However, the treatment effect on 6MWD in the Study 020 ITT population (13 meters) was much smaller, if any, than the treatment effect observed in the ambulatory decline phase subgroup in Study 007 (44 meters, Table 7). The applicant stated that "despite efforts to enrich for patients in the ambulatory decline phase of the disease, the Study 020 population remained heterogeneous. The range of baseline 6MWD in Study 020 (142 to 521 meters) was broad… Baseline 6MWD ≥80%-predicted corresponded to baseline 6MWD of ~450 meters in Study 007…Furthermore, mean baseline 6MWD was 23 meters higher in Study 020 ITT than in the Study 007 ambulatory decline phase subgroup. Collectively, these observations demonstrate that Study 020 failed to enrich for patients in the ambulatory decline phase of DMD (module 2.7.3, page 129)." To assess the impact of the higher mean baseline 6MWD in Study 020, this reviewer conducted an analysis on a subgroup of patients with baseline 6MWD <433 meters. The cutoff of 433 meters was chosen so that the mean baseline 6MWD for this subgroup was the same as the Study 007 ADP subgroup. The result was given in Table 20. From the table, the treatment effect increased only slightly (i.e., the estimate was 15 meters, nominal p-value = 0.233), still much smaller than that of the treatment effect observed in the ADP subgroup in Study 007. This suggested that the discrepancy in the treatment effects between the two studies cannot be explained by differences in mean baseline 6MWD.

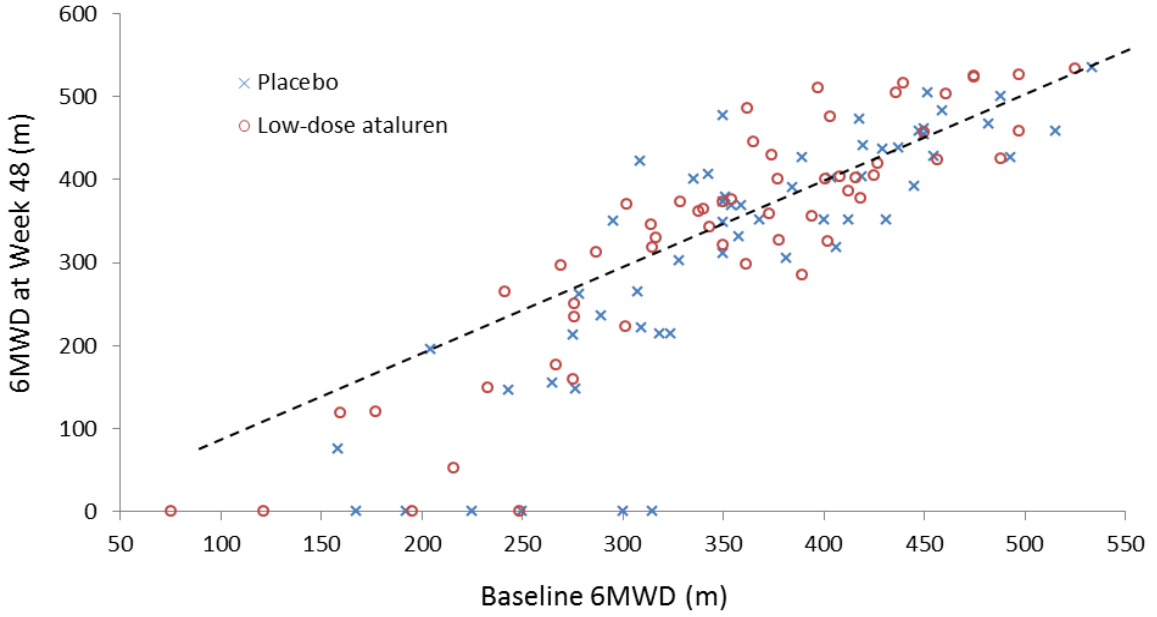
Table 20: Study 020: Change in 6MWD at Week 48 for Subgroup of Baseline 6MWD <433m

	LS Means	Δ (SE)	95% Confidence Interval	p-value
Ataluren (n=92)	-54.7		(-75.32, -34.13)	
Placebo (n=91)	-69.5		(-90.18, -48.84)	
Ataluren vs Placebo		14.8 (12.4)	(-9.51, 39.08)	0.233

Source: FDA reviewer

The applicant also stated that "replication of a large treatment effect in the baseline 6MWD ≥300 to <400 meters range was observed" in Study 007. The LS mean differences in the ≥300 to <400-meter subgroup were 51 meters in Study 007 (Table 7) and 47 meters in Study 020 (Table 18). Figure 5 showed the values of 6MWD at Week 48 versus Baseline for Study 007. The figure showed that the separation between the two groups was mostly in the ≥300 to <350-meter range. Within this range, 2 patients in the placebo group and none in the ataluren group lost ambulation.

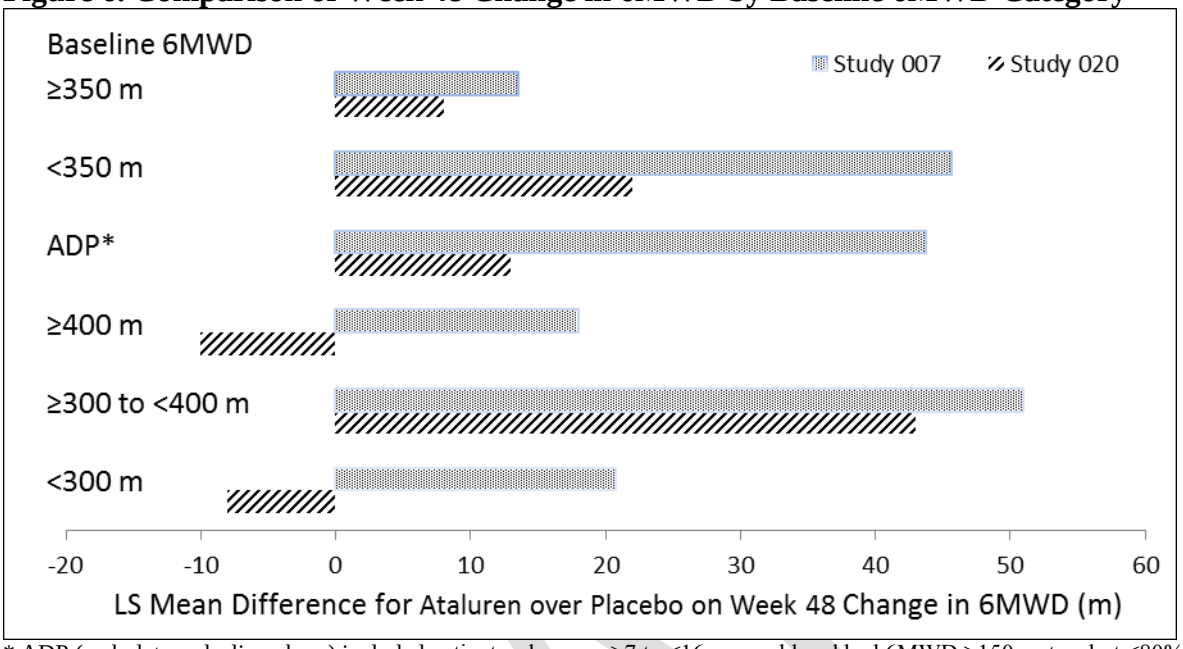
Figure 5. Study 007: 6MWD at Week 48 versus 6MWD at Baseline



Note: 2 patients in each group did not have a valid 6MWD at Week 48 and the last available values were used.
Source: FDA reviewer

Of note, the ≥300 to <400-meter subgroup in Study 007 was from a broader population with a wider range of age, including patients with baseline 6MWD >80% of predicted for age and height, and/or not on stable corticosteroid use. The median age in the ≥300 to <400-meter subgroup was 9 years in Study 020, and 7 years in Study 007 (the minimum age in Study 020 was 7). About 75% patients in the ≥300 to <400-metersubgroup in Study 007 were on corticosteroid, while all patients in Study 020 were stable corticosteroid use. Therefore, the similar treatment effects seen in this subgroup did not necessarily mean consistent treatment effects between the two studies. As illustrated in Figure 6, the only consistent effects shown in the two studies were the ≥300 to <400-meter subgroup. In Study 007, all other subgroups by baseline 6MWD seemed to have a treatment effect much larger than that in Study 020 which is a larger study than Study 007. Additionally, the two studies showed opposite numerical trends for the subgroup of baseline 6MWD <300 meters and the subgroup of ≥400 meters. This further suggested that the results of the subgroup of ≥300 to <400 meters might be by chance.

Figure 6. Comparison of Week 48 Change in 6MWD by Baseline 6MWD Category



* ADP (ambulatory decline phase) included patients who were ≥7 to ≤16 years old and had 6MWD ≥150 meters but ≤80%-predicted at baseline while receiving a stable dose of corticosteroid therapy.
Positive differences indicate ataluren is better than placebo
Source: FDA reviewer

3.3 Evaluation of Safety

Please see the clinical review.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, and Age

Subgroup analysis was not applicable for gender (only males were included) or race (90% and 76% Caucasian in Study 007 and Study 020 respectively). Both studies were stratified by age (<9 or ≥9 years). The subgroups of younger patients appeared to have numerically larger treatment differences in 6MWD at Week 48 (Table 21).

Table 21: Change in 6MWD at Week 48 by Age Subgroups

Subgroup	n		Ataluren vs Placebo	
	Placebo	Ataluren 10/10/20 mg/kg	Δ (95%CI)	p-value
Study 020[a]				
<9 years	53	57	16 (-13, 46)	0.279
≥9 years	61	57	10 (-18, 31)	0.494

Subgroup	n		Ataluren vs Placebo	
	Placebo	Ataluren 10/10/20 mg/kg	Δ (95%CI)	p-value
Study 007[b]				
<9 years	32	32	32 (-6, 70)	0.100
≥9 years	25	25	18 (-31, 67)	0.462

[a] Analysis method: ANCOVA/MI including an age-by-treatment interaction term
[b] Analysis method: original MMRM on untransformed data
Source: FDA reviewer

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

Both studies failed to conclude that ataluren has a treatment effect on the primary endpoint, change in 6MWD at Week 48. The applicant conducted numerous post-hoc analyses.

For Study 007, the applicant performed an augmented MMRM with the addition of baseline-by-visit interaction term. As this was a post-hoc analysis, and a model could be "refined" using covariates in various ways with p-values change in either direction, the pre-specified analysis should carry the most credibility. The applicant defined a post-hoc analysis set, cITT, in which two baseline 6MWD values were replaced with screening values, as the applicant stated that "baseline 6MWTs that should have been classified as invalid were incorrectly classified as valid". This reviewer did not find this statement supported by the study protocol. The appropriateness of the cITT set is deferred to the clinical evaluation.

Study 020 was enriched to enroll patients in ambulatory decline phase, based upon the results of a post-hoc subset in Study 007, and was twice the size of Study 007. However, the treatment effect in 6MWD in this type of patients in Study 020 was much smaller, if any, than the treatment effect in Study 007 (13 meters in Study 020 versus 44 meters in Study 007).

For Study 020, 9 subgroups were specified in the SAP without a multiplicity adjustment plan to explore the treatment effect on the relevant subgroups. One of the subgroups was the patients with baseline 6MWD ≥300 to <400 meters. The applicant stated that this subgroup was chosen based on natural history data documenting that patients with baseline 6MWD ≥400 meters tend to remain stable over 48 weeks whereas patients with baseline 6MWD <300 meters are at risk for loss of ability to perform the 6MWT. Nominal statistical significance was seen in this subgroup for the primary endpoint and most of the secondary endpoints on function tests. However, multiplicity adjustment was not pre-specified for testing this subgroup (or any of the 9 subgroups). Additionally, for the primary endpoint, the numerical trend was opposite in the complementary subgroups, i.e., the subgroup of baseline 6MWD <300 meters and the subgroup of ≥400 meters (see Figure 6). The subgroup of ≥400 meters also showed an opposite trend on most of the function tests. This suggested that the results of the subgroup of ≥300 to <400 meters might be by chance or resulting from excluding subsets with negative results.

A similar treatment effect on 6MWD in the patients with baseline 6MWD ≥300 to <400 meters was observed in Study 007. This subgroup in Study 007 was from a broader population with a wider range of age, including patients with baseline 6MWD >80% of predicted for age and height, and/or not on stable corticosteroid use. The median age in the ≥300 to <400-meter subgroup was 9 years in Study 020, and 7 years in Study 007 (the minimum age in Study 020 was 7). About 75% patients in the ≥300 to <400-meters subgroup in Study 007 were on corticosteroid, while all patients in Study 020 were on stable corticosteroid use. Therefore, the similar treatment effects seen in this subgroup did not necessarily mean consistent treatment effects between the two studies. Additionally, the treatment effects on 6MWD in all other subgroups by baseline 6MWD seemed to be much larger in Study 007 than in Study 020, and the subgroup of baseline 6MWD <300 meters and the subgroup of ≥400 meters showed opposite numerical trends in the two studies (see Figure 6). This further suggested that the results of the subgroup of ≥300 to <400 meters might be by chance.

5.2 Collective Evidence

For Study 007, the primary endpoint failed to achieve statistical significance. The p-value based on the pre-specified primary analysis was 0.15 for low dose ataluren (adjusted p-value = 0.30 based on pre-specified Holm's procedure). The estimated difference in least-squares mean change in 6MWD at Week 48 was 26 meters. The permutation test, a pre-specified sensitivity analysis to incorporate the distinct feature of dynamic randomization, yielded a nominal p-value of 0.08 (adjusted p-value = 0.15 based on Dunnett's test). The permutation test does not rely on normality assumption and therefore does not require rank transformation. All analyses of secondary endpoints for physical functions failed to achieve nominal statistical significance, although most showed a numerical trend in favor of the low-dose ataluren.

The high-dose ataluren had little effect on the primary endpoint and the secondary endpoints.

For Study 020, the primary endpoint also failed; the observed treatment effect of 13 meters on 6MWD was not statistically significant (p-value = 0.21). Secondary endpoints for physical functions showed a numerical trend in favor of ataluren, and one of them (time to descend 4 steps) reached nominal statistical significance (nominal p-value = 0.01). The exploratory endpoint of NSAA total score showed a non-significant treatment effect of 0.8 in favor of ataluren (nominal p-value = 0.13). A post-hoc subgroup of baseline 6MWD ≥300 to <400 meters showed nominal statistical significance on the primary endpoint of change in 6MWD and most of the secondary endpoints of function tests.

A similar treatment effect on 6MWD in the patients with baseline 6MWD ≥300 to <400 meters range was observed in Study 007. The LS mean differences in the subgroup of baseline 6MWD ≥300 to <400 meters were 51 meters in Study 007 and 47 meters in Study 020. Within this subgroup, none of the ataluren patients lost ambulation in either study, while 4 placebo patients in Study 020 and 2 in Study 007 lost ambulation.

5.3 Conclusions and Recommendations

A few observations suggested a possible signal of treatment effect for ataluren at dose regimen of 10/10/20 mg/kg.

1. There appeared to be numerical trends in favor of ataluren on the primary endpoint of 6MWD and secondary endpoints of timed function tests in both studies.
2. In Study 020, time to descend 4 stairs (a secondary endpoint) reached nominal statistical significance (nominal p-value = 0.012). A post-hoc analysis examining the shift of score for each NSAA item from "1" or "2" (able to perform function) to "0" (unable to perform function) suggested that fewer patients in the ataluren arm lost the ability to perform NSAA functions.
3. The subgroup of baseline 6MWD ≥300 to <400 meters in both studies suggested a treatment effect of ~50 meters on 6MWD and reached nominal statistical significance. A treatment effect of ataluren on most of the secondary endpoints was suggested in this subgroup in Study 020. No ataluren patients lost ambulation in either study, while 4 placebo patients in Study 020 and 2 in Study 007 lost ambulation in this subgroup.

However, these results were very difficult to interpret based on the observations below.

1. For Study 007, the nominal p-value of the low dose was in the range of 0.04 to 0.15 without multiplicity adjustment. The high dose did not even have a numerical trend in favor of ataluren.
2. The treatment effect on 6MWD was inconsistent, 44 meters in Study 007 versus 13 meters in Study 020, in ambulatory decline phase patients. Of the five subgroups based on baseline 6MWD category, the ≥300 to <400-meter subgroup was the only one giving a numerically consistent ataluren effect on 6MWD in the two studies. In all other baseline 6MWD subgroups, the treatment effect was seen much larger in Study 007 than in Study 020. See Figure 6.
3. Multiplicity adjustment was not pre-specified for testing the ≥300 to <400-meter subgroup. This subgroup was the only one of the 9 pre-specified subgroups reaching nominal significance for the treatment difference in the change from baseline to Week 48 in 6MWD.
4. Opposite trends were observed in the complementary subgroup of patients (i.e., baseline 6MWD <300 or ≥400 meters) in Study 020, suggesting that the treatment effect observed in the baseline ≥300 to <400 meters group might have resulted from excluding subsets of patients with negative results.

In summary, both studies failed to conclude that ataluren has a treatment effect on the primary endpoint, change in 6MWD at Week 48. When a trial failed, it means either the treatment had no effect or the study was not able to detect a treatment effect. In this submission, both studies showed a numerical trend in the primary analysis favoring the low-dose ataluren. A post-hoc analysis of the subgroup of baseline 6MWD ≥300 to <400 meters in Study 020 was nominally significant for the primary endpoint. A numerically similar treatment effect was also observed in

Study 007. Based on these results, there appeared to be a signal of treatment effect for the low-dose ataluren. However, the suggestion of the treatment effect in the baseline 6MWD ≥300 to <400-meter subgroup was not a confirmation of an ataluren treatment effect on 6MWD. Whether this could be sufficient evidence to support approval of ataluren for the treatment of nonsense-mutation-mediated Duchenne Muscular Dystrophy is up for discussion.

DRAFT

Summary

of

Office of Clinical Pharmacology Findings

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NDA or BLA Number	200896
Link to EDR	Ataluren NDA
Submission Date	02/24/17
Submission Type	Standard
Brand Name	Translarna®
Generic Name	Ataluren
Dosage Form and Strength	Packets containing white to off-white vanilla-flavored granules. Each packet delivers 125 mg, 250 mg, or 1000 mg of ataluren.
Route of Administration	Oral
Proposed Indication	For the treatment of dystrophinopathy resulting from a nonsense mutation in the dystrophin gene.
Applicant	PTC Therapeutics, Inc.
Associated IND	068431
OCP Review Team	Atul Bhattaram, Ph.D., Xinning Yang, Ph.D., Kevin Krudys, Ph.D., Sreedharan Sabarinath, Ph.D.
OCP Final Signatory	Mehul Mehta, Ph.D.

The Review Team acknowledges the input from OCP Guidance and Policy Team to this review.

1. EXECUTIVE SUMMARY

This is an original NME NDA seeking approval of ataluren (PTC124, Translarna®), dosed orally, for the the treatment of dystrophinopathy resulting from a nonsense mutation in the dystrophin gene. The presence of a nonsense mutation would be determined by genetic testing. Ataluren is an orally bioavailable small molecule that is hypothesized to correct the phenotypic expression of certain types of genetic defects and was developed for use in patients with genetic disorders such as Duchenne Muscular Dystrophy (DMD)/Becker's Muscular Dystrophy (BMD) caused by nonsense mutations.

The applicant relies on the results from two double-blind, placebo-controlled, 48-week clinical trials (Studies 007 and 020) in 404 male patients (age 5-16 years) with dystrophinopathy resulting from a nonsense mutation in the dystrophin gene. Per the applicant, Study 007 showed that the patients treated with higher dose (80 mg/kg total dose administered three times daily (TID) as 20/20/40 mg/kg) did not show any benefit compared to placebo, while a lower dose (40 mg/kg administered as 10/10/20 mg/kg TID) was better than placebo. Subsequent trial (Study 020) employed similar design features as Study 007 and was conducted in a larger enriched patient pool (≥7 to ≤16 years old with baseline 6MWD ≥150 meters but ≤80%-predicted 6MWD and receiving a stable regimen of corticosteroid therapy) with 40 mg/kg total daily dose. Taken together, the evidence from these two studies did not provide conclusive evidence of ataluren's efficacy. For details regarding the findings on efficacy and safety of ataluren, refer to the review by Drs. David Hosford and Veneeta Tandon (Division of Neurology Products, CDER).

The applicant has conducted exposure-response analyses using the data from Study 007 and provided these results as supportive evidence of efficacy. The applicant asserts that a biologically explainable bell-shaped dose-response phenomenon exists for ataluren, whereby effectiveness is seen at lower but not higher doses. From a clinical pharmacology standpoint, a dose- or exposure-response relationship would be supportive of drug activity in the intended population. Additionally, a strong effect on a physiologically relevant pharmacodynamic biomarker or robust findings from in vitro models could be mechanistically supportive of a potential treatment effect. The applicant identified a concentration threshold of 19 μg/mL at 2hr post-dose for efficacy with concentrations ≥19 μg/mL potentially resulting in loss of efficacy. The applicant also provided information from *in vitro* models as support for the mechanism of action and the dose-response findings from Study 007.

The primary objectives of this review are to evaluate:

- Exposure-response analyses as supportive evidence of effectiveness.
- Non-clinical and *in vitro* data regarding the purported bell-shaped dose-response of ataluren.

1.1 Recommendations

The Office of Clinical Pharmacology has reviewed the information contained in NDA 200896. The OCP review team does not consider the exposure-response analyses and *in vitro* data as supportive evidence of effectiveness for the following reasons.

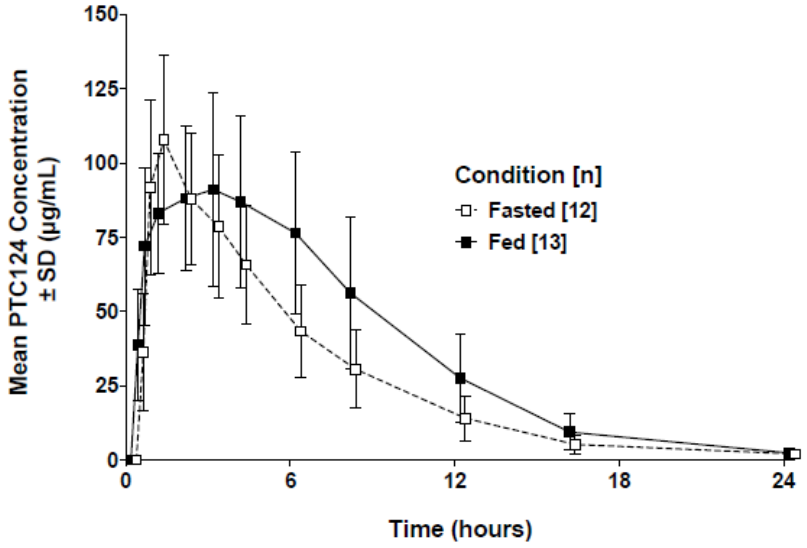
- Imbalances in baseline clinical variables such as 4-step climb, 4-step descent, 10m walk/run and 6MWD between patients in the ataluren concentration groups in 80 mg/kg dose group from Study 007 (See **Table 1**). Exposure-response analyses without adequate balance of prognostic factors across the concentration groups cannot be interpreted properly.
- Among the various studies the applicant presented to support a bell-shaped dose response, only the in vitro study using myotube cultures from DMD patients (Study 004) may suggest such a relationship. However, this study has multiple intrinsic problems. These include a lack of adequate dystrophin quantification, irregularities in immunofluorescence methods and results, , and the immature status of the cultured cells in vitro. These issues call for additional and higher quality data to determine if the dose response relationship is real or simply an artifact of poorly designed experiments.

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

Mechanism of Action: Per the applicant, ataluren is a selective, rather than universal nonsense mutation suppressor. Its mode of action appears to vary greatly from target to target, promoting premature termination codon readthrough for some alleles while stabilizing naturally occurring readthrough proteins for others. For most targets, including the nonsense mutation alleles of dystrophin, the exact mechanism behind ataluren's apparent effects is not clear.

Absorption: Peak plasma levels (C_{max}) are achieved around 3 h after administration as an oral suspension. At least 55% of the dose is absorbed after oral administration. Intake of a high-fat meal delays ataluren T_{max} by 2 h, decreases C_{max} by 5% and increases $AUC_{0-\infty}$ by 35% (**Figure 1**).

Figure 1. Plasma concentrations of ataluren by fed-fasting status in healthy subjects receiving single 50-mg/kg dose)



Source : Figure 2 on page 70 in ptc124-gd-001-hv-body.pdf

In clinical trials, administration of ataluren within 30 minutes after a meal was recommended. However, the protocols did not specify the type of meal that patients should be taking. It is not clear how any shift in T_{max} would influence clinical outcome. The proposed mode of administration for Translarna® is by mixing it to a suspension in liquid (e.g. water, milk, fruit juice, fruit punch) or in semi-solid food (e.g. yogurt, pudding, or applesauce).

Distribution: The volume of distribution (Vz) is reported to be 672 mL/kg.

Metabolism: Ataluren is mainly metabolized by UDP-glucuronosyltransferase (UGT) 1A9 isoform to generate an aryl glucuronide conjugate.

Elimination: The mean terminal half-life ($t_{1/2}$) in the plasma is about 4 h. It is mainly excreted in the urine as aryl glucuronide conjugate that is not considered active. Urinary excretion of intact ataluren represented only a small fraction of the dose (0.2%).

3.3 Clinical Pharmacology Review Questions

3.3.1 To what extent does the available clinical pharmacology information provide pivotal or supportive evidence of effectiveness?

The available clinical pharmacology information (i.e., exposure-response analyses from Study 007 and dystrophin expression in cultured myotubes from Study 004) do not support the reported differences in efficacy between 80 mg/kg vs 40 mg/kg daily doses in Study 007. The applicant states that findings from Study 007 and Study 004 provide supportive evidence of effectiveness towards the approval of ataluren. However, the review team does not agree with these findings. The major reasons for these conclusions are :

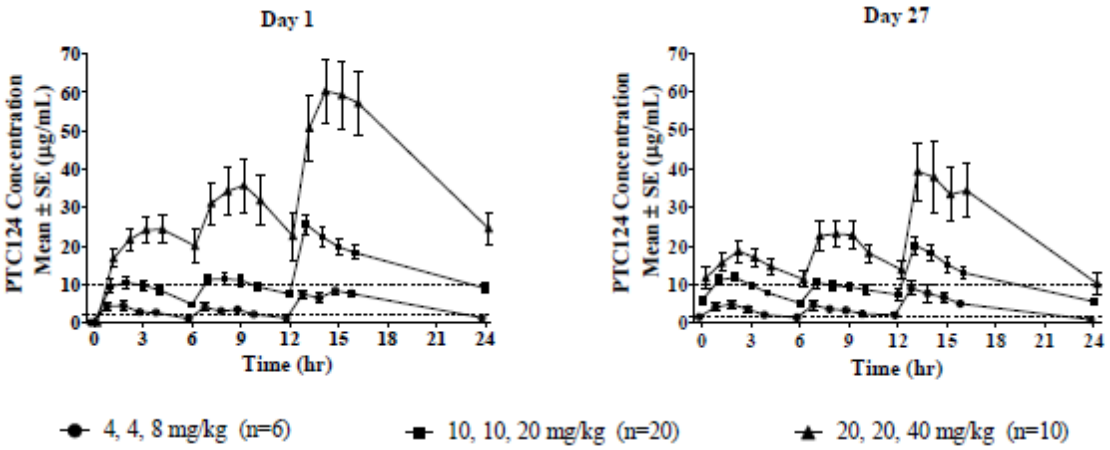
- Imbalances in the baseline clinical condition between the ataluren high and low concentration groups in Study 007 (Patients with 2h post-dose concentrations greater than 19.3 μg/mL were classified as having "high" concentrations. Patients with 2h post-dose concentrations less than or equal to 19.3 μg/mL were classified as having "low" concentrations). Less efficacy was noted in patients with "high" concentrations relative to those with "low" concentrations (**Figure 8**). However, upon examination of the baseline clinical condition between the two concentration groups (i.e., high vs. low), it was observed that patients classified as having "high" concentrations took a longer time to rise compared to those with "low" concentrations and thus had a greater likelihood of losing ambulatory capacity(**Table 1**) relative to those with "low" concentrations. Given the sample size (N~50 per group) from Study 007 and the reported multiple prognostic factors likely to influence the ambulatory capacity in DMD patients, it is not possible to adequately balance various prognostic factors between the concentration groups for exposure-response analyses. Exposure-response analyses without adequate balance of prognostic factors across the concentration groups cannot be interpreted properly.
- Among the various studies the applicant presented to support a bell-shaped dose response, only the in vitro study using myotube cultures from DMD patients (Study 004) may suggest such a relationship. However, this study has multiple intrinsic problems. These include a lack of adequate dystrophin quantification, irregularities in immunofluorescence methods and results, and the immature status of the cultured cells in vitro. These issues call for additional and higher quality data to determine if the dose response relationship is real or simply an artifact of poorly designed experiments. Most importantly, in vivo data from the same set of patients did not corroborate the observed dose response in vitro. Taken together, the applicant did not present unequivocal evidence supporting bell-shaped dose response in the studies evaluated.

The subsequent sections provide more detailed description for the findings discussed above.

An open label Phase 2a study (Study 004) in DMD patients evaluated whether ataluren (16, 40 and 80 mg/kg administered as 4/4/8, 10/10/20 and 20/20/40 mg/kg, respectively) could safely provide clinical activity at concentrations that spanned the range of pharmacodynamic activity seen in nonclinical pharmacology studies (>2 to 10 μg/mL) and that had been well tolerated in previous studies in healthy volunteers.

Study 004 showed that the target plasma concentrations (>2 to 10 μg/mL) were achieved with 40 mg/kg (10/10/20 mg/kg) dose (**Figure 2**).

Figure 2. Ataluren plasma concentrations over time in Study 004

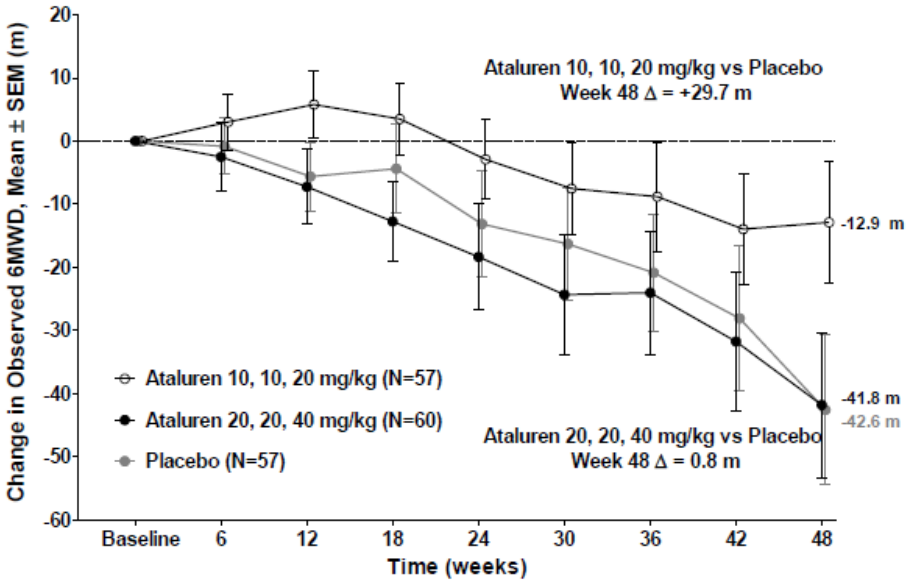


Source : From the applicant (Page 73 in report for Study 004)

The mean C_{min} (SD) on day 27 after 40 and 80 mg/kg daily doses was 3.49 (1.82) and 7.07 (3.87) µg/mL. The variability (%CV) in C_{min} was approximately 50%. Similar estimate of variability was observed for C_{max}.

In a subsequent randomized, double blind, placebo controlled Phase 2b study (Study 007), the applicant evaluated efficacy and safety of two dose levels (40 and 80 mg/kg/day) along with placebo in 174 patients. Study 007 showed that the changes in 6MWD (6-minute walking distance) in patients treated with 80 mg/kg dose were similar to those treated with placebo. However, patients treated with 40 mg/kg dose did better than placebo. The applicant characterized this as "inverted U shaped" dose response where the high dose is worse than low dose (**Figure 3**, **Figure 4**).

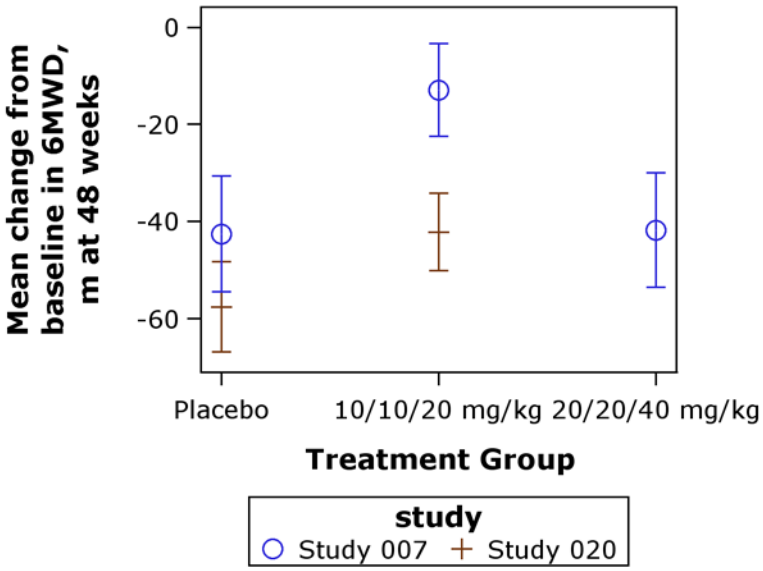
Figure 3. Mean change in observed 6MWD by visit (ITT) in Study 007



Source : From the applicant (Page 90 in report for Study 007)

The trends in 6MWD from Study 007 favored further evaluation of 40 mg/kg dose in patients defined as being in "ambulatory decline phase" in further studies. An ambulatory decline phase subgroup was identified as: ≥7 to ≤16 years old, ≥150 m 6MWD but ≤80%-predicted 6MWD at baseline, and on a stable dose of corticosteroids. For more discussion on this subgroup, please refer to the review by Dr. Veneeta Tandon the Division of Neurology Products, CDER. Based on the findings from Study 007, the applicant evaluated the efficacy and safety of 40 mg/kg in a randomized, double blind, placebo controlled phase 3 study (Study 020). **Figure 4** shows the changes in 6MWD from Study 007 and 020.

Figure 4. Dose response of ataluren for 6MWD (Mean±SE) at 48 weeks in Studies 007 and 020. 40 mg/kg dose is labeled as 10/10/20 mg/kg and 80 mg/kg dose is labeled as 20/20/40 mg/kg. Study 020 included only 10/10/20 dose level.



Source : Reviewer's Analysis

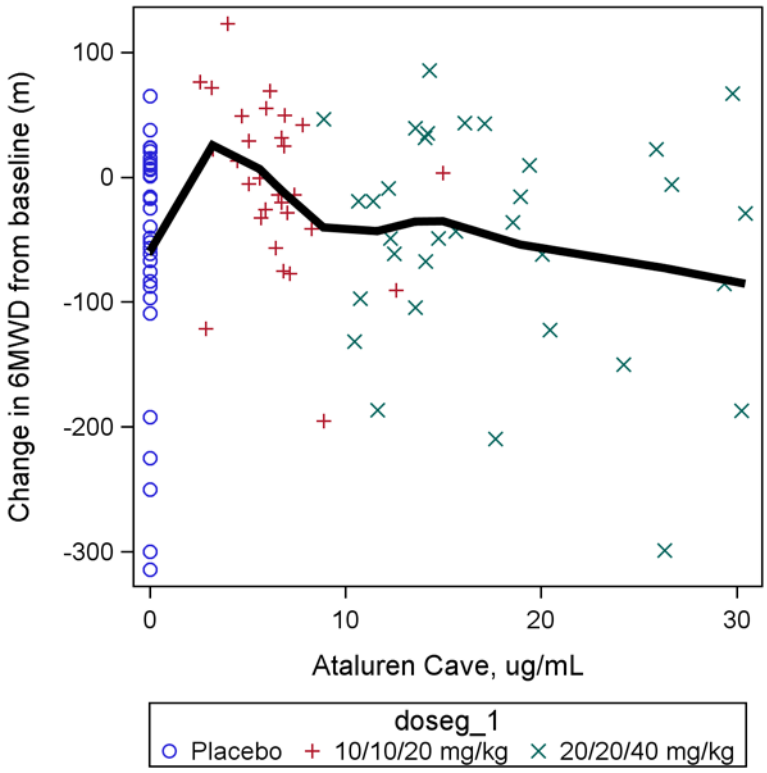
Study 020 had larger sample size (~115 subjects/arm in Study 020 vs. ~57 subjects/arm for Study 007)but similar duration as Study 007. The aim of Study 020 was to enroll as many patients as possible in the "ambulatory decline phase" as observed from Study 007. The results from Study 020 were not in line with the expectations from Study 007. For more details, please refer to the review by Dr. Xiang Ling (Office of Biostatistics, CDER). To provide additional support for approval of 40 mg/kg dose, the applicant analyzed the link between blood levels of ataluren and clinical endpoints which will be discussed below.

Exposure-response analyses based on average steady state ataluren concentrations

The applicant conducted exposure-response analyses to describe the data from Study 007 with the aim of providing additional support towards a potential approval for 40 mg/kg dose. It should be noted that exposure-response analyses was not conducted for Study 020. The applicant collected blood levels of ataluren in Study 007 and conducted model based analyses that described the natural progression of 6MWD and the lesser effect at 80 mg/kg dose relative to 40 mg/kg dose using a bell-shaped two-binding site model. The exposure metrics chosen by the applicant include average steady state concentrations (C_{ave}) or concentrations at 2-hour post dose (C_{2h}). These were derived using a population pharmacokinetic model.

Figure 5 shows the relationship between change from baseline 6MWD at 48 weeks and estimated C_{ave} (calculated as $AUC_{0\text{-}24hr}/24$) along with a trend line in Study 007.

Figure 5. Observed change in 6MWD relative to baseline versus ataluren C_{ave} in Study 007. Shown in the graph (solid black line) is the trend line.



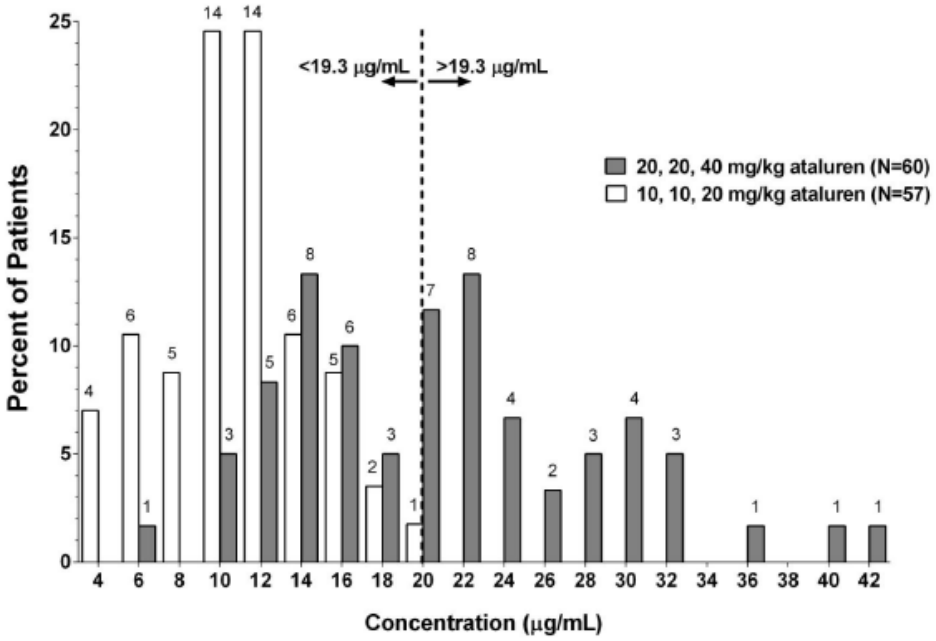
Source : Reviewer's Analysis

The applicant concluded that the maximal ataluren effect is predicted to occur at an ataluren C_{ave} of 4.15 µg/mL. The range of ataluren C_{ave} values in this "inverted U shaped" exposure-response relationship within which at least 50% of the maximal effect is achieved was predicted to be 0.97 to 17.6 µg/mL, respectively. Per the applicant, the analysis suggested that patients should be maintained at concentrations below 18 µg/mL to achieve benefit with ataluren.

Exposure-response analyses based on 2-hour (C_{2h}) post-dose ataluren concentrations

Figure 6 shows the range of ataluren concentrations at 2-hour post-dose (C_{2h}) in 40 and 80 mg/kg dose groups. Data at 2-hour post-dose at various visits was available from each patient. The applicant calculated the mean C_{2h} across visits in each patient and used this estimate in exposure-response analyses.

Figure 6. Ataluren plasma concentration at 2-hour post-dose (C_{2h}), distribution by dosage in Study 007



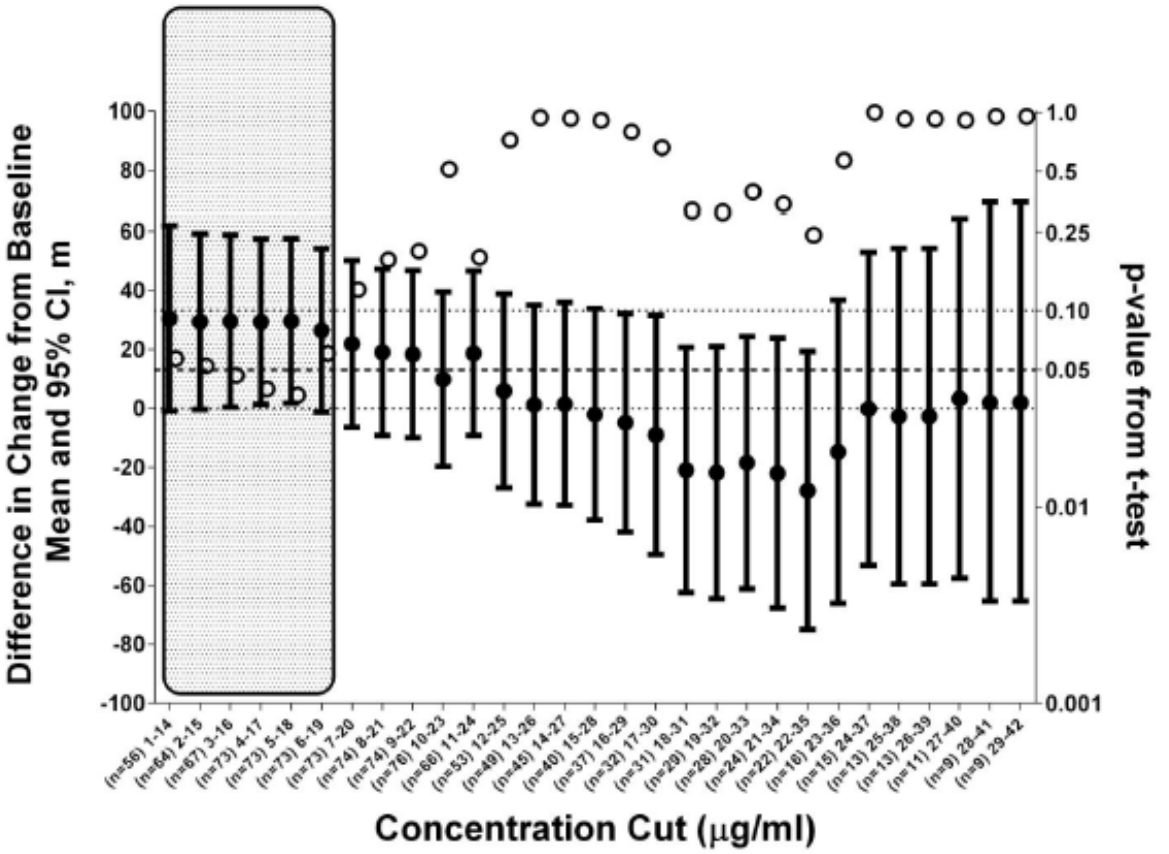
Each bar represents a range of y-axis values, with the number shown being the middle of the range and the upper bound of each interval not included (4 is the middle of the range from 3 to <5, 6 is the middle of the range from 5 to <7, etc).

Source : From the applicant (Page 133 in report for Study 007)

A moving concentration analysis was performed comparing the changes in 6MWD of patients within a range of C_{2h} intervals versus the placebo group in Study 007 (**Figure 7**). Per the applicant, when patients with mean C_{2h} above 19 µg/mL were included, the mean changes progressively decreased (left Y-axis) and p-values worsened (right Y-axis),

indicating that a mean C_{2h} of 19 µg/ml appears to be an inflection point in the concentration response.

Figure 7. Concentration interval analysis of 6MWD results (cITT) from Study 007



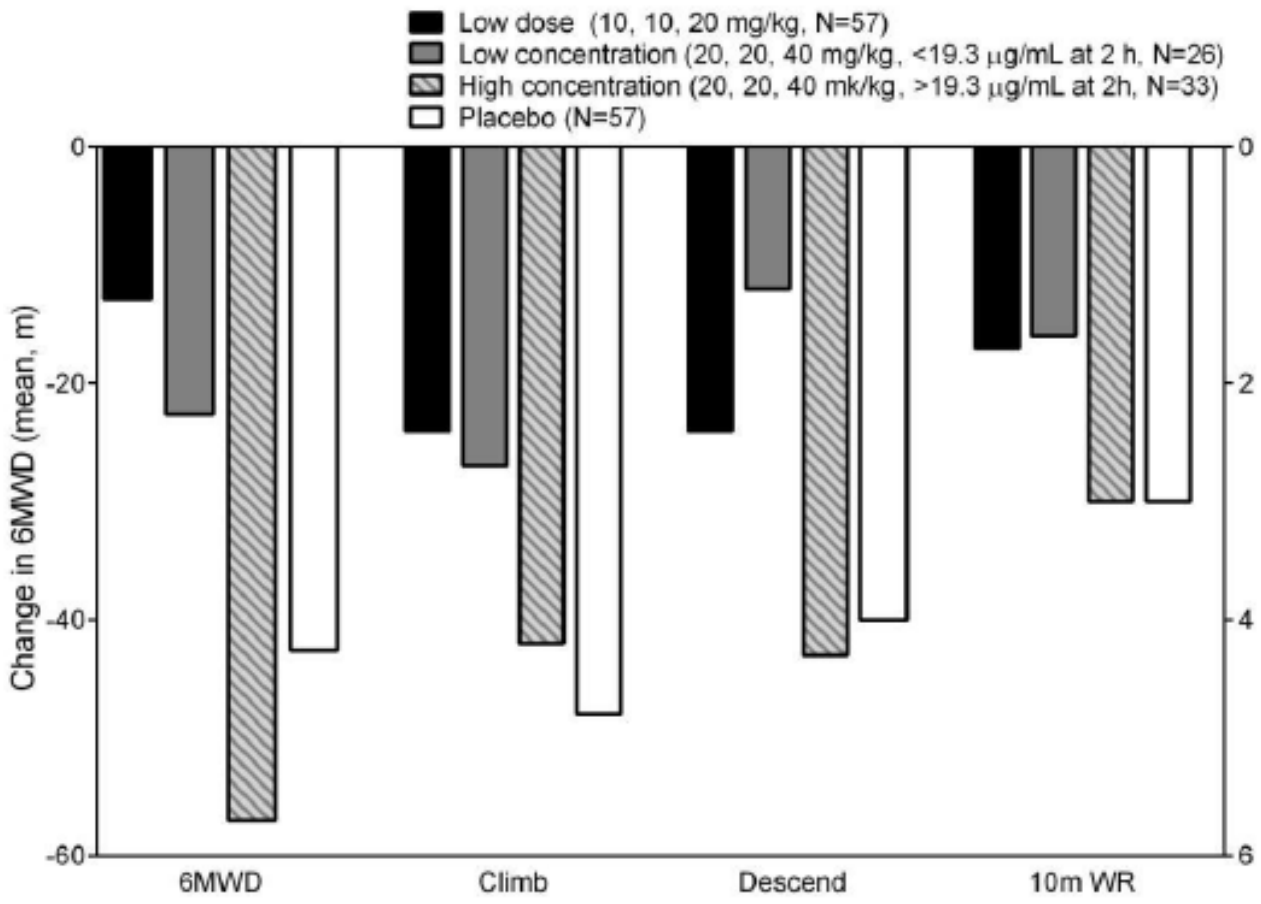
Moving concentration interval analysis of 6MWD data from Study 007. Graph of mean difference in change from baseline versus placebo for 6MWD (solid circles, left axis) as a function of mean 2-hour concentration (C2h) interval. For example, the first data points on the left represent the mean difference in change of 6MWD between patients with mean 2-hour ataluren concentration between 1 and 14 µg/ml versus the placebo group. The next data points are the comparison of patients with mean 2-hour ataluren concentrations between 2 and 15 µg/ml versus the placebo group. Corresponding p-values for each comparison are represented by open circles (right axis). The grey box, covering the range from (1 through 19 µg/ml) indicates the intervals over which the greatest benefit is observed and p-values are close to 0.05.
Abbreviation: cITT = corrected intent-to-treat

Source : From the applicant (Page 134 in report for Study 007)

The applicant also conducted analyses using a cut-off based on mean C_{2h} levels in Study 007. The cut-off was chosen as 19.3 µg/mL. **Figure 8** showes the analyses of 6MWD and timed function tests (TFTs) by mean C_{2h} of ataluren. Per the applicant, the analyses of 6MWD and TFTs by mean C_{2h} revealed that patients in 80 mg/kg (20/20/40 mg/kg) dose group with lower concentrations responded better compared to patients in 80 mg/kg (20/20/40 mg/kg) dose group with higher concentrations. Also, per the applicant, changes in the clinical endpoints in 80 mg/kg (20/20/40 mg/kg) dose group with lower

concentrations were similar to those seen in 40 mg/kg (10/10/20 mg/kg) dose group, thus providing support for the approval of 40 mg/kg dose in all patients.

Figure 8. Mean change in 6MWD and timed function tests (TFTs) in ataluren groups by mean C2h ≤19.3 µg/mL vs >19.3 µg/mL in Study 007



Source : From the applicant (Page 132 in report for Study 007)

To better understand the applicant's position on 40 mg/kg dose, the reviewer conducted analysis of the data from Study 007. The aim was to understand potential imbalances in baseline factors that could result in "inverted U shaped" dose response.

Possible imbalances in baseline factors that could result in "inverted U shaped" dose response.

While the applicant utilizes findings in **Figure 8** as supportive evidence of effectiveness, information on potential imbalances that could have contributed to differences in changes in clinical endpoints between ataluren concentration groups was not provided. The reviewer conducted analyses and the findings suggest that the baseline values of 6MWD and TFTs (Climb, Descend and 10 m Walk-Run (WR)) of patients in "High concentration (20,20,40 mg/kg =>19.3 ug/mL at 2h)" are different from other groups (**Table 1**). Reports in literature suggest that patients with such baseline state of disease condition would lose ambulation sooner than others. For example, **Table 1** shows that the mean baseline 6MWD in "High Concentratrion (20,20,40 mg/kg, =>19.3 μg/ml)" group is 333 m which is about 60-m less than for "Low Concentration(20,20,40 mg/kg, <19.3 μg/ml) group. This could be a reason for the differences in change in 6MWD between the two groups as shown in **Figure 8**. Similar differences are also seen for TFTs (Climb, Descend and 10 m WR). These findings suggest that the differences in ataluren concentrations between various groups is not the primary reason for lesser effect with 80 mg/kg dose relative to 40 mg/kg dose (**Figure 4**).

Table 1. Summary of baseline clinical endpoints by treatment and/or concentration groups in Study 007

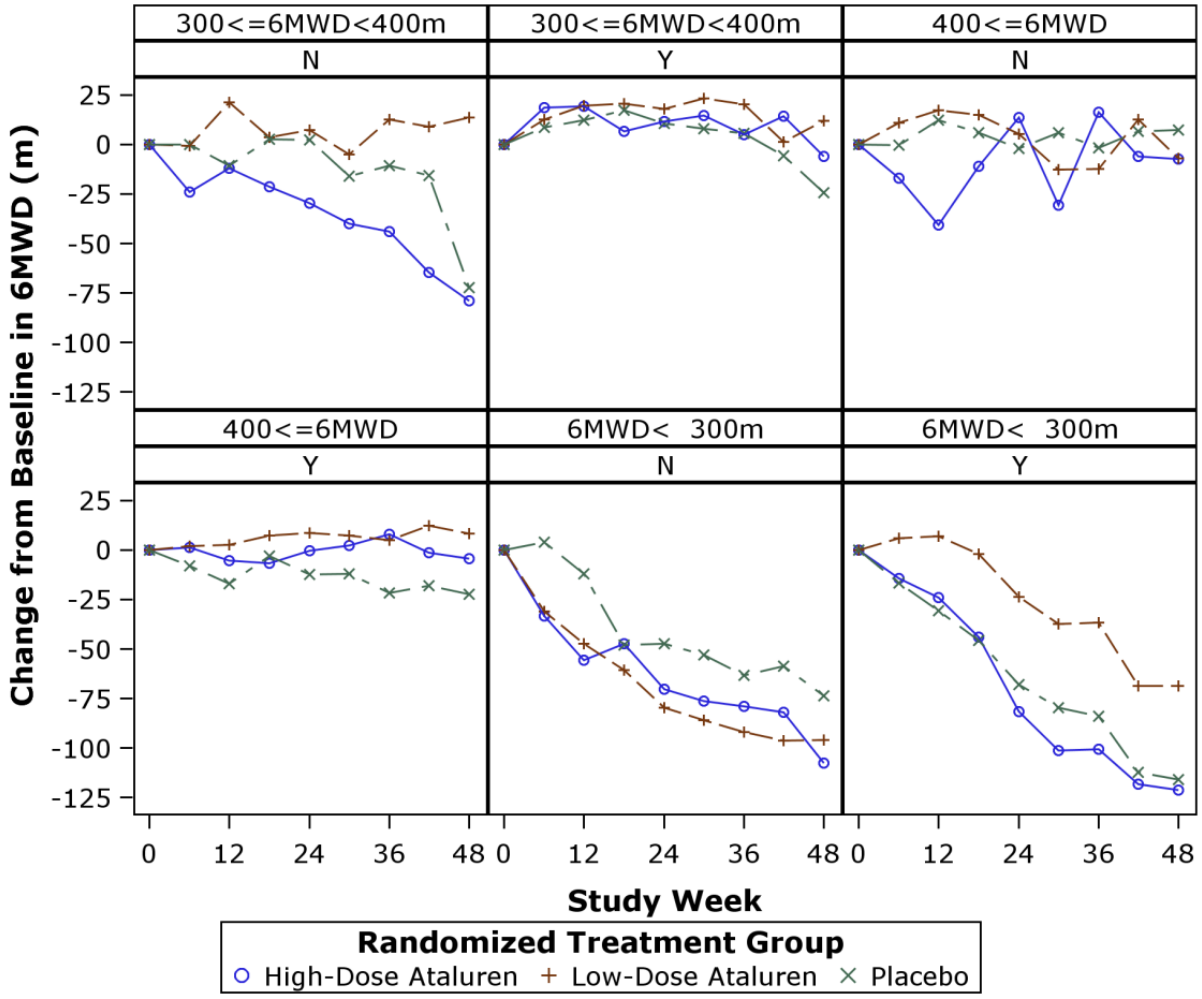
	Baseline Time(s) to Descend 4 Stairs		Baseline Time(s) to Climb 4 Stairs	Baseline Time(s) Taken to Walk/Run 10m	Baseline Time(s) to Rise from Supine	6 Minute walk Distanc at Baseline (m)	Age at Baseline
	N	Mean	Mean	Mean	Mean	Mean	Mean
High Dose (20/20/40 mg/kg) High Concentration =>19.3 ng/mL	30	8.53	10.25	9.66	15.63	332.91	9.23
High Dose (20/20/40 mg/kg) Low Concentration <19.3 ng/mL	29	4.97	5.05	5.94	9.04	391.09	7.53
Low Dose 10,10,20 mg/kg	57	6.08	6.94	7.45	10.80	355.59	8.77
Placebo	56	5.53	6.02	6.81	11.36	361.52	8.32
All	172	6.14	6.90	7.37	11.53	359.59	8.49

Source : Reviewer's Analysis

Considering the observation that baseline factors could have contributed to the findings shown in **Figure 8**, the reviewer conducted additional analyses and calculated mean change in 6MWD by baseline 6MWD (<300, 300-400 m, ≥400m) and steroid use (Y/N) in

Study 007 (**Figure 9**). These factors were selected since they are reported by the applicant as important predictors of disease progression.

Figure 9. Mean change in 6MWD by week in Study 007. Shown are mean changes by dose group (Low-Dose: 40 mg/kg, High-Dose: 80 mg/kg) stratified by baseline 6MWD and steroid use (Y/N)



Source : Reviewer's Analysis

The findings, based on reviewer's analysis, are shown in **Figure 9** and suggest that on average:

1. Patients with <u>6MWD ability between 300-400m</u> at baseline and <u>not taking steroids(N)</u> show <u>more effect at 48 weeks in 40 mg/kg</u> group compared to placebo and 80 mg/kg.

2. Patients with 6MWD ability between 300 and 400m at baseline and taking steroids (Y) show no differences between 40 mg/kg, 80 mg/kg and placebo groups.

3. Patients with 6MWD ability less than 300 m at baseline and taking steroids (Y) show more effect in 40 mg/kg group compared to placebo and 80 mg/kg. However, patients with 6MWD ability less than 300 m at baseline and not taking steroids (N) in the placebo group show more effect than both ataluren groups.

The findings, discussed above, show inconsistent effects of ataluren in various subgroups and make the observed differences between 40 and 80 mg/kg treatment groups, less credible. Further analyses were conducted to rule out differential effects due to differences in ataluren concentrations across subgroups shown in **Figure 9**. **Table 2** shows the mean ataluren concentrations (across 24, 30, 36, 42 and 48 weeks in Study 007) at 2 h post-dose (C_{2h}) by subgroups, as shown in **Figure 9**. **Table 2** shows that the ataluren concentrations (C_{2h}) are similar across various subgroups shown in **Figure 9**, thus ruling out any differential effects due to differences in ataluren concentrations.

Table 2. Ataluren concentrations (2-hour post dose, C2h) by randomized treatment group, corticosteroid use and baseline 6MWD category

			Mean C2h (µg/mL)	
			N	Mean
Randomized Treatment Group	Corticosteroids Used	Baseline 6MWD		
High-Dose Ataluren (20/20/40 mg/kg)	N	300<=6MWD<400m	9	17.99
		400<=6MWD	3	25.03
		6MWD< 300m	5	24.16
	Y	300<=6MWD<400m	12	19.73
		400<=6MWD	20	18.91
		6MWD< 300m	10	22.79
Low-Dose Ataluren (10/10/20 mg/kg)	N	300<=6MWD<400m	4	15.15
		400<=6MWD	6	11.60
		6MWD< 300m	6	10.25
	Y	300<=6MWD<400m	18	10.66
		400<=6MWD	14	10.09
		6MWD< 300m	9	13.38

Source : Reviewer's Analysis

Pre-dose levels of ataluren, from patients treated with 40 mg/kg dose, were compared across Study 020 and Study 007 to rule out potential study outcome differences due to differences in PK. **Table 3** shows that the pre-dose levels of ataluren between studies are similar, thus ruling out any study differences due to different blood levels of ataluren.

Table 3. Ataluren pre-dose concentrations for 40 mg/kg dose group by study

	Pre-dose Conc. (µg/mL)		
	N	Mean	Median
Study 007	57	4.54	3.82
Study 020	110	3.54	2.31

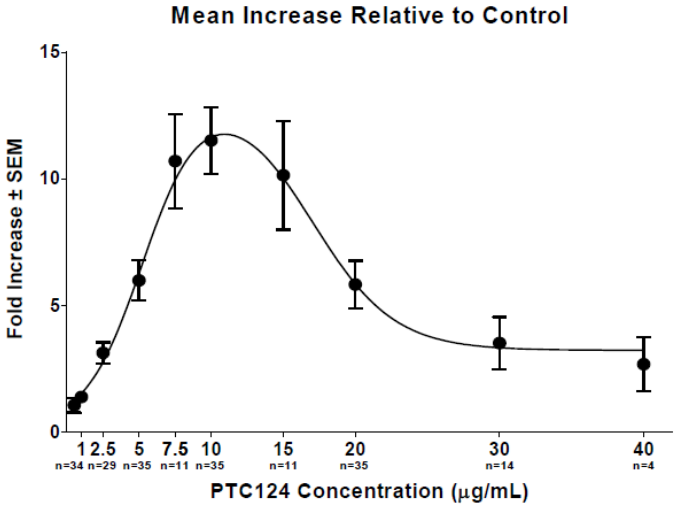
Source : Reviewer's Analysis

Non-clinical and in vitro data from the applicant regarding the bell-shaped dose response of ataluren

The applicant also provided information on dystrophin expression in cultured myotubes from patients in Study 004. The intent was to further support the "inverted U" shaped dose and concentration response in Study 007.

Per the applicant, pretreatment primary muscle cells from 35 of the 38 patients were available for *in vitro* myotube culture in Study 004. When cultured *in vitro* in the presence of ataluren at concentrations ranging from 0.5 to 20 µg/mL, 35 of the 35 pretreatment muscle biopsy samples (100%) showed evidence of an increase in dystrophin expression, suggesting the potential for nonsense mutation suppression in all patients. Peak dystrophin expression was observed at 5 µg/mL in myotubes from 7 of 35 (20%) patients, at 10 µg/mL in myotubes from 21 of 35 (60%) patients, and at 20 µg/mL in myotubes from 7 of 35 (20%) patients (**Figure 10**).

Figure 10. In Vitro dystrophin expression concentration-response in cultured myotubes from phase 2a study of ataluren (PTC 124) in DMD patients



Source : From the applicant (Page 66 in report for Study 004)

In addition, for all 38 patients in Study 004 *in vivo* dystrophin expression measured in clinical biopsies before and after ataluren treatment are also available. The reviewer in DARS (Division of Applied Regulatory Sciences, OCP) looked into the *in vitro* and *in vivo* dystrophin measurement data in Study 004, as well as a seires of animal models presented by the applicant that could provide mechanistic basis for a therapeutic concentration window that could result in umbrella shaped dose-response.

Detailed evaluation of the evidence presented by the applicant suggests that some of the studies were not scientifically sound or were of limited relevance. The only *in vitro* study that may suggest such a bell-shaped dose response has intrinsic problems and thus needs independent verification. More importantly, this observed dose response relationship *in vitro* is not corroborated by the *in vivo* study using the same set of patients. Taken together, the applicant did not present strong evidence of a biologically or clinically meaningful bell-shaped dose response for ataluren in DMD.

Overall Comments

After review of the evidence submitted by the applicant, OCP reviewers do not consider the exposure-response analyses and *in vitro* data as supportive evidence of effectiveness.

APPENDICES

APPENDIX A

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 200896

REFUSAL TO FILE

PTC Therapeutics, Inc.
Attention: Manal Morsy, M.D., Ph.D, M.B.A.
Vice President, Regulatory Affairs
100 Corporate Court
South Plainfield, NJ 07080

Dear Dr. Morsy:

Please refer to your March 31, 2011, New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for TRANSLARNA (ataluren) Granules 125 mg, 200 mg, 325 mg, 400 mg, 500 mg.

After a preliminary review, we find your application is not sufficiently complete to permit a substantive review. Therefore, we are refusing to file this application under 21 CFR 314.101(d) for the following reasons:

We are refusing to file this application because on its face it does not contain information required under section 505(b) of the Federal Food, Drug, and Cosmetic Act, as described in 21 CFR 314.101. Specifically, the application does not contain substantial evidence of effectiveness. By the usual statistical standards, the single controlled trial supporting this application, PTC1124-GD-007-DMD, is clearly and convincingly negative. Although you have performed numerous additional analyses of the trial, these analyses, besides being post hoc and not obviously more appropriate than the protocol-specified analyses, clearly do not reach statistical significance for any dose-placebo comparison, when taking into account any reasonable adjustment for multiple comparisons. Likewise, by an approach considering the totality of evidence, on its face the application does not contain substantial evidence of effectiveness. It is clear to us that this application cannot be approved based on the data submitted.

Within 30 days of the date of this letter, you may request in writing a meeting about our refusal to file the application. To file this application over FDA's protest, you must avail yourself of this informal conference.

If, after the meeting, you still do not agree with our conclusions, you may request that the application be filed over protest. In that case, the filing date will be 60 days after the date you requested meeting.

If you have any questions, contact Stephanie N. Keefe, Regulatory Project Manager, at (301) 796-4098.

Sincerely,

{See appended electronic signature page}

Russell Katz, MD
Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

RUSSELL G KATZ
05/26/2011

APPENDIX B

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 200896

MEETING MINUTES

PTC Therapeutics, Inc.
Attention: Manal Morsy, M.D., Ph.D, M.B.A.
Vice President, Regulatory Affairs
100 Corporate Court
South Plainfield, NJ 07080

Dear Dr. Morsy:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for TRANSLARNA (ataluren) Granules.

We also refer to the meeting between representatives of your firm and the FDA on July 19, 2011.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, contact Stephanie N. Keefe-Parncutt, Regulatory Project Manager, at (301) 796-4098.

Sincerely,

{See appended electronic signature page}

Russell Katz, MD
Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURE:
Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type C
Meeting Category: Informal Meeting

Meeting Date and Time: July 19, 2011; 9:00 – 10:00 AM EST
Meeting Location: CDER WO Room 1311

Application Number: 200896
Product Name: TRANSLARNA (ataluren) Granules
Indication: **Treatment of Nonsense Mutation Dystrophinopathy**
Sponsor/Applicant Name: PTC Therapeutics, Inc.

Meeting Chair: Russell Katz, M.D.
Meeting Recorder: Stephanie N. Keefe-Parncutt

FDA ATTENDEES
Russell G. Katz, M.D.
Ron Farkas, M.D., Ph.D.
Chris Breder, M.D., Ph.D.
Xiang Ling, Ph.D.
Tristan Massie, Ph.D.
Jeff Fritsch, R.Ph.
Martha Heimann, Ph.D.
Tony El Hage, Ph.D.
Angela Men, M.D., Ph.D.
Laurie Kelley, PA-C
Tien Mien Chen, Ph.D.
Patrick Marroum, Ph.D.
Anne Pariser, M.D.
Stephanie N. Keefe-Parncutt

SPONSOR ATTENDEES
Stuart Peltz, Ph.D.
Manal Morsy, M.D., Ph.D., MBA
Rose Gao, M.S.
Robert Spiegel, M.D.
Jay Barth, M.D.
Craig McDonald, M.D.
Gary Koch, Ph.D.
Gary Elfring, M.S.
Jethro Ekuta, DVM, Ph.D., RAC, FRAPS
Paul Ambrose, Pharm.D., FIDSA
Nicolas Lamontagne, R.Ph., M.S.
Allen Reha, B.A.

Reference ID: 3018333

BACKGROUND

Reference is made to the Refuse to File correspondence dated May 26, 2011, regarding the ataluren granules 125 mg, 200 mg, 325 mg, 400 mg, and 500 mg for NDA 200896, submitted on March 31, 2011. PTC Therapeutics requested a face-to-face meeting to discuss the Division's decision, as offered in the Refuse to File communication. In addition to the Meeting Minutes provided, from our face-to-face meeting, Dr. Katz informed the company that our review team would meet internally to discuss the company's arguments further. The comments from our internal discussions are provided, at the end of the minutes, as well.

2. MEETING MINUTES

The Meeting began with the Sponsor expressing their views on the importance of finding an effective drug for the treatment of the population studied in the development program. They commented that from their perspective several of the secondary outcomes and sensitivity analyses showed a trend toward demonstrating some drug effect. The Division replied that it was most appropriate to talk about next steps, because the study [-007] was not positive by the protocol specified primary outcomes and analyses, and the additional analyses provided by the sponsor recently, though of interest, were not considered to be sufficiently persuasive. This was especially problematic, given that the sponsor proposed that this single study be the sole support for approval of the application. To satisfy this condition, the trial would have had to have been robustly positive with supporting data reinforcing this finding. Another trial could be informed from the results of -007, as well as other data gained from the development program

The Sponsor replied that they felt ataluren was a well tolerated drug with the low dose showing signs of efficacy. They asserted that there are few patients that may be studied and this could delay our consideration for several years. Dr Katz replied that by stating -007 was "negative", he was not implying that there may not be some supportive evidence of drug effect, but rather that the support provided did not rise to the threshold generally used to consider a study to be 'positive'. He further asserted that from the Division's perspective, the secondary measures did not support the Sponsor's claim of effectiveness. He then inquired as to whether the Sponsor had considered a trial design such as a randomized withdrawal study, considering the number of available patients and the natural history of the disease. The Sponsor commented that they had but were concerned of potential ethical and practical issues with this design.

The conversation then shifted to a consideration of Dr Koch's recommendations for the post-hoc analysis. Dr Koch began with explaining his logic for this alternative analysis.

- First, he stated that the interaction of baseline by visit should be included in the MMRM model; the reason being that he believed including this interaction has become standard practice and the result of the refined MMRM model is consistent with the pre-specified ANCOVA on LOCF Week 48 changes from baseline.

Reference ID: 3018333

- Second, he remarked that the permutation test can be used to address the issue of departure from normality. The permutation test is a pre-specified sensitivity analysis for dynamic randomization.

- Thirdly, he commented that the two cases that the Sponsor considered having invalid baseline values needed to be corrected.

As a general response to Dr Koch's comments, Dr Katz noted that the original primary analysis was deemed reasonable by both the Division and the Sponsor and short of a fundamental flaw in this plan, our practice is to consider the prespecified analysis as primary. The statistical reviewer of the Division made three specific responses to Dr. Koch's remarks:

- To the first issue, one should look at rank data because the normality assumption of the MMRM is not satisfied. The interaction term was not statistically significant in the MMRM model on rank data. The results are almost the same with or without the interaction term.

- In the second issue, Dr. Koch recommended using the permutation test to address the issue of non-normality. However, this permutation test is different from the protocol-specified permutation test. The protocol-specified permutation test is to assess the sensitivity of the primary analysis to dynamic randomization; therefore, it should be based on the ranked data. Additionally, the permutation test may not control the type I error rate. The null hypothesis is "no difference" between the average 6MWDs. However, the permutation test requires the distributions of 6MWD to be identical when the null hypothesis is true —not only the same means, but also the same spreads and shapes. The sponsor acknowledged that even with the permutation test analysis, the multiplicity adjusted significance level was not attained.

- To the third issue, the two patients with invalid baseline value should be included in the analysis according to the ITT principle. Patients with protocol deviations may be excluded in the analysis on the per-protocol population (PP). Patients excluded from the PP population should be determined prior to unblinding the data. The analysis excluding the two patients identified after unblinding is regarded as a post-hoc sensitivity analysis.

In later discussions, there was a disagreement on whether the use of the baseline by visit interaction made the "refined" MMRM analysis in one aspect closer to a completer's analysis.

The Sponsor asked about whether their endpoint, 6MWD, could be used in a trial under Subpart H. Dr Katz replied that this would not be appropriate since the 6MWD was a clinical endpoint.

The Sponsor then commented that they were performing exposure response analyses with subjects on the high dose paradigm and they asked if this would be acceptable as evidence. Dr Katz replied that he could not know the answer at this point. He concluded the meeting by suggesting that the Sponsor consider what sources of evidence could augment an additional trial.

Reference ID: 3018333

He also explained that the Sponsor could file over protest. Further information regarding this course of action is found at 21 CFR 314.101(a)(3).

The Sponsor concluded by inquiring if they could assemble the materials from their most recent submission and ongoing analyses for consideration in a meeting later. The Division stated that they would consider a future meeting regarding how to proceed with the program.

Subsequent to the meeting with the sponsor, the Division review team met with the Director of the Office of Drug Evaluation I. The sponsor's submissions sent after the RTF action were reviewed and discussed. There was agreement among all parties that all of the data, taken together, could not support approval, and that a re-submission of the application would result in another RTF action. It was clear that Agency staff felt that a second study, adequately designed, could, and should, be performed. If such a study were robustly positive, it, in conjunction with the study already performed, might support approval of the application.

In a telephone call subsequent to this internal meeting, Dr. Katz transmitted this message to the sponsor. Specifically, he stated that the results of the first study clearly did not, in any way, establish that the drug is not effective, only that it did not establish the effectiveness of the drug. He acknowledged that there were certain findings in that study that perhaps suggested a drug effect, despite the conclusion that the study, by itself, could not support approval. He again transmitted the Agency's view that a second study, appropriately designed and conducted, if robustly positive, in conjunction with the first study, might be the basis for a subsequent approval.

Reference ID: 3018333

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/s/

RUSSELL G KATZ
09/23/2011

APPENDIX C

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 200896

DISPUTE APPEAL - RESPONSE

PTC Therapeutics, Inc.
Attention: Manal Morsy, M.D., Ph.D., M.B.A.
Vice President, Regulatory Affairs
100 Corporate Court
South Plainfield, NJ 07080

Dear Dr. Morsy:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ataluren granules.

We also refer to your December 22, 2011, request for formal dispute resolution, received on December 23, 2011. Your request for dispute resolution concerns two issues. One is the refuse to file (RTF) action taken on this application on May 26, 2011, because the application was not considered to, on its face, contain substantial evidence of effectiveness, together with a conclusion in minutes of a meeting held on July 19, 2011 that an updated version of the NDA would not be filed for full review. You also have appealed the conclusion in the minutes of the July 19, 2011, meeting that NDA 200896 is not eligible for accelerated approval under Subpart H of 21 CFR 314. Specifically, you request:

1) that PTC be allowed to resubmit NDA 200896 with the updated new information and analyses that were presented to the Division of Neurology Products (DNP) at a July 19, 2011, meeting and that you believe support the effectiveness of ataluren in the indicated patient population;

2) that DNP accept NDA 200896 for filing after resubmission and that the submission receive a full review and presentation to an FDA advisory committee; and

3) that the resubmitted NDA 200896 be considered for accelerated approval under Subpart H.

I have reviewed the materials you submitted in support of your appeal, the May 26, 2011, refuse to file letter, the materials submitted as background for the July 19, 2011, meeting between PTC Therapeutics, Inc. and the Division of Neurology Products, and the minutes of the July 19, 2011, meeting. I have also met with DNP to discuss your submission and the issues you have raised.

Your fundamental contention is that RTF is limited to situations in which a critical element of the application is missing and is not appropriate where there is concern about the adequacy or meaning of study findings or quality, which are review issues. For reasons I will provide below, I believe it was appropriate to refuse to file NDA 200896 for ataluren granules on the basis of data presented in the application. If further data and analyses were to be offered in a

resubmission, however, that resubmission would be considered for filing. I cannot say at this time whether we would file the resubmitted NDA, but I do not support the division's conclusion that it definitely would not be filed. I also conclude that at present there is no basis for an accelerated approval of the initial or resubmitted application. The basis for these conclusions follows.

Appropriateness of the Refuse to File Action

In your appeal, you assert that the refuse to file decision was inappropriately based on the ability of the data to support ultimate approvability, rather than on the regulatory standard governing filing decisions, and that it was not appropriate for DNP to proceed to a substantive evaluation of the efficacy data in the NDA at the pre-filing stage, because such evaluations are appropriate only after an NDA is accepted for filing. You note that, under 21 CFR 314.101(d)(3), FDA may refuse to file an NDA if it does not "on its face" contain information required under 21 U.S.C. 355(b) and 21 CFR 314.50. You further note that, with respect to efficacy, the "information required under section 505(b)" is limited to "full reports of investigations which have been made to show…..whether such drug is effective in use." You assert that NDA 200896 contains "reports" that satisfy this standard. You further note that the efficacy "information required under… [21 CFR] 314.50" constitutes a description of "the clinical investigations of the drug" and an "integrated summary of the data demonstrating substantial evidence." You note that NDA 200896 describes the clinical investigations of ataluren and summarizes the data and assert that the RTF therefore should not have been issued because the NDA contained the required information and was therefore complete "on its face."

You also refer to FDA's 1993 *New Drug Evaluation Guidance Document: Refusal to File* to support your appeal. You assert that the 1993 guidance makes it clear that lack of evidence of effectiveness provides the basis for a not approvable action, but does not provide the basis for a refuse to file decision. You also assert that even if it were appropriate for DNP to apply this standard in the refuse to file context, the standard would be met by the data that PTC would include in a resubmitted NDA.

The distinction between the conclusions following detailed review of data and an RTF decision is valid. Studies that appeared on their face to support effectiveness might, after review, lead to a conclusion that a drug should not be approved, but an application with such data would be filed. Presentation of only a single study, however, could be a basis for refuse to file and we have always maintained that a study that on its face does not demonstrate effectiveness could be a basis for RTF.

FDA has long asserted that a study can be so clearly not supportive of effectiveness that it can be considered essentially absent. The 1993 guidance describing FDA's policy on refusal to file states that RTF could be based on an advance judgment about what had been shown in a trial, e.g., lack of evidence of effectiveness, as well as failure to show why a single study should be considered sufficient to provide substantial evidence of effectiveness.

Your application did not provide adequate explanation of why the single trial conducted to support this application should be regarded as fulfilling the legal requirement for adequate and

well-controlled investigations when it failed, on its face, to show a significant effect on its specified endpoint. Not only does the study not provide the kind of statistically strong evidence of an effect that would support reliance on a single study, but it is apparent, as is described in greater detail in the following section, that the study did not, on its face, demonstrate a statistically significant finding of evidence of an effect.

Lack of substantial evidence of effectiveness

In this discussion, it is critical to distinguish the contents of your initial submission, which was the basis for our RTF, and the proposed alternative analyses you have submitted. These alternatives could be included in a resubmission and I am not prepared to say that such a resubmission would not be filed. I am thus disagreeing with the conclusion in the minutes of the July 19, 2011, meeting. It is apparent that we have concerns about the revised analyses and I will describe these so that you can address them in a resubmission, but I am concluding that it is premature to say what our decision in response to a resubmission would be. The following discussion describes our concerns.

You dispute the statement in the refuse to file letter that the application lacks substantial evidence of effectiveness. You assert that study PTC124-GD-007-DMD (study 007), the only placebo-controlled efficacy trial included to support this NDA, identified an effective dose and demonstrated clinically meaningful differences in the primary endpoint (6-minute walk distance [6MWD]) and positive trends in the most well-established secondary endpoints (timed function tests).

The statistical analysis plan for study 007 pre-specified a mixed-model repeated-measures (MMRM) analysis for change in 6MWD from baseline to week 48 in the intent-to-treat (ITT) populations. Holm's method of sequential p-value adjustment was used to adjust for comparisons of the two doses tested (referred to here as "low" and "high"). Consequently, for the study to be considered positive, it was necessary for the p-value for either dose to be $\leq$ 0.025.

Essentially no difference in change in the 6MWD primary endpoint was observed for the high dose (p=0.48). For the low dose, the pre-specified MMRM analysis had a p-value of 0.15, i.e., not close to the planned p-value of 0.025. None of the secondary endpoints were even nominally positive, including the "timed function tests" (stair ascend, stair descend, 10-meter run/walk, supine to stand) that you state in your appeal are the most well-established and sensitive of the secondary endpoints in changes in disease status. Therefore, by the usual statistical standards, the study, on its face, was clearly negative, i.e., did not provide substantial evidence of effectiveness, even if one ignores the one study/two study issue.

The primary and secondary efficacy endpoints and statistical analysis plan for study 007 had been discussed extensively at meetings with DNP, including the pre-NDA meeting for this application that was held on November 12, 2009. No efficacy endpoints or statistical analysis obviously more appropriate than those ultimately used for the protocol-specified analysis were identified. In your appeal, however (and as discussed at the July 19, 2011 meeting with DNP),

you assert that because of the lack of regulatory precedent for studies to treat this condition, the pre-specified analysis was, in fact, fundamentally flawed, as follows:

1. An important term (baseline-by-visit interaction) was missing from the pre-specified statistical analysis model.
2. The pre-specified method for addressing non-normality, rank transformation, was not necessary because non-normality is more appropriately addressed by a permutation test, which was already pre-specified as a sensitivity analysis for the effect of dynamic randomization.
3. Two patients had lower limb injuries at baseline that substantially affected their 6MWD.

Although you recognize and acknowledge that post-hoc analyses have inherent limitations, you assert that your proposed post-hoc analysis is scientifically justifiable and more accurately characterizes the results of study 007 and should therefore be considered in determining whether study 007 is plainly non-supportive.

Although DNP considered your arguments for revised analysis at the July 19, 2011, meeting, it must be stressed that the question under consideration was not primarily the specific p-values obtained using the post-hoc analysis, but rather whether there was a clear basis for concluding that the pre-specified analysis was unreasonable and the post hoc analysis clearly represented the appropriate approach. This reflected the well-recognized concern that revised analyses with "data in hand" invariably raise problems of multiplicity and bias and need to be approached with great caution. That noted, however, we would not assert that there can never be a basis for concluding that an analysis plan was defective. DNP found no basis for concluding that the initial plan was unreasonable and the posthoc analysis preferable and discussed the reasons for their conclusions in detail at the July 19, 2011, meeting. As is reflected in the final minutes of the July 19, 2011, meeting, DNP concluded that, even with the knowledge gained about the condition and endpoint during the conduct of the study, the pre-specified analysis was reasonable and the post-hoc analysis is not a clearly more appropriate approach.

In your appeal, you provide additional rebuttal to DNP's rejection of your arguments, as represented in the July 19, 2011, meeting minutes. Although we have not received a resubmission fully explaining those arguments, so that we are offering no final conclusion about them, I believe it will be useful to understand, for use in developing a resubmission, what our concerns are. Our primary concern is that your arguments, even if individually accepted as valid, appear unpersuasive in aggregate. You propose applying simultaneously no less than three essentially unrelated post-hoc adjustments, again with full knowledge of the data, to generate p-values for the primary endpoint that turn out to be just within the range of those normally considered to provide weak statistical support for efficacy, not a level of support suitable for a single study, and a level of support generally interpreted as only high enough to warrant the conduct of additional studies. Even within the set of secondary endpoints that you determined post-hoc to be most likely reflective of efficacy (the timed function tests), all but one of the four remained negative, despite the post-hoc analysis. Given the known potential for introduction of bias through post-hoc adjustments to statistical analyses, these results do not appear, on face, to be persuasive.

Further, in considering these post-hoc analyses, it is appropriate to reconsider the high-dose ataluren arm, which seems in some sense to represent a second study. Clearly, however, the findings for the high-dose arm remain negative, despite post-hoc adjustments to the analysis. You attribute this lack of efficacy to a fourth post-hoc conclusion, plainly not recognized when the study was designed, that the high dose arm could have been predicted to be ineffective based on preclinical studies, and that positive findings in the low dose arm, and the resulting unusual "umbrella-shaped" dose-response curve, were clearly to be expected.

Even if accepted individually, the series of post-hoc adjustments simultaneously necessary to explain the negative findings of study 007 are, on face, difficult to accept as a basis for concluding that study 007 is a positive study, i.e., provides any support at all for effectiveness. I would note that although there may be some merit to excluding from the analysis the two patients with lower limb injuries at baseline that you identified, this measure alone would not lead to a positive finding for study 007. Should you decide to resubmit NDA 200896, these issues will need to be addressed. As noted above, in reaching a filing conclusion we would consider all of the information and arguments presented.

Appropriateness of Accelerated Approval

In your appeal, you assert that the primary endpoint of change in 6-minute walk distance (6MWD) could be used in a trial to support approval under 21 CFR 314 Subpart H – Accelerated Approval of New Drugs for Serious or Life-Threatening Illnesses (accelerated approval), because the change in 6MWD is not an endpoint of "survival or irreversible morbidity." You note that, under accelerated approval, FDA "may grant marketing approval for a new drug product….on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity."

You further assert that the ataluren Phase 2b trial included an analysis of the time to 10% worsening in 6MWD as a surrogate measure for total loss of ambulation and that study 007 also contained other endpoints that would be suitable for accelerated approval. You indicate that FDA has the regulatory authority to determine that any of these endpoints are suitable for approval under 21 CFR 314, Subpart H and grant accelerated approval for ataluren during the NDA review process. You believe that accelerated approval of ataluren would serve the purpose of permitting patient access to ataluren in parallel with PTC's conduct of a second clinical trial.

It is certainly true that under 21 CFR 314, Subpart H, and as explained in FDA's Fast Track guidance, FDA can approve a marketing application on the basis of adequate and well-controlled trials establishing that the drug (or biological) product has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit or on the basis of an effect on a clinical endpoints other than survival or irreversible morbidity. The guidance also explains that to meet the statutory standard for approval, which requires the submission of "substantial evidence" to demonstrate effectiveness, there must be evidence from adequate and well-controlled studies showing that the drug will have its claimed effect on the surrogate or clinical endpoint other than survival or irreversible morbidity. That is, accelerated approval does not in any way lower the requirement that there be substantial evidence of the effect on which approval would be based. If there were evidence of an effect of ataluren on 6MWD, there would be no need for further

studies to evaluate longer term clinical benefit, because we would find such an effect a sufficient basis for full NDA approval. Accelerated approval does not constitute an "escape" from the requirement for adequate and well-controlled studies.

If you wish to appeal this decision to the next level, your appeal should be directed to John Jenkins, M.D., Director, Office of New Drugs, Center for Drug Evaluation and Research. The appeal should be sent to the NDA administrative file as an amendment, and a copy should be sent to the Center's Dispute Resolution Project Manager, Amy Bertha. Any questions concerning your appeal should be addressed to Ms Bertha at (301) 796-1647.

Sincerely,

{See appended electronic signature page}

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

ROBERT TEMPLE
01/20/2012

APPENDIX D

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 200896

REFUSAL TO FILE

PTC Therapeutics, Inc.
Attention: Murad Husain, R.Ph., M.S.
Vice President, Global Regulatory Affairs
100 Corporate Court
South Plainfield, NJ 07080

Dear Mr. Husain:

Please refer to your New Drug Application (NDA) dated December 23, 2015, received December 24, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Translarna (ataluren) granules, 125 mg, 250 mg, and 1000 mg.

After a preliminary review, we find your application is not sufficiently complete to permit a substantive review. Therefore, we are refusing to file this application under 21 CFR 314.101(d) for the following reasons:

We are refusing to file this application because on its face it does not contain information required under section 505(b) of the FDCA, as described in 21 CFR 314.101. Specifically, the application does not contain substantial evidence of effectiveness.

As discussed both in our May 26, 2011, Refusal to File letter, and in the subsequent January 20, 2012, Dispute Appeal-Response letter, your first pivotal efficacy trial (PTC124-GD-007-DMD) that examined ataluren in the treatment of nonsense-mutation (nm) dystrophinopathy was clearly negative, and the multiple post hoc adjustments you proposed to explain its negative findings were not found to be persuasive or to provide any support for effectiveness of ataluren.

You subsequently designed a second pivotal placebo-controlled efficacy trial (PTC124-GD-020-DMD), based on hypotheses generated from the results of Study 007, which included both a larger sample size and enrichment for patients with baseline characteristics predicted by you to increase ability to identify drug effect, if present. Study 020, on face, is also clearly and convincingly negative. Most of the secondary endpoints (again, in the setting of a failed primary endpoint) in Study 020 are also nominally negative. You proposed a post hoc adjustment of Study 020 that eliminates data from a majority of enrolled patients, but that analysis presents the same issues as those previously discussed in the Refusal to File letter and Dispute Appeal-Response letter for your post hoc analyses of Study 007, and do not provide any support for effectiveness.

Thus, it is clear to us that, on face, these two negative studies do not provide substantial evidence of effectiveness, and that this application cannot be approved based on the data submitted.

Abuse Potential Assessment

There is inadequate information in this application regarding the abuse potential of ataluren.

There are a number of central nervous system (CNS) adverse events that are more commonly reported in ataluren-treated patients than in placebo-treated patients. This supports the possibility that ataluren is a CNS-active new molecular entity (NME). It is therefore necessary for ataluren to undergo an abuse potential assessment and for this information to be included in your NDA.

Your general approach in assessing the abuse potential of ataluren as part of your drug development program should follow the outline provided below. Your abuse potential assessment will allow the Agency to determine ataluren's risk of abuse. The FDA draft *Guidance for Industry: Assessment of the Abuse Potential of Drugs* (2010) describes the process of evaluating a drug for abuse potential, which includes the following:

Nonclinical Assessment:

- Chemistry
- Pharmacology
  - i. Safety pharmacology
  - ii. Active metabolites
- Receptor binding at relevant central nervous system sites
- Self-administration studies in animals
- Drug discrimination studies in animals
- Physical dependence studies in animals

Clinical Assessment:

- Human abuse potential studies (HAPS)*
- Clinical safety and efficacy studies (abuse signals):
  - i. Abuse-related adverse events profile
  - ii. Drug withdrawal symptoms
  - iii. Patient narratives, including those related to suspected abuse, misuse, overuse or overdose (intentional or unintentional)
  - iv. Drug accountability during trials to include drug lost, stolen, diverted or missing as well as an accounting of participants who withdraw without returning study medication

* HAPS may not be applicable. A recommendation to conduct a human abuse potential study (HAPS) is recommended if there is a signal for abuse in nonclinical studies. This *Guidance for Industry* is found on the Internet at:
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf

If ataluren produces abuse potential signals that warrant Controlled Substance Act (CSA) scheduling, you will need to include a proposal for scheduling based on an analysis of the

NDA's nonclinical and clinical studies which is consistent with the draft *Guidance for Industry on Assessment of Abuse potential of Drugs (2010).*

ADDITIONAL COMMENTS AND REQUESTS

The following issues are not related to our refusal to file this application; however, you should address these issues if the application is resubmitted.

Biopharmaceutics:

1. Provide the following additional information to support your position that the proposed in vitro dissolution testing method (USP 2, in 900 mL (125 mg and 250 mg) and 1800 mL (1000 mg) of 50 mM Phosphate Buffer, pH 7.4 at 50 rpm) is discriminating and the acceptance criterion (Q = 80% in 30 minutes) is meaningful for product quality assurance.

    - The selection of dissolution media using surfactant such as Tween 80, SLS in water, or other buffer to meet the sink condition for ataluren granules should be adequately justified. Complete in vitro dissolution profile data (i.e., individual, mean, %RSD, and graphical representative plots) for each surfactant type and amount tested should be included for method development. The minimum amount of surfactant to achieve sink conditions and robust dissolution performance is recommended.

    - We acknowledge that you provided data to assess the discriminatory capability of the dissolution method by comparing the dissolution profiles of ataluren granules stressed to temperature and humidity and by comparing dissolution profiles for different granule sizes. The provided data did not show that the proposed method is able to detect the changes in granule sizes. The proposed in vitro dissolution method should have discriminatory capability with regard to the Critical Material Attributes (CMAs, such as granule size) or Critical Process Parameters (CPPs, such as milling method). The testing should compare the dissolution profiles of the reference (target) product vs. the test product(s) that are intentionally manufactured with meaningful variations for the most relevant critical material or manufacturing variables (i.e., ± 10-20% change to the specification-ranges of these variables). In addition, if available, submit data showing that the selected dissolution method and acceptance criterion are adequate to reject batches that are not bioequivalent.

2. If available, submit in vivo data (e.g., pharmacokinetic (PK) data) demonstrating that batches with different granule size (74-125 μm) and (>500 μm) with similar dissolution profiles do not have an impact on systemic exposure. If in vivo data are not available, please use in silico predictions (it is noted that you have established a PBPK (GastroPlus) model within Module 2.7.2 Summary of Clinical Pharmacology of this submission) using GastroPlus to predict the impact of granulate size (74-125 μm) and (>500 μm) on the systemic exposure of your drug product. Submit model database file (.mdb), support files (.sdb, .dsd, and .psd), physiology files (.cat and .pbk), excel datasheet with relevant input data, and your model report file.

3. Provide in vitro dissolution profile comparison (use f2 test if applicable) among the three formulations used in clinical trials (i.e., Phase 1, Phase 2a, and Phase 2b) using the same selected dissolution method (USP 2, in 900 mL (125 mg and 250 mg) and 1800 mL (1000 mg) of 50 mM Phosphate Buffer, pH 7.4 at 50 rpm).

Microbiology:

The method suitability testing for microbial limits testing per USP <61> and <62> could not be located in the submission. Provide either the location in the submission or provide the reports.

Clinical Pharmacology

Please submit the data and NONMEM code used for conducting population PK and PK-PD analyses.

The following are the general expectations for submitting pharmacometric data and models:

- All datasets used for model development and validation should be submitted as a SAS transport files (*.xpt). A description of each data item should be provided in a Define.pdf file. Any concentrations and/or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.

- Model codes or control streams and output listings should be provided for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. These files should be submitted as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt).

- A model development decision tree and/or table which gives an overview of modeling steps.

- For the population analysis reports, we request that you submit, in addition to the standard model diagnostic plots, individual plots for a representative number of subjects. Each individual plot should include observed concentrations, the individual predication line and the population prediction line. In the report, tables should include model parameter names and units. For example, oral clearance should be presented as CL/F (L/h) and not as THETA(1). Also provide in the summary of the report a description of the clinical application of modeling results.

- In terms of where the code and data should be submitted, the following folders can be used as one example for population PK related codes and data. The codes should be submitted under "module5/datasets/poppk/analysis/programs/" folder (such as run1.ctl.txt, run1.lst.txt, plot1.R.txt) with a define pdf file to explain the role of each file and sometimes with a pdf file as the revieweraid.pdf to explain the flow of running the code if necessary. The datasets should be submitted under

"module5/datasets/poppk/analysis/datasets/" folder (such as poppk.xpt, pkpd.xpt) with a define pdf file to explain the variables within each data file.

Statistical

There is a list of the names of submitted SAS programs in the reviewers-guide.pdf for study PTC124-GD-020. However, we could not locate the programs. Please submit the programs (including all necessary macro programs) or indicate the location of those files in the submission if you have already submitted them.

Prescribing Information

- In your application, you must submit proposed Prescribing Information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. Prior to resubmission of your application, please review these regulations. Also, please ensure your Prescribing Information is in compliance with the formatting requirements of the regulations by completing the "Selected Requirements for Prescribing Information (SRPI)", which is a checklist of 42 important format items that can be found at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/UCM373025.pdf.

- In addition, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information website (http://www.fda.gov/drugs/guidancecomplianceregulatoryinformation/lawsactsandrules/ucm084159.htm), which includes:

  - The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
  - The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential
  - Regulations and related guidance documents
  - A sample tool illustrating the format for Highlights and Contents, and
  - FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

- We also note that results from your abuse potential assessment may necessitate inclusion in the *Drug Abuse and Dependence* section in the Prescribing Information. If the information obtained with your abuse potential assessment is appropriate and warrants inclusion into labeling as required by 21 CFR 201.57(c)(10), you should develop the language for this section of the Prescribing Information to include in your resubmission.

Please note that this filing review represents a preliminary review of the application and is not indicative of deficiencies that would be identified if we performed a complete review.

Within 30 days of the date of this letter, you may request in writing a Type A meeting about our refusal to file the application. A meeting package should be submitted with this Type A meeting request. To file this application over FDA's protest, you must avail yourself of this meeting.

If, after the meeting, you still do not agree with our conclusions, you may request that the application be filed over protest. In that case, the filing date will be 60 days after the date you requested the meeting. The application will be considered a new original application for user fee purposes, and you must remit the appropriate fee.

PROPOSED PROPRIETARY NAME

If you intend to have a proprietary name for the above-referenced product, submit a new request for review of a proposed proprietary name when you resubmit the application. For questions regarding proprietary name review requests, please contact the OSE Project Management Staff via telephone at 301-796-3414 or via email at OSECONSULTS@cder.fda.gov.

If you have any questions, please contact Fannie Choy, Regulatory Project Manager, by phone or email at (301) 796-2899 or fannie.choy@fda.hhs.gov.

Sincerely yours,

{See appended electronic signature page}

Billy Dunn, M.D.
Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

WILLIAM H Dunn
02/22/2016

APPENDIX E

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 200896

MEETING MINUTES

PTC Therapeutics, Inc.
Attention: Murad Husain, R.Ph., M.S.
Vice President, Global Regulatory Affairs
100 Corporate Court
South Plainfield, NJ 07080

Dear Mr. Husain:

Please refer to your New Drug Application (NDA) dated December 23, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Translarna (ataluren) granules, 125 mg, 250 mg, and 1000 mg.

We also refer to the meeting between representatives of your firm and the FDA on April 19, 2016. The purpose of the meeting was to discuss the next steps for the application following the Agency's Refusal to File letter dated February 22, 2016.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, please contact me by phone or email at (301) 796-2899 or fannie.choy@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Billy Dunn, M.D.
Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	**Type A**
Meeting Category:	**Other**
Meeting Date and Time:	April 19, 2016, 11:00 a.m. – 12:15 p.m. EDT
Meeting Location:	FDA White Oak Campus, Building 22, Room 1415
Application Number:	NDA 200896
Product Name:	Translarna (ataluren)
Indication:	Treatment of nonsense mutation dystrophinopathy
Applicant Name:	PTC Therapeutics, Inc.
Meeting Chair:	Billy Dunn, M.D.
Meeting Recorder:	Fannie Choy, R.Ph.

FDA ATTENDEES

Office of Drug Evaluation I
Ellis Unger, MD, Director
Robert Temple, MD, Deputy Director
Naomi Lowy, MD, Associate Director for Regulatory Science (Acting)

Division of Neurology Products
Billy Dunn, MD, Director
Ronald Farkas, MD, PhD, Clinical Team Leader
Nicholas Kozauer, MD, Clinical Team Leader
David Hosford, MD, PhD, Clinical Reviewer
Fannie Choy, RPh, Regulatory Project Manager

Office of Clinical Pharmacology
Sreedharan Sabarinath, PhD, Clinical Pharmacology Team Leader
Atul Bhattaram, PhD, Pharmacometrics Reviewer

Division of Biometrics I
Kun Jin, PhD, Biometrics Team Leader
Xiang Ling, PhD, Statistical Reviewer

Controlled Substance Staff
Martin Rusinowitz, MD, Senior Medical Officer

Rare Diseases Program
Lucas Kempf, MD, Medical Officer

APPLICANT ATTENDEES

PTC Therapeutics, Inc.
Stuart Peltz, PhD, Chief Executive Officer and Founding Scientist
Robert Spiegel, MD, Chief Medical Officer
Tuyen Ong, MD, Senior VP and Head of Clinical Development and Translational Research
Joseph McIntosh, MD, Vice President, Clinical Development
John Babiak, PhD, Senior Vice President, Discovery Technologies (via teleconference)
Murad Husain, RPh, MS, Senior Vice President, Global Regulatory Affairs
Alyssa Wyant, Vice President, Global Regulatory Affairs (ataluren)
Xiaohui Luo, PhD, Executive Director, Biostatistics
Hans Kroger, Associate Director, Biostatistics
Peter Riebling, Director, Clinical Sciences
Marcio Souza, PharmD, Ataluren Program Team Leader
Megan Sniecinski, Vice President, Business Operations
Brian Spar, Associate Director, Drug Development Project Management
Ellen Welch, PhD, Vice President, Biology
Janet Hamilton, PhD, Vice President, Toxicology
James Takasugi, PhD, Associate Director, API Process Development
Mark Boulding, JD, Executive Vice President and Chief Legal Officer

University of California, Davis
Craig McDonald, MD, Professor and Chairman, Department of Physical Rehabilitation (consultant)

University of North Caroline at Chapel Hill
Gary Koch, PhD, Professor of Biostatistics (via teleconference)

1.0 BACKGROUND

PTC Therapeutics, Inc. (PTC) has been developing ataluren (PTC124) for the treatment of muscular dystrophy resulting from a nonsense mutation in the dystrophin gene.

Orphan Drug designation for the treatment of muscular dystrophy resulting from premature stop mutations in the dystrophin gene was granted on January 10, 2005. Subpart E designation to expedite development was granted on March 11, 2006.

On March 31, 2011, the applicant submitted the original New Drug Application (NDA). The Division issued a Refuse-to-File (RTF) letter on May 26, 2011, because the NDA, on face, did not contain substantial evidence of effectiveness. On December 11, 2011, the applicant submitted a request for formal dispute resolution. The Agency upheld the RTF decision on January 20, 2012.

On November 6, 2013, the Agency denied the sponsor's request for Breakthrough Therapy designation for ataluren for the treatment of nonsense mutation Duchenne muscular dystrophy.

The Agency met with the sponsor on August 4, 2014, to discuss the sponsor's proposal to submit an NDA for consideration for accelerated approval, and possible next steps. On October 20, 2014, the applicant proposed to resubmit the NDA under rolling submission and the Division granted this request on December 1, 2014. The final portion of the NDA (Resubmission after RTF) was received on December 24, 2015. After a preliminary review, the Division determined that the application was not sufficiently complete to permit a substantive review. The Division issued a RTF letter on February 22, 2016.

On March 23, 2016, PTC submitted a request for the meeting to discuss issues noted in the RTF letter and the next steps for the application.

2.0 DISCUSSION

Question 1:

Would the Division be prepared to reconsider and/or reverse the RTF decision and accept the application for review under Subpart H? This would involve reliance on the meta-analysis as the primary source of evidence of effect on 6MWD (an intermediate clinical endpoint), reliance on the remaining data in the application as supportive evidence of efficacy, and the provision of post-approval data to verify clinical benefit.

FDA Response to Question 1:

The policies that FDA cited in the Division's RTF Appeal Denial letter of January 20, 2012, also apply to your current application, which now contains the results of two trials that are, on face, negative. We stated in that letter that "FDA has long asserted that a study can be so clearly not supportive of effectiveness that it can be considered essentially absent. The 1993 guidance [New Drug Evaluation Guidance Document: Refusal to File] describing FDA's policy on refusal to file states that RTF could be based on advance judgment about what had been shown in a trial, e.g., lack of evidence of effectiveness…"

We describe below in more detail the basis of our conclusion that, on face, studies 007 and 020 do not provide substantial evidence of effectiveness of ataluren.

A. Study 007

The pre-specified primary endpoint was "the 6MWD from baseline to Week 48 in the intent-to-treat (ITT) population…analyzed using a likelihood-based, mixed-model, repeated-measures analysis of covariance (RANCOVA)…[and] if a rank transformation is required…Holm's method of sequential p-value adjustment will be used [SAP, section 10.1]." Per Table 24 in the

Complete Study Report (CSR) for Study 007 the mean change in 6MWD for the high-dose group (20,20,40 mg/kg ataluren; n = 60) was 0.1 meters favoring placebo (n = 57; adjusted untransformed p-value = 1.00; rank-transformed p-value = 0.70). The rank-transformed values analysis was "considered primary due to non-normal distribution of the untransformed 6MWD data." The mean change in 6MWD for the low-dose group (10,10,20 mg/kg ataluren; n = 57) was 26.4 meters favoring ataluren (adjusted rank transformed p-value 0.25). Thus, based on the prospectively planned primary analysis, Study 007 was clearly negative.

None of the timed function tests (secondary endpoints) were nominally positive when analyzed in the intent to treat (ITT) population per the pre-specified statistical analysis plan (SAP). Hence there was no evidence of effectiveness of ataluren based on the pre-specified primary or secondary endpoints.

You performed a variety of *post hoc* analyses of the primary and secondary endpoints using the ITT population or sub-groups of the ITT population, and some of these analyses showed nominal statistical significance favoring ataluren. One example (section 11.4.5.2.1 of the CSR) is a *post hoc* analysis in the low-dose arm only of an "ambulatory decline" sub-group composed of patients with the following characteristics: age 7 to 16 years; baseline 6MWD at least 150 meters and no greater than 80% of predicted; and on stable doses of concomitant corticosteroid therapy. In this analysis, there was a 49.9-meter difference in 6MWD at Week 48 favoring ataluren (n = 32) compared to placebo (n = 31), with a nominal p-value of 0.01. As we explained in the Appeal Denial letter, however, given the known potential bias associated with multiple *post hoc* adjustments to statistical analyses, these results are, on face, not persuasive.

B. Study 020

The pre-specified primary endpoint was "change in 6MWD from baseline to Week 48 in the ITT population with the analysis of covariance method (ANCOVA) [SAP, section 9.1]." Per Figure 3 (section 11.4.1.1) in the CSR for Study 020, the mean change in 6MWD for ataluren (10,10,20 mg/kg; n = 114) as compared to placebo (n = 114) was 15.4 meters favoring ataluren (p = 0.21). This study was, therefore, also clearly negative. We note that: 1) Study 020 enrolled cohorts twice the size of those in Study 007. More importantly, Study 020 used hypotheses generated from Study 007 to specify inclusion criteria to select a population much like the "ambulatory decline" subgroup of Study 007. In spite of these enrichment factors, which would be expected to enhance the effect size of ataluren in Study 020, the observed treatment effect was approximately half the size of the overall non-significant treatment effect in Study 007.

The statistical analysis plan for Study 020 defined 5 subgroups based on 6MWD and an additional 4 subgroups based on other characteristics at baseline. You did not pre-specify whether any of the subgroups would be included in the primary analyses with adjustments to control type-I error. Therefore, any subgroup findings would be considered exploratory and cannot provide evidence of effectiveness. These subgroup analyses, as described in the SAP (section 9.2.3), were the following:

- Baseline 6MWD stratification factor of: 1) at least 350 meters vs. 2) less than 350 meters
- Baseline 6MWD groups with: 1) less than 300 meters; 2) at least 300 but less than 400 meters; and 3) at least 400 meters

- Duration of prior corticosteroid use at baseline in groups with: 1) at least 6 months but less than 12 months; and 2) at least 12 months
- Baseline age of 1) less than 9 years; and 2) at least 9 years.

You chose to highlight the subgroup with baseline 6MWD of at least 300 meters but less than 400 meters, where the mean change in the 6MWD at 48 weeks compared to baseline was 47.2 meters, favoring ataluren (n = 47) vs. placebo (n = 52; nominal p = 0.01; Figure 5 and section 11.4.1.1 of the CSR). Although these analyses were identified in the statistical analysis plan, no plan to control type-I error was identified; therefore, these analyses are considered hypothesis-generating in the setting of an overall negative study.

Secondary endpoints included three timed function tests, of which only one, the Time to Descend 4 Stairs, was nominally positive (p = 0.01) in the ITT population (CSR, section 11.4.1.2.2). This result too can only be viewed as hypothesis-generating in the context of a negative primary endpoint, and is not supportive of the effectiveness of ataluren.

Many other *post hoc* analyses were performed using a variety of endpoints and subgroups, and some were nominally positive. For example, analysis of the Time to Descend 4 Stairs in the subgroup of patients with a baseline 6MWD of at least 300 meters but less than 400 meters (Figure 15, section 11.4.1.2.2, CSR) favored ataluren with a nominal p-value < 0.001. It is well recognized that non-pre-specified *post hoc* statistical analyses of multiple subgroups and multiple endpoints will result in false positive findings and cannot be taken at face value. Thus, the *post hoc* analyses do not support the effectiveness of ataluren when the pre-specified analysis of the primary endpoint was negative.

C. Pooled Results from Study 007 and Study 020

The Briefing Document (BD) for the Type A meeting that was submitted on March 23, 2016, describes a variety of meta-analyses using pooled data from both studies. Several examples or types of methods of pooling are described below.

- Figure 2 (section 3.1, BD) depicts a meta-analysis in which a corrected ITT population from the low-dose group of Study 007 only ([and replacing baseline values of 6MWD with screening values in 2 patients with lower limb injuries at baseline]; n = 114) is pooled with the ITT population from Study 020 (n = 228) to produce a combined population of 342 patients. In the combined population, there was a nominally significant change from baseline to Week 48 in 6MWD favoring ataluren (p = 0.02).
- Figure 1 (Appendix B, BD) depicts a meta-analysis in which the "ambulatory decline" subgroup of the low-dose group of Study 007 (n = 63) is combined with the ITT population of Study 020 to produce a combined population of 291 patients. The "ambulatory decline" subgroup of Study 007 was described above, and its inclusion criteria match those in the ITT population of Study 020. In this combined population, change from baseline to Week 48 in the 6MWD favored ataluren (p = 0.02).
- A number of timed function tests (TFTs) were analyzed using both the first pooling method described above (corrected ITT population of Study 007 plus ITT population of Study 020) or the second pooling method (ambulatory decline phase subgroup of Study

007 plus ITT population of Study 020). Four out of four TFTs showed a nominally statistically significant difference favoring ataluren using the first meta-analysis method; and three out of four showed nominally statistically significant differences favoring ataluren using the second method.

Although some of the meta-analyses described in the BD showed nominally statistically positive results favoring ataluren, they do not support the effectiveness of ataluren for the following reasons:

- These meta-analyses were neither pre-specified nor planned, and were performed after the study results were known, such that they can only be considered hypothesis-generating.
- The analysis method was different from the pre-specified primary analysis in Study 007
- Omission of the high-dose arm in Study 007 is an additional *post hoc* adjustment

D. Dystrophin measurements

In two clinical studies (Study 004 and Study 007), the effect of ataluren on dystrophin production was examined in muscle biopsy samples obtained from patients with DMD. However, the data, on face, do not appear capable of supporting a marketing application, and you acknowledge many of the shortcomings of these data and the difficulty of assessing dystrophin levels in DMD.

In summary, neither of these two studies presents evidence supporting the effectiveness of ataluren in nonsense mutation DMD.

Meeting Discussion:

Following introductory comments, the sponsor presented slides that summarized the following: the clinical development program for ataluren in this indication; published literature on the levels of dystrophin that might result in clinical benefit; results from Study 004 regarding dystrophin expression; a variety of results from Studies 007 and 020 (alone and pooled); and previously unsubmitted data showing the loss of ambulatory function in patients in the ongoing open-label extension study (Study 020e).

Discussion ensued about the statistical analysis plan (SAP)-prespecified primary endpoint (6MWD in the ITT population) and the sponsor's approach to the prespecified subgroup analyses (in particular, analyses of patients with baseline 6MWD of 300-400 meters) in the context of a negative primary endpoint. FDA stated that the results of the subgroup analyses, while potentially hypothesis-generating for future studies, did not provide evidence of effectiveness of ataluren in the face of a negative primary endpoint.

The sponsor asked if an NDA for ataluren could be filed based on subgroup analysis of 6MWD (e.g., the subset of patients with baseline 6MWD of 300-400 meters) as an intermediate clinical endpoint. FDA discussed that the appropriateness of the accelerated approval pathway relates to the nature of the endpoint used to support approval, i.e., a surrogate or an intermediate clinical

endpoint considered reasonably likely to predict clinical benefit and that the level of evidence necessary to demonstrate an effect on such an endpoint is the same as for a clinical endpoint that would support regular approval. FDA further indicated that in the context of the current application, the 6MWD was a clinically meaningful endpoint presumably capable of supporting a full approval if the data showing an effect on that endpoint provided substantial evidence of effectiveness.

The sponsor asked if the totality of the original and newly submitted data, which it stated favors ataluren in a variety of subgroup, post hoc, and pooled meta-analyses, could serve as a basis for filing the NDA submission. FDA stated that, though it did not appear that such analytical maneuvers would provide more than hypothesis generation, any additional thoughts in this regard would be reflected in the meeting minutes. FDA reiterated its willingness to review a new clinical trial protocol that specified an enriched patient population based on hypotheses generated from studies 007 and 020.

Post-meeting note: FDA believes that the accumulation of various additional analyses and explorations provided by the sponsor can only be characterized as hypothesis generating at this time, but notes that the findings can possibly provide supportive data that might accompany the results of a single adequate and well-controlled study. Such an overall data package would have the potential to provide substantial evidence of effectiveness. FDA again reiterates its willingness to work closely with PTC Therapeutics to efficiently develop a clinical trial protocol based on hypotheses generated from studies 007 and 020.

Question 2:

Given the evolving understanding of the natural history of DMD and the fact that PTC did pre-specify subgroup analyses in the SAP for Study 020 to reflect the natural history data, please explain the Division's basis for the conclusion that we proposed a "post hoc adjustment" and the basis for the conclusion that this adjustment presents the same issues as the analyses in the 2011 application?

FDA Response to Question 2:

See our responses to Question 1. We note particularly that the population adjustment in Study 020, using the information in Study 007 suggesting a possible subset of better responders, did not successfully predict such a response.

***Meeting Discussion*:**

See meeting discussion under Question 1.

Question 3:

a. **Would the FDA be willing to share the analyses or queries used to support the comment regarding a possible imbalance in CNS adverse events suggestive of abuse potential and which CNS adverse events may have been of concern to the Division?**

b. **Does the Division agree that the proposed consolidated report will be sufficient for the Agency to accept the ataluren NDA and conduct its abuse potential assessment?**

FDA Response to Question 3:

a. Although we have not performed any formal analyses that we can share, a preliminary examination of the adverse events that you have submitted provided the basis for our comment.

b. No, your report does address some of the components of a nonclinical abuse potential assessment, but lacks others. The data related to your drug's chemistry, pharmacology and receptor binding at relevant CNS sites appear sufficient. CSS's review of this data will ultimately determine the adequacy of your NDA submission.
Your abuse potential assessment still needs to include animal self-administration, drug discrimination and physical dependence studies as part of your IND. Based on the totality of our review of this nonclinical abuse related data, CSS will decide whether or not there is a signal for abuse such that a human abuse potential study is recommended before your NDA's filing review.

Meeting Discussion:

The sponsor requested a follow up teleconference with CSS to further review its analyses of the adverse events determined to be associated with potential abuse. It was recommended that, in advance, the sponsor submit specific questions so that an appropriate meeting format might be arranged.

Question 4:

When and how will DNP provide PTC with a response to the Company's reconsideration/reversal request?

FDA Response to Question 4:

See our response to Question 1.

Meeting Discussion:

See meeting discussion under Question 1.

3.0 ADDITIONAL COMMENTS

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.
Because this drug product for this indication has an orphan drug designation, you are exempt from these requirements. Please include a statement that confirms this finding, along with a reference to this communication, as part of the pediatric section (1.9 for eCTD submissions) of your application. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

5.0 ACTION ITEMS

There were no action items identified during the meeting.

6.0 ATTACHMENTS AND HANDOUTS

PTC's handout distributed at the meeting, titled "FDA Type A Meeting, NDA 200896: Ataluren (PTC124), April 19, 2016, FINAL."

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

WILLIAM H Dunn
05/19/2016

APPENDIX F

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 200896

MEETING MINUTES

PTC Therapeutics
Attention: Murad Husain, R.Ph., M.S.
Senior Vice President, Global Regulatory Affairs
100 Corporate Court
South Plainfield, NJ 07080

Dear Mr. Husain:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Translarna (ataluren) 125, 250, and 1000 mg. oral granules.

We also refer to the meeting between representatives of your firm and the FDA on August 29, 2016. The purpose of the meeting was to discuss your July 13, 2016, request for formal dispute resolution that concerns the February 22, 2016, refuse-to-file action taken by the Division of Neurology Products on this application.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, please call me at (301) 796-1114.

Sincerely,

{See appended electronic signature page}

Colleen LoCicero, R.Ph.
Associate Director for Regulatory Affairs
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type A
Meeting Category: Formal Dispute Resolution Request

Meeting Date and Time: August 29, 2016
Meeting Location: White Oak Campus, Building 22, Room 1311

Application Number: NDA 200896
Product Name: Translarna (ataluren) 125, 250, and 1000 mg. oral granules
Indication: Treatment of Nonsense Mutation Dystrophinopathy
Sponsor/Applicant Name: PTC Therapeutics, Inc.

Meeting Chair: Robert Temple, M.D.
Meeting Recorder: Colleen LoCicero, R.Ph.

FDA ATTENDEES

Deborah Chasan-Sloan, J.D., Attorney, Office of Chief Counsel (OCC)
Dominic Chiapperino, Ph.D., Regulatory and Liaison Team Lead, Controlled Substances Staff (CSS)
Fannie Choy, R.Ph., Regulatory Project Manager, Division of Neurology Products (DNP)
Billy Dunn, M.D., Director, DNP
Ronald Farkas, M.D., Ph.D., Team Leader, Medical, DNP
David Hosford, M.D., Ph.D., Medical Officer, DNP
Jim Hung, Ph.D., Director, Division of Biometrics I (DB1)
Kun Jin, Ph.D., Team Leader, Statistical, DB1
Nicholas Kozauer, M.D., Team Leader, Medical, DNP
Xiang Ling, Ph.D., Statistical Reviewer, DB1
Naomi Lowy, M.D., Associate Director for Regulatory Science, Office of Drug Evaluation I (ODE 1)
Jovita Randall-Thompson, Ph.D., Pharmacologist, CSS
Martin Rusinowitz, M.D., Medical Officer, CSS
Eva Temkin, J.D., Attorney, OCC
Robert Temple, M.D., Deputy Director (Acting), ODE 1
Ellis Unger, M.D., Director, ODE 1
Colleen LoCicero, R.Ph., Associate Director for Regulatory Affairs, ODE 1

SPONSOR ATTENDEES

Mark Boulding, J.D., Chief Legal Officer and Executive Vice President
Pat Furlong, Founding President and CEO, Parent Project Muscular Dystrophy (PPMD)

Janet Hamilton (Petruska), Ph.D., Vice President, Toxicology
Murad Husain, R.Ph., M.S., Senior Vice President, Global Regulatory Affairs
Joanna Johnson, Board Member, PPMD
Gary Koch, Ph.D., Statistical Consultant, Professor of Biostatistics, University of North Carolina
William McConagha, Sidley Austin, LLP
Craig McDonald, M.D., Professor and Chair, Department of Physical Medicine and Rehabilitation, Professor of Pediatrics, University of California Davis Medical Center
Joe McIntosh, M.D., Vice President, Clinical Development
Tuyen Ong, M.D., Chief Medical Officer
Stuart Peltz, Ph.D., Chief Executive Officer and Founding Scientist
Peter Riebling, Senior Director, Clinical Sciences
Edward M. Sellers, M.D., Ph.D., Professor Emeritus, Pharmacology and Toxicology, Medicine, and Psychiatry, University of Toronto
Megan Sniecinski, Vice President, Business Operations
Marcio Souza, Pharm.D., Senior Vice President, Ataluren Program Team Leader
Brian Spar, Director, Project Management
Robert Spiegel, M.D., Clinical Consultant (former Chief Medical Officer)

1.0 BACKGROUND

This meeting was scheduled at the request of PTC Therapeutics, Inc. (PTC) to discuss their July 13, 2016, request for formal dispute resolution (FDRR) regarding the February 22, 2016, refuse-to-file action taken by the Division of Neurology Products (DNP) on NDA 200896 for Translarna (ataluren) oral granules for the treatment of nonsense mutation dystrophinopathy.

NDA 200896 was originally submitted on March 31, 2001. The DNP issued a refuse-to-file letter for the application on May 26, 2011. A Type A meeting between PTC and the DNP was held on July 19, 2011, to discuss the refuse-to-file action. Following the meeting on December 22, 2011, PTC submitted a request for formal dispute resolution regarding the refuse-to-file action. In his January 20, 2011, response to the FDRR, Dr. Temple upheld the division's May 26, 2011, refuse-to-file action.

On August 4, 2014, PTC Therapeutics announced the conditional approval of ataluren for the treatment of nonsense mutation Duchenne Muscular Dystrophy in the European Union (EU). On that same day, PTC met with the DNP to discuss the resubmission of NDA 200896. During the meeting, the DNP agreed to a rolling review for the NDA. On December 14, 2014, PTC resubmitted the first part of the rolling NDA and, on 12/23/15, the second, and final, part of the NDA.

On February 22, 2016, the DNP refused to file the NDA for a second time. At the request of PTC, a Type A meeting was held on April 19, 2016, to discuss the February 2016 refuse-to-file action. Subsequent to that meeting, PTC submitted a request for formal dispute resolution regarding the February 2016 refuse-to-file action on July 13, 2016.

In the FDRR, PTC seeks reversal of the February 22, 2016, refuse-to-file action, and full review of the ataluren NDA, including discussion of the application at an Advisory Committee meeting.

2. DISCUSSION

During the meeting, representatives of Parent Project Muscular Dystrophy (PPMD) described their experiences with ataluren and the support within the Muscular Dystrophy community for filing the ataluren NDA. PTC presented the three main points on which the FDRR is based, as follows.

Similar Treatment

PTC noted that, under the Administrative Procedures Act (APA), FDA is not permitted to treat similarly situated parties in a different manner. PTC believes the Agency may have violated the APA when it refused to file the ataluren NDA, but filed and reviewed two other applications for drugs for the treatment of Duchenne muscular dystrophy (DMD), drisapersen and eteplirsen, that PTC asserts also relied solely on negative studies. Of the three applications, PTC considers the ataluren application to contain the most robust data, observing that while the ataluren NDA contains data from two adequate and well-controlled studies, the eteplirsen NDA includes data from no adequate and well controlled studies and the drisapersen NDA is based on pooled data from multiple studies. Despite this factor, PTC emphasized, the Agency refused to file the ataluren NDA, but filed the eteplirsen and drisapersen NDAs, and permitted the submission of additional data to support those applications during their reviews. Finally, in comparing the three development programs and applications, PTC pointed out that ataluren is approved in the EU, whereas the applicants for eteplirsen and drisapersen have not pursued, and do not intend to pursue, marketing authorization in the EU.

Basis of Refuse to File

PTC does not believe FDA had the legal authority to refuse to file the ataluren NDA based on what it considers approvability concerns, noting that a filing determination is distinct from an approval determination. PTC explained its view that the standard for filing is completeness of the application. PTC does not believe the ataluren application was "incomplete on its face," noting that the application contains data from the two largest controlled studies conducted to date in DMD.

When asked about the language in the attachment to MAPP 6025.4, *Good Review Practice: Refuse to File*, which specifies that FDA may refuse to file an application that relies solely on trials that fail on their primary endpoints, without an adequate explanation of why such an approach is reasonable, PTC indicated they are aware of the language and do not believe it is consistent with FDA's regulatory authority. Furthermore, PTC maintained that the ataluren application contains an *adequate explanation*, noting that there is a strong rationale to support an analysis based on the 300- to 400-meter 6-minute walking distance test (6MWDT) subgroup.

Finally, PTC noted that FDA has filed applications in other therapeutic areas for which the studies supporting the application failed on their primary endpoint and that examples of such applications can be found in the FDRR submission.

Abuse Potential

PTC does not believe the adequacy of the abuse potential information provided in an application constitutes a filing issue, but is instead an approvability issue. Furthermore, PTC believes the information on abuse potential provided in the ataluren application adequately addresses the abuse potential of ataluren. PTC noted that information on use of ataluren in Europe, where it is approved, provides real world data to support an abuse potential determination.

File Over Protest

PTC Therapeutics believes they can have a complete and comprehensive dialogue regarding ataluren with FDA only in the context of a full review and, therefore, do not consider filing over protest an acceptable option.

Path forward

PTC outlined the three potential paths for filing and reviewing the application described in the FDRR, as follows:

- File and review the application for full approval, based on all of the 6MWDT findings.
- File and review the application under 21 CFR 314, subpart H, for approval based on an intermediate clinical endpoint of 6MWDT in the 300- to 400-meter subgroup; PTC noted that DNP proposed using 6MWD as an intermediate clinical endpoint to Prosensa during the development of drisapersen.
- File and review the application under 21 CFR 314, subpart H, for approval based on a surrogate endpoint of increased dystrophin production, if FDA has changed its opinion on the acceptability of this endpoint as a surrogate; PTC has dystrophin data that they collected to support and inform the conduct of their clinical trials.

Conclusion

Dr. Temple will consider the information presented by PTC and their consultants today, along with the information in the FDRR, and expects to provide his response to PTC on their appeal by the goal date of 9/28/16. PTC encouraged Dr. Temple to let them know if they can provide any additional information to help him in his review and decision on the FDRR.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

COLLEEN L LOCICERO
09/28/2016

APPENDIX G

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 200896

APPEAL DENIED

PTC Therapeutics, Inc.
Attention: Murad Husain, R.Ph., M.S.
Senior Vice President, Global Regulatory Affairs
100 Corporate Court
South Plainfield, NJ 07080

Dear Mr. Husain:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Translarna (ataluren) 125, 250, and 1000 mg oral granules.

I also refer to your request for formal dispute resolution submitted and received on July 13, 2016. The appeal concerned the Division of Neurology Product's decision, communicated to you in correspondence dated February 22, 2016, to refuse to file (RTF) this NDA.

I also refer to the meeting held between FDA and PTC Therapeutics, Inc., on August 29, 2016, where the issues raised in your request for formal dispute resolution were discussed.

Dr. Ellis Unger has delegated your Office of Drug Evaluation I level appeal to me, in my capacity as acting deputy director of the Office of Drug Evaluation I.

In consultation with other FDA staff, I have carefully reviewed the administrative file, the materials you submitted in support of your appeal, as well as the February 22, 2016 Refuse to File letter, and minutes from the April 19, 2016 Type A meeting between the Division of Neurology Products and PTC Therapeutics.

I have completed my review of your request for formal dispute resolution and deny your appeal. I describe below the basis for my decision and provide recommendations for a possible path forward.

Your appeal is based upon four principal arguments challenging the Refusal to File (RTF) decision. Each of those arguments is restated and addressed here:

1. *You assert that under the regulations at 21 CFR 314.101, which reference section 505(b) of the FDCA and 21 CFR 314.50, FDA cannot refuse to file an application based on concerns about the ultimate approvability of the drug, specifically "whether the clinical trials included in the NDA for ataluren provide substantial evidence of efficacy." You argue that the requirements of section 505(b) can be met equally by either positive or*

negative studies. (PTC's July 13, 2016 FDRR submission at 12). You argue further that because the requirement for substantial evidence of efficacy is located in section 505(d) of the FDCA (which you note is not cited in 21 CFR 314.101), the lack of substantial evidence of efficacy cannot serve as the basis to RTF an NDA.

I have reviewed your arguments, and I disagree with your assertion that DNP did not have the authority to RTF the ataluren NDA. Section 505(b)(1)(A) of the FDCA requires inclusion in an NDA of "full reports of investigations which have been made to show whether or not such drug is safe for use and whether such drug is effective in use." And, under 21 CFR 314.101(d)(3), FDA may refuse to file an NDA that does not "on its face" contain information required under FDCA section 505(b). It is not the case, as you assert, that under 21 CFR 314.101 FDA is precluded from refusing to file an application so long as there are full reports of investigations made to determine effectiveness, regardless of the results of those trials. To the contrary, FDA has the discretion to RTF applications in which the submitted studies are so negative (or otherwise non-supportive) that they essentially render the application incomplete, *i.e.*, that FDA cannot make a threshold determination that the application is sufficiently complete to permit a substantive review as required by 21 CFR 314.101. This may include an application that relies solely on trials that fail to achieve statistical significance on the primary endpoint or endpoints, without an adequate explanation of why this approach is reasonable.

In addition, the RTF regulation at 21 CFR 314.101 cites as an additional basis for refusal to file, lack of information required under 21 CFR 314.50. In referring to 21 CFR 314.50, the regulations in 21 CFR 314.101 incorporate 21 CFR 314.50(d)(5)(v), which specifically requires the application to include an integrated summary of the data (the Integrated Summary of Effectiveness (ISE)) "demonstrating substantial evidence of effectiveness for the claimed indications." Thus, if an NDA includes only an ISE summarizing data that cannot – on their face – demonstrate substantial evidence of effectiveness, FDA may refuse to file the NDA pursuant to 21 CFR 314.101. Further, as substantial evidence of effectiveness can only be based on findings from adequate and well-controlled studies, the regulations at 21 CFR 314.101 allow FDA to consider the adequacy of the design and analysis of the studies as well as the outcome of the studies in deciding whether to file an NDA. FDA's consideration of such factors in making an RTF decision is reflected in FDA's Manual of Policy and Procedures (MAPP) (MAPP 6025.4, effective 10/11/2013), which elaborates, in Attachment 2, on "examples of complex and significant deficiencies that may provide support for an RTF." These include "failure to include evidence of effectiveness compatible with statute and regulations." Examples of such deficiencies include, but are not limited to (only some are listed below):

- Reliance solely on trials that fail to achieve statistical significance on the primary endpoint or endpoints, without an adequate explanation of why this approach is reasonable.

- Use of a statistical analysis plan that was finalized after data unblinding, raising integrity concerns, without a compelling explanation of why this should be considered reasonable.

Clearly these reasons for RTF contemplate that judgments will be made prior to filing about the design and results of the studies submitted to support an application for marketing approval and their failure to provide such support, not solely an assessment of the presence or absence of data from such studies. As these examples show, FDA may base a decision to RTF on its conclusion that an NDA does not contain the requisite information, including full reports of investigations under FDCA 505(b) and an ISE summarizing data that demonstrates substantial evidence of effectiveness under 21 CFR 314.50. In this case, the results of the two studies are clearly negative, as communicated in Dr. Dunn's February 22, 2016 RTF letter and in minutes of the April 19, 2016 meeting between PTC and FDA. As will be explained below, I agree with the conclusion that Studies 007 and 020 are negative and clearly cannot provide substantial evidence of effectiveness. I should add that if I perceived even a small likelihood that on further review of the application and consideration of PTC's explanation, we would conclude that the studies could in fact provide substantial evidence of effectiveness, I would reverse the RTF decision.

2. *You contend that the results of Studies 007 and 020 do in fact provide substantial evidence of effectiveness and that Study 004 "clearly demonstrated that ataluren promoted dystrophin production."*

Studies 007 and 020 clearly failed on their primary analysis of 6-minute walk distance (6MWD) in all patients despite the effort to enrich Study 020 based on the results of Study 007. Study 007 evaluated two dosing regimens (not very different, just a 2-fold difference between them) with 55 patients per group, and showed no treatment effect in either group. Study 020 was enriched on the basis of the Study 007 results to include patients who could walk at least 150 m on their baseline 6MWD and whose 6MWD was < 80% of 6MWD predicted for age, a subgroup of 007 that had a nominally statistically significantly favorable result. Study 020 was larger than Study 007 (220 patients, 110 per group) and evaluated the lower dose regimen from Study 007. Results of Study 020 trended favorably (15.4 m difference from placebo) but the *p*-value was 0.21 and other plausible endpoints, i.e., North Star Ambulatory Assessment, health related quality of life, 10-meter walk/run, also failed. The Study 020 results in an enriched trial plainly show, as is well-recognized, that post-facto subset analyses (such as 6MWD > 150 m and 6MWD < 80% of predicted in Study 007), despite nominal significance in a prior trial, are not reliable effectiveness assessments, as that group, incorporated into Study 020 entry criteria to enrich the study population with likely responders, did not show an ataluren effect ($p = 0.21$).

Analysis of the subset of patients with a baseline 6MWD ≥ 300 m and < 400 m (hereafter 300-400m 6MWD) in Study 020 showed a nominally statistically significant result on the primary endpoint, and the results for the secondary endpoints in this subgroup were also generally favorable. It is thus clear there was a suggestion of an ataluren treatment effect on 6MWD in this post-study selected subset of Study 020, as well as suggestions of effects on measures expected to correlate with 6MWD. As is well-recognized, however, and as illustrated in the previous discussion of the enrichment of Study 020, looking within a study at non-prespecified subsets increases the type 1 error rate substantially; the concern is greatest when there are many potential subsets, as is the case here. We do not

consider the baseline 300-400 m 6MWD to have been pre-specified, as it was clearly not identified as a planned effectiveness analysis, with planned control of the type I error rate, in the statistical analytic plan (SAP). The meta-analysis was similarly unplanned as a primary endpoint.

The statistical analysis of a study factors importantly into the determination of whether a study is adequate and well controlled, as is clear from the regulations at 21CFR 314.126. When analysis plans are developed with data in hand, without a prospective plan for controlling the type I error rate, the study lacks the statistical rigor needed to consider it an adequate and well controlled trial. In the present case, the statistical plan clearly defined the primary analysis as including all patients in Study 020, noting again that the study group was specifically selected as a prognostically enriched population based on Study 007.

I thus conclude that the 007 and 020 trials, analyzed as prospectively planned, clearly cannot provide the basis for a finding of substantial evidence of effectiveness.

In addition, while an NDA for an application seeking approval pursuant to section 506(c) of the FDCA could be filed based upon a demonstration of increased dystrophin as a surrogate endpoint, I do not believe that evidence of such an increase has been provided in his instance:

In two clinical studies (004 and 007), the effect of ataluren on dystrophin production was examined in muscle biopsy samples obtained from patients with nmDMD. No reliable quantitative information (e.g., Western Blot) on dystrophin changes with ataluren treatment are available.

- In Study 004 (38 patients), immunofluorescence methods were used in biopsy samples taken from extensor digitorum brevis. They were said to show an overall mean relative increase of 11% after 28 days of treatment with ataluren, as compared to pre-treatment. Whether microscopic fields used for this analysis were chosen in a blinded fashion has not been stated. Notwithstanding the methodological limitations of this study, immunofluorescence methods are not quantitative; the potential significance of an 11% relative increase is therefore unknown. Western blot data were not obtained in this study.

- In the same study (004), myotubes were cultured *in vitro* from pre-treatment samples taken from extensor digitorum brevis. After exposure of these myotubes to increasing concentrations of ataluren, immunofluorescence methods demonstrated a bell-shaped response with a maximal 11-fold increase in dystrophin expression at 10 µg/mL ataluren. The relevance of this model to potential efficacy of the drug is unclear.

- In Study 007, the objective was to apply immunofluorescence methods *in vivo* to muscle biopsy samples taken from biceps brachii in patients with nmDMD after treatment with ataluren or placebo. The Complete Study Report of Study 007 (section 11.4.2.1) states that, "the majority of muscle biopsy samples were compromised with regards to quality…[and] the difficulties encountered in this study with regard to muscle biopsy sample collection and processing resulted in poor quality histological specimens and preclude interpretation of dystrophin data." Western blot data were not obtained from samples in this study.

- No muscle biopsies were obtained in Study 020.

- In the Clinical Overview of the December, 2015, NDA application (section 1.3.3.6), PTC stated that "muscle biopsy dystrophin expression is not useful as a surrogate endpoint…[and] correlation between muscle biopsy dystrophin expression and clinical outcomes has not been demonstrated."

- After FDA issued a RTF letter to the sponsor on 2/22/16, PTC requested a Type A meeting, which was held on 4/19/16. FDA's comments related to dystrophin, which were based on the application and the meeting package, stated:

"In two clinical studies (Study 004 and Study 007), the effect of ataluren on dystrophin production was examined in muscle biopsy samples obtained from patients with DMD. However the data, on face, do not appear capable of supporting a marketing application, and you acknowledge many of the shortcomings of these data and the difficulty of assessing dystrophin levels in DMD."

PTC noted briefly during the April 19, 2016, meeting that it agreed with our comment and the topic was not discussed.

3. *You assert that FDA is being unfair and inconsistent in refusing to file the ataluren NDA when it accepted for filing NDAs for drisapersen and eteplirsen, which "relied solely on negative studies."*

   I will not go into detail on these determinations, but the drisapersen application included one apparently positive (statistically significant) controlled study as well as a second controlled study with a strongly positive trend and the eteplirsen application included a historically controlled trial that was represented by the sponsor as positive and that appeared to favor eteplirsen. It also included reports claiming to show increased production of dystrophin, which also needed detailed evaluation.

4. *Finally, you object to RTF based on inadequate assessment of abuse potential*.

   We have reconsidered the adverse event data and agree that, in this case, inadequate assessment of abuse potential should not be a basis for RTF.

Potential Solutions:

PTC has suggested possible pathways forward.

1. *Traditional approval pathway based on outcome on 6MWD overall*.

   For the reasons provided above, we do not believe the subset analysis of the baseline 6MWD 300-400 represents a valid finding.

2. *Accelerated approval using 6MWD as an intermediate clinical endpoint.*

   We do not consider 6MWD in a one-year study an "intermediate clinical endpoint," but even if we did, the evidence for an effect on an intermediate clinical endpoint must, under section 505(d) of the FDCA and FDA's regulations, meet the substantial evidence requirement. As we cannot conclude that ataluren had an effect on 6MWD, we cannot reach a conclusion that the NDA s is capable of supporting an approval under section 506(c) of the FDCA based on an effect on a full or intermediate endpoint. Without the requisite evidence of an effect based on adequate and well-controlled trial(s), as discussed above, accelerated approval does not provide an alternative basis for filing.

3. *Accelerated approval based on evidence that ataluren promotes dystrophin production*

   For the reasons described above we do not believe there is evidence of increased dystrophin production and therefore, accelerated approval does not provide an alternative basis for filing.

You indicated in your appeal that filing over protest is not "an adequate form of relief because the NDA would not receive the same quality of review." I recognize the perception that filing over protest does not lead to a prompt review or a review of adequate quality, but this is not the case. We are required for an application filed over protest to undertake a complete review and to issue a complete response detailing all deficiencies identified. We also are not prohibited from engaging in some, or all, of the interactions with sponsors that occur under our current review model for NME applications if we determine those to be of value to a timely completion of the review (they do, after all, facilitate our review in many cases). We would conduct the review of the application if filed over protest in a fair and timely manner. You might ask, given that, why we even distinguish filing over protest from responding favorably to an RTF appeal, as in both cases we need to conduct the full review.

I believe RTF represents in part (it is, of course, also intended to avoid effort and use of FDA's limited resources in a manner likely to be of little value) an effort to advise applicants on the most efficient way forward, which I believe in this case is prompt conduct of another trial, perhaps enriching for the 300-400m 6MWD population. The likelihood that two statistically negative trials (neither close to p=0.05), examined in after-the-fact identified subgroups, would be considered well-controlled studies providing substantial evidence of effectiveness, is so low

that we do not consider the NDA to contain "on its face" the information required under FDCA section 505(b) and 21 CFR 314.101. Such post hoc subset analyses suffer from multiplicity and inflation of the type I error rate, and have long been widely recognized as not credible. Your appeal repeatedly describes the subset and the pooled analysis as "pre-specified," but that is incorrect, at least with regard to the usual meaning of pre-specified, which refers to the planned primary analysis that will be statistically tested. It is true that examining the 300-400 m subset (as well as a number of others) was mentioned in the SAP, but there was clearly no planned use of these as primary study endpoints, and they cannot properly be described as "planned" or "pre-specified." Moreover, neither examination of Study 007 results to identify a possible enrichment population, nor the evidence you cite that "patients with baseline 6MWD between 300 and 400 m are most likely to deteriorate," led you to enrich the 020 population with such patients (they accounted for 43% of patients in Study 020), or to designate the effect in that population the primary endpoint, which could have been done at any time prior to unblinding. Thus, what you now find obvious after examining Study 020 results was plainly not recognized by PTC prior to the study.

One of FDA's principal goals is to accelerate drug development, i.e., to get effective and safe drugs to market as rapidly as practicable. Because we believe that this application cannot be successful in its current form, we believe your most efficient path forward would be to conduct a new study. Should you decide to file over protest, however, an approach we believe would, in the long run, probably delay any potential approval, we will carry out a fair and timely review.

Questions regarding next steps as described in this letter should be directed to Fannie Choy, Regulatory Health Project Manager, Division of Neurology Products, Office of Drug Evaluation I at (301) 796-2250.

This constitutes the final decision at the Office of Drug Evaluation I level. If you wish to appeal this decision to the next level, your appeal should be directed to John Jenkins, M.D., Director, Office of New Drugs, Center for Drug Evaluation and Research. The appeal should be sent to the NDA administrative file as an amendment, and a copy should be sent to the Center's Formal Dispute Resolution Project Manager, Khushboo Sharma. Any questions concerning your appeal should be addressed to Khushboo Sharma at (301) 796-1270.

Sincerely,

{See appended electronic signature page}

Robert Temple, M.D.,
Deputy Director (Acting)
Office of Drug Evaluation I
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ROBERT TEMPLE
10/13/2016

APPENDIX H

May 16, 2014

Ataluren Phase 3 Trial Results in Nonsense Mutation Cystic Fibrosis Published in The Lancet Respiratory Medicine

Data Demonstrate Positive Trends in Lung Function and Pulmonary Exacerbations

SOUTH PLAINFIELD, NJ – May 16, 2014 – PTC Therapeutics, Inc. (NASDAQ: PTCT) today announced that the results of a Phase 3 study of ataluren in patients with nonsense mutation cystic fibrosis (nmCF) were published in Lancet Respiratory Medicine. The results demonstrated positive trends in both the primary endpoint, lung function as measured by relative change in % predicted FEV1 (forced expiratory volume in one second) and in the secondary outcome measure, rate of pulmonary exacerbations. The collective data from this trial, including retrospective and subgroup analyses support the conclusion that ataluren was active and showed clinically meaningful improvements over placebo in these trials.

"The overall data from this trial are promising. Patients on ataluren experienced fewer pulmonary exacerbations and showed a stabilization in their FEV1 results, particularly in the subgroup of patients that did not use chronic inhaled aminoglycosides. Such stabilization of disease is an important clinical endpoint, particularly for this patient population that has one of the most severe forms of CF. CF patients with nonsense mutations do not produce any functional CFTR protein and therefore generally have a more severe form of cystic fibrosis. Current treatments for nonsense mutation cystic fibrosis focus on alleviating symptoms and reducing infections, whereas ataluren targets the underlying cause of disease," stated Michael Konstan, M.D., lead study investigator, and Chairman of Pediatrics, at University Hospitals Rainbow Babies & Children's Hospital in Cleveland, Ohio.

The Phase 3 double-blind, placebo-controlled study, which was conducted across 11 countries, compared ataluren (n=116) to placebo (n=116) in nmCF patients. The primary endpoint, the relative change from baseline in %-predicted FEV1 at 48 weeks, showed a positive trend favoring ataluren versus placebo, and a larger effect in patients not receiving chronic inhaled tobramycin. In the intent-to-treat population, there was a 3% difference in the relative change from baseline

in %-predicted FEV1 between the ataluren and placebo groups at Week 48 (-2.5% change on ataluren vs. -5.5% change on placebo; p=0.12) which was not statistically significant. An analysis of the relative change from baseline in %-predicted FEV1 across all post-baseline study visits demonstrated an average difference between ataluren and placebo of 2.5% (-1.8% average change on ataluren vs. -4.3% average change on placebo; p= 0.048). There were 23% fewer pulmonary exacerbations in the ataluren group compared to placebo (p=0.0992). Further results from a post hoc analysis of the subgroup of patients not receiving chronic inhaled tobramycin showed a 5.7% difference in relative change from baseline in % predicted FEV1 favoring ataluren, with a mean change from baseline of -0.7% in the ataluren arm, and – 6.4% in the placebo arm (nominal p=0.0082). In addition, there were 40% fewer exacerbations in ataluren-treated patients in this subgroup. The outcomes observed in multiple endpoints between the subgroup of patients who were not prescribed chronic inhaled tobramycin and the subgroup of patients who were prescribed chronic inhaled tobramycin as well as post-hoc in vitro testing showing the interference of aminoglycoside antibiotics with ataluren activity support the hypothesis that inhaled tobramycin may interfere with ataluren's mechanism of action.

Safety results indicate that ataluren was generally well tolerated. The overall incidence of adverse events through Week 48 was similar in the ataluren and placebo groups, except for the occurrence of creatinine elevations that occurred more frequently in the ataluren group in connection with concomitant treatment with systemic aminoglycosides. Most treatment emergent adverse events were of mild (Grade 1) or moderate (Grade 2) severity, and no life-threatening adverse events were reported. Most serious adverse events reported in this study were CF pulmonary exacerbations and were considered unrelated to ataluren treatment. Eight patients in the ataluren arm and three patients in the placebo arm discontinued treatment due to an adverse event.

"We are very encouraged by the data from this trial. Given spirometry and pulmonary exacerbation results in the subgroup of patients not receiving chronic inhaled tobramycin, and a favorable safety profile, this study supports further clinical testing of ataluren as a potential first-in-class treatment for nmCF patients not receiving chronic inhaled tobramycin," stated Stuart W. Peltz, Ph.D., Chief Executive Officer of PTC Therapeutics, Inc. "We look forward to initiating a confirmatory ataluren trial in nmCF patients later this year."

ABOUT THE PHASE 3 TRIAL

The primary endpoint of the randomized, double-blind, placebo-controlled study was the relative change in % predicted FEV1 from baseline to Week 48 as assessed by spirometry. Spirometry was performed at screening, at randomization, and every eight weeks during the 48 week study duration. The secondary objective was rate of pulmonary exacerbations. Additional endpoints

evaluated other aspects of patient function, drug activity, and safety. The 48-week trial enrolled 238 patients, ages six years and older, at 36 sites in 11 countries in North America and Europe. Patients were randomly assigned to one of two treatment arms: ataluren (10 mg/kg morning, 10 mg/kg midday, 20 mg/kg evening) or placebo (morning, midday, evening). Patients who completed the study were eligible to receive open-label ataluren in an ongoing extension study.

ABOUT CYSTIC FIBROSIS

Cystic fibrosis (CF) is a disabling and life-threatening autosomal recessive disorder resulting from mutations that cause dysfunction in the cystic fibrosis transmembrane conductance regulator (CFTR). In nmCF, an interruption in the genetic code - known as a nonsense mutation - prematurely halts the synthesis of CFTR, causing the protein to be short and non-functioning. Nonsense mutations are categorized as Class I mutations that result in little or no production of the CFTR protein. CF patients with Class I mutations typically experience more severe disease symptoms than those with other genotypes, including a shorter life span, a higher probability of end-stage lung disease, and a higher prevalence of pancreatic insufficiency. Approximately 10% of patients have CF due to a Class I nonsense mutation in at least one allele of the CFTR gene. Available therapies for treatment of lung manifestations of CF, such as inhaled antibiotics do not address the underlying defect. There are no marketed treatments that target the defect associated with CF caused by nonsense mutations.

ABOUT ATALUREN

Ataluren, an investigational new drug discovered and developed by PTC Therapeutics, is a protein restoration therapy designed to enable the formation of a functioning protein in patients with genetic disorders caused by a nonsense mutation. A nonsense mutation is an alteration in the genetic code that prematurely halts the synthesis of an essential protein. The resulting disorder is determined by which protein cannot be expressed in its entirety and is no longer functional, such as dystrophin in nmDMD. The development of ataluren has been supported by grants from Cystic Fibrosis Foundation Therapeutics Inc. (the nonprofit affiliate of the Cystic Fibrosis Foundation); Muscular Dystrophy Association; FDA's Office of Orphan Products Development; National Center for Research Resources; National Heart, Lung, and Blood Institute; and Parent Project Muscular Dystrophy. ABOUT PTC THERAPEUTICS, INC. PTC is a biopharmaceutical company focused on the discovery and development of orally administered, proprietary small molecule drugs that target post-transcriptional control processes. Post-transcriptional control processes regulate the rate and timing of protein production and are essential to proper cellular function. PTC's internally discovered pipeline addresses multiple therapeutic areas, including rare disorders, oncology and infectious diseases. PTC has developed proprietary technologies that it applies in its drug discovery activities and which form the basis

for collaborations with leading biopharmaceutical companies. For more information on the company, please visit our website www.ptcbio.com.

FOR MORE INFORMATION PLEASE CONTACT:
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FORWARD LOOKING STATEMENTS:
Any statements in this press release about future expectations, plans and prospects for the Company, the development of and potential market for the Company's product candidates, the timing and conduct of our clinical trial of ataluren for the treatment of cystic fibrosis caused by nonsense mutations, including statements regarding the timing of initiation and completion of the trial and the period during which the results of the trial will become available, the potential advantages of ataluren, and our estimates regarding the potential market opportunity for ataluren, and other statements containing the words "anticipate," "believe," "estimate," "expect," "intend," "may," "plan" "predict," "project," "target," "potential," "will," "would," "could," "should," "continue," and similar expressions, constitute forward-looking statements within the meaning of The Private Securities Litigation Reform Act of 1995. Forward-looking statements involve substantial risks and uncertainties that could cause our future results, performance or achievements to differ significantly from those expressed or implied by these forward-looking statements. Such risks and uncertainties include, among others, those related to the initiation and conduct of clinical trials, availability of data from clinical trials, expectations for regulatory approvals, our scientific approach and general development progress, the availability or commercial potential of our product candidates and other factors discussed in the "Risk Factors" in our most recent Quarterly Report, which is on file with the Securities and Exchange Commission. In addition, the forward-looking statements included in this press release represent the Company's views only as of the date of this release. The Company anticipates that subsequent events and developments will cause the Company's views to change. However, while the Company may elect to update these forward-looking statements at some point in the future, the Company specifically disclaims any obligation to do so. These forward-looking statements should not be relied upon as representing the Company's views as of any date subsequent to the date of this release.

APPENDIX I

Mar 2, 2017

PTC Therapeutics Announces Results from Pivotal Phase 3 Clinical Trial of Ataluren in Patients Living with Nonsense Mutation Cystic Fibrosis

- ACT CF trial missed primary and secondary endpoints - - Company to host conference call today, March 2nd at 9:00 am ET -

SOUTH PLAINFIELD, N.J., March 2, 2017 /PRNewswire/ -- PTC Therapeutics, Inc. (NASDAQ: PTCT), today announced that the Ataluren Confirmatory Trial (ACT CF) in nonsense mutation cystic fibrosis (nmCF) did not achieve its primary or secondary endpoints. Ataluren was generally well tolerated and ACT CF confirmed a favorable safety profile for ataluren, which has now been used by more than 1,000 patients across multiple indications. PTC plans to discontinue current clinical development of ataluren in cystic fibrosis, close ongoing extension studies and withdraw its application for marketing authorization in cystic fibrosis in Europe.

"We are disappointed with the outcome of this trial as there are no treatments that target the underlying cause of nonsense mutation cystic fibrosis, one of the most difficult forms to treat," said Stuart W. Peltz, Ph.D., chief executive officer of PTC Therapeutics. "We are particularly grateful to patients and investigators who participated in our trials. We remain committed to patients receiving ataluren in other indications."

ACT CF was a double-blind, placebo-controlled, 48-week clinical trial comparing ataluren to placebo in nmCF patients six years of age or older not receiving chronic inhaled aminoglycosides. The Phase 3 study, conducted in 16 countries, enrolled 279 patients who were randomized to receive either ataluren or placebo. In the intent-to-treat population, the primary endpoint of lung function as measured by absolute change in percent-predicted FEV1 (forced expiratory volume in one second), over 48 weeks from baseline, there was a 0.6% difference in favor of ataluren versus placebo (-1.4% change on ataluren versus -2.0% change on placebo; p=0.534). For the secondary endpoint of rate of pulmonary exacerbations, there was a trend in favor of ataluren, with the rate in the ataluren group being 14% lower than the placebo group (p=0.401). The results were not statistically significant.

The safety profile of ataluren in the ACT CF study was consistent with previous studies and no new safety signals were identified.

About Cystic Fibrosis

Cystic fibrosis is among the most common life-threatening genetic disorders worldwide. It is caused by defects in a single gene known as the cystic fibrosis transmembrane conductance regulator, or CFTR. The CFTR gene encodes the CFTR protein, which is used by the body to transport chloride across cell membranes. Genetic mutations that result in the loss of function of the CFTR protein cause the body to produce abnormally thick and sticky mucus that clogs multiple organs, including the lungs, pancreas and liver. In particular, the absence or very low levels of CFTR leads to progressive loss of lung function, potentially life-threatening lung infections, permanent pancreatic damage and malnutrition because digestive enzymes from the pancreas do not reach the intestines to help break down and absorb food. The average age of death for CF patients is in their mid-thirties.

About ataluren (Translarna™)

Ataluren (brand name: Translarna™), discovered and developed by PTC Therapeutics, Inc., is a protein restoration therapy designed to enable the formation of a functioning protein in patients with genetic disorders caused by a nonsense mutation. A nonsense mutation is an alteration in the genetic code that prematurely halts the synthesis of an essential protein. The resulting disorder is determined by which protein cannot be expressed in its entirety and is no longer functional, such as dystrophin in Duchenne muscular dystrophy. Ataluren is licensed in the European Economic Area for the treatment of nonsense mutation Duchenne muscular dystrophy in ambulatory patients aged five years and older. Ataluren is an investigational new drug in the United States. The development of ataluren has been supported by grants from Cystic Fibrosis Foundation Therapeutics Inc. (the nonprofit affiliate of the Cystic Fibrosis Foundation); Muscular Dystrophy Association; FDA's Office of Orphan Products Development; National Center for Research Resources; National Heart, Lung, and Blood Institute; and Parent Project Muscular Dystrophy.

About PTC Therapeutics

PTC is a global biopharmaceutical company focused on the discovery, development and commercialization of orally administered, proprietary small molecule drugs targeting an area of RNA biology we refer to as post-transcriptional control. Post-transcriptional control processes are the regulatory events that occur in cells during and after a messenger RNA, or mRNA, molecule is copied from DNA through the transcription process. PTC's internally discovered pipeline addresses multiple therapeutic areas, including rare disorders and oncology. PTC has discovered all of its compounds currently under development using its proprietary technologies. PTC plans to continue to develop these compounds both on its own and through selective collaboration arrangements with

leading pharmaceutical and biotechnology companies. For more information on the company, please visit our website www.ptcbio.com.

Today's Conference Call

The call can be accessed by dialing (877) 303-9216 (domestic) or (973) 935-8152 (international) five minutes prior to the start of the call and providing the passcode 82242185.

A live, listen-only webcast of the conference call can be accessed on the investor relations section of the PTC website at www.ptcbio.com. A webcast replay of the call will be available approximately two hours after completion of the call and will be archived on the company's website for two weeks.

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Forward-looking Statements

This press release contains forward-looking statements within the meaning of The Private Securities Litigation Reform Act of 1995. All statements, other than those of historical fact, contained in this release are forward-looking statements, including statements regarding the future expectations, plans and prospects for PTC, with respect to regulatory and clinical actions or otherwise; the clinical utility and potential advantages of Translarna (ataluren); PTC's strategy, future operations, future financial position, future revenues or projected costs; and the objectives of management. Other forward-looking statements may be identified by the words "plan," "anticipate," "believe," "estimate," "expect," "intend," "may," "predict," "project," "target," "potential," "will," "would," "could," "should," "continue," and similar expressions.

PTC's actual results, performance or achievements could differ materially from those expressed or implied by forward-looking statements it makes as a result of a variety of risks and uncertainties, including those related to PTC's scientific approach and general development progress; the outcome of ongoing or future clinical studies in Translarna and PTC's other product candidates; expectations for regulatory approvals; PTC's ability to meet existing or future regulatory standards with respect to Translarna; the sufficiency of PTC's cash resources and its ability to obtain adequate financing in the future for its foreseeable and unforeseeable operating expenses and capital expenditures; PTC's

ability to maintain its marketing authorization of Translarna for the treatment of nonsense mutation Duchenne muscular dystrophy (nmDMD) in the European Economic Area (EEA), including whether the European Medicines Agency (EMA) determines in future annual renewal cycles that the benefit-risk balance of Translarna authorization supports renewal of such authorization; PTC's ability to enroll, fund, complete and timely submit to the EMA the results of Study 041, a randomized, 18-month, placebo-controlled clinical trial of Translarna for the treatment of nmDMD followed by an 18-month open label extension; PTC's ability to resolve the matters set forth in the Refuse to File letter it received from the United States Food and Drug Administration (FDA) in connection with its New Drug Application (NDA) for Translarna for the treatment of nmDMD, including whether filing the NDA over protest with the FDA will result in a timely or successful review of the NDA, and whether PTC will be required to perform additional clinical and non-clinical trials or analyses at significant cost; the eligible patient base and commercial potential of Translarna and PTC's other product candidates; PTC's ability to commercialize and commercially manufacture Translarna in general and specifically as a treatment for nmDMD; the outcome of pricing and reimbursement negotiations in those territories in which PTC is authorized to sell Translarna for the treatment of nmDMD; and the factors discussed in the "Risk Factors" section of PTC's most recent Quarterly Report on Form 10-Q as well as any updates to these risk factors filed from time to time in PTC's other filings with the SEC. You are urged to carefully consider all such factors.

As with any pharmaceutical under development, there are significant risks in the development, regulatory approval and commercialization of new products. There are no guarantees that Translarna will receive full regulatory approval in any territory or maintain its current marketing authorization for Translarna for the treatment of nmDMD in the EEA, or prove to be commercially successful in general, or specifically with respect to the treatment of nmDMD.

The forward-looking statements contained herein represent PTC's views only as of the date of this press release and PTC does not undertake or plan to update or revise any such forward-looking statements to reflect actual results or changes in plans, prospects, assumptions, estimates or projections, or other circumstances occurring after the date of this press release except as required by law.

To view the original version on PR Newswire, visit: http://www.prnewswire.com/news-releases/ptc-therapeutics-announces-results-from-pivotal-phase-3-clinical-trial-of-ataluren-in-patients-living-with-nonsense-mutation-cystic-fibrosis-300416860.html

SOURCE PTC Therapeutics, Inc.

News Provided by Acquire Media

APPENDIX J

Food and Drug Administration
Center for Drug Evaluation and Research

Summary Minutes of the Oncologic Drugs Advisory Committee
September 14, 2016

Location: Tommy Douglas Conference Center
10000 New Hampshire Avenue, Silver Spring, Maryland 20903

Topic: The committee met to discuss new drug application 208714, apaziquone for intravesical instillation, application submitted by Spectrum Pharmaceuticals, Inc. The proposed indication (use) for this product is for immediate intravesical instillation post-transurethral resection of bladder tumors in patients with non-muscle invasive bladder cancer.

These summary minutes for the September 14, 2016, meeting of the Oncologic Drugs Advisory Committee of the Food and Drug Administration were approved on October 14, 2016.

I certify that I attended the September 14, 2016, meeting of the Oncologic Drugs Advisory Committee of the Food and Drug Administration and that these minutes accurately reflect what transpired.

/S/
Lauren D. Tesh, PharmD, BCPS
Designated Federal Officer, ODAC

/S/
Bruce J. Roth, MD
Chairperson, ODAC

Oncologic Drugs Advisory Committee Meeting
September 14, 2016

The following is the final report of the Oncologic Drugs Advisory Committee (ODAC) meeting held on September 14, 2016. A verbatim transcript will be available in approximately six weeks, sent to the Office of Hematology and Oncology Products and posted on the FDA website at: http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/ucm486395.htm

All external requests for the meeting transcript should be submitted to the CDER Freedom of Information Office.

The Oncologic Drugs Advisory Committee (ODAC) of the Food and Drug Administration, Center for Drug Evaluation and Research met on September 14, 2016, at the Tommy Douglas Conference Center, 10000 New Hampshire Avenue, Silver Spring, Maryland. Prior to the meeting, members and temporary voting members were provided copies of the briefing materials from the FDA and Spectrum Pharmaceuticals, Inc. The meeting was called to order by Bruce J. Roth, MD (Chairperson); the conflict of interest statement was read into the record by Lauren D. Tesh, PharmD, BCPS (Designated Federal Officer). There were approximately 80 people in attendance. There were five (5) Open Public Hearing speakers.

Issue: The committee discussed new drug application 208714, apaziquone for intravesical instillation, application submitted by Spectrum Pharmaceuticals, Inc. The proposed indication (use) for this product is for immediate intravesical instillation post-transurethral resection of bladder tumors in patients with non-muscle invasive bladder cancer.

Attendance:
ODAC Members Present (Voting): Bernard F. Cole, PhD; Grzegorz S. Nowakowski, MD; Vassiliki Papadimitrakopoulou, MD; Gregory J. Riely, MD, PhD; Brian I. Rini, MD, FACP; Bruce J. Roth, MD (Chairperson); Thomas S. Uldrick, MD, MS

ODAC Members Present (Non-Voting): Phuong Khanh (P.K.) Morrow, MD, FACP (Industry Representative)

ODAC Members Not Present (Voting): Harold J. Burstein, MD, PhD; Heidi D. Klepin, MD, MS; Jeffrey E. Lancet, MD; Albert S. Pappo, MD; Courtney J. Preusse, MA (Consumer Representative); Alice T. Shaw, MD, PhD

Temporary Members (Voting): Karim Chamie, MD, MSHS; Mark L. Gonzalgo, MD, PhD; Pamela J. Haylock, PhD, RN (Acting Consumer Representative); Brent Logan, PhD; Patricia A. Spears (Patient Representative); Jennifer M. Taylor, MD, MPH; John A. Taylor, III, MD, MS

FDA Participants (**Non-Voting):** Richard Pazdur, MD; Geoffrey Kim, MD; V. Ellen Maher, MD; Gwynn Ison, MD; Chana Weinstock, MD; Erik Bloomquist, PhD

Designated Federal Officer (Non-Voting): Lauren D. Tesh, PharmD, BCPS

Open Public Hearing Speakers: Mark Krivel; Ed Silver; Andrea Maddox-Smith (The Bladder Cancer Advocacy Network); Michaela O'Hearn; Raoul S. Concepcion, MD, FACS (Vanderbilt University School of Medicine and The Comprehensive Prostate Center)

The agenda proceeded as follows:

Call to Order and Introduction of Committee	**Bruce J. Roth, MD** Chairperson, ODAC
Conflict of Interest Statement	**Lauren Tesh, PharmD, BCPS** Designated Federal Officer, ODAC
Opening Remarks	**Chana Weinstock, MD** Medical Officer, Genitourinary Cancers Team Division of Oncology Products 1 (DOP1) Office of Hematology & Oncology Products (OHOP) Office of New Drugs (OND), CDER, FDA
GUEST SPEAKER PRESENTATION	
Overview of Diagnosis and Management of Non-Muscle Invasive Bladder Cancer	**Seth P. Lerner, MD, FACS** Professor, Scott Department of Urology Beth and Dave Swalm Chair in Urologic Oncology Director of Urologic Oncology Director of the Multidisciplinary Bladder Cancer Program Baylor College of Medicine Medical Center Houston, Texas
APPLICANT PRESENTATIONS	**Spectrum Pharmaceuticals, Inc.**
Introduction	**Anil K. Hiteshi, RAC** Global Regulatory Affairs Spectrum Pharmaceuticals, Inc.
Post-Operative Intravesical Therapy	**Neal Shore, MD** Medical Director Carolina Urologic Research Center

APPLICANT PRESENTATIONS (CONT.)

Clinical Efficacy and Safety	**Gajanan Bhat, PhD** Vice President, Biostatistics, Data Management and Medical Writing Spectrum Pharmaceuticals, Inc.
Benefit-Risk and Clinical Utility of Apaziquone	**Alfred Witjes, MD** Professor of Urologic Oncology Radbound University Nijmegen Medical Centre
Clinical Perspective	**Mark Soloway, MD** Chief of Urological Oncology Memorial Cancer Institute, Miami
Concluding Remarks	**Rajesh Shrotriya, MD** Chairman and Chief Executive Officer Spectrum Pharmaceuticals, Inc.

FDA PRESENTATIONS

NDA 208714 - Apaziquone	**Gwynn Ison, MD** Medical Officer DOP1, OHOP, OND, CDER, FDA
FDA Statistical Analysis	**Erik Bloomquist, PhD** Statistical Reviewer Division of Biometrics V (DBV) Office of Biometrics (OB) Office of Translational Sciences (OTS) CDER, FDA

Clarifying Questions to the Presenters

BREAK

Open Public Hearing

Questions to the Committee/Committee Discussion

ADJOURNMENT

Questions to the Committee:

1. **VOTE:** Has substantial evidence of a treatment effect for apaziquone over placebo been demonstrated?

   Voting Results YES: 0 NO: 14 ABSTAIN: 0

   Committee Discussion:

   The committee noted that this drug may have activity in patients with NMIBC but based on the data that was presented, it was unanimously agreed that substantial evidence of efficacy had not been shown. One statistician on the panel stated that the sponsor did not meet their primary endpoints in both studies, 611 and 612, and that the subgroup analyses were ad-hoc and could lead to potentially biased estimates of the treatment effect in the subgroups of interest. In addition, it was commented that the pooled analysis of the two studies didn't have a prospective protocol. The pooled analysis of 611 and 612 was done post-hoc and doesn't provide the same level of statistical certainty or robustness as the two separate trials would have. Also, the committee noted there was a substantial amount of missing data and that this may have impacted the estimated effect. The committee recommended that the sponsor continue the development of this drug because of the unmet need in this population and the seemingly low toxicity profile of apaziquone compared to current therapy. One committee member noted that to encourage development in nonmuscle-invasive bladder cancer that the urologic community needs to further define appropriate endpoints for clinical trials. Please see the transcript for details of the committee discussion.

2. **DISCUSSION:** For those who voted "yes" to question 1 that an effect has been demonstrated, please discuss the clinical meaning of the results of studies 611 and 612.

   Committee Discussion: *The unanimous vote of NO to question 1 precluded the need for this discussion. Please see the transcript for details of the committee discussion.*

   The meeting was adjourned at approximately 11:57 a.m.