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ADVISORY COMMITTEE BRIEFING MATERIALS: AVAILABLE FOR PUBLIC RELEASE

PERIPHERAL AND CENTRAL NERVOUS SYSTEM DRUGS
ADVISORY COMMITTEE
SEPTEMBER 28, 2017
ADDENDUM TO
ATALUREN BRIEFING DOCUMENT
NDA 200896
PTC THERAPEUTICS, INC.

PTC Therapeutics, Inc. (PTC) would like to provide a complete and fair record for consideration by the Peripheral and Central Nervous System Drugs Advisory Committee (PCNSDAC) at its meeting of September 28, 2017 regarding PTC's NDA 200896 for ataluren (Translarna™) for the treatment of dystrophinopathy resulting from nonsense mutation in the dystrophin gene (nonsense mutation Duchenne muscular dystrophy or nmDMD).

FDA recently provided PTC with its draft Briefing Document for the upcoming meeting of the PCNSDAC. In its memorandum to the committee, FDA discusses the regulatory history of ataluren, including the refuse-to-file letter received by PTC with respect to the NDA in 2015 and the subsequent dispute resolution request and filing over protest of the NDA. In support of its account of the regulatory history, FDA includes only documents it generated and sent to PTC, and none of PTC's documents or responses. The memorandum also references other regulatory matters outside of the normal scope of a presentation to an advisory committee, including minutes of a recent negative advisory committee meeting for an oncology drug. We consider this to be inappropriate since it could lead to an incorrect interpretation by the committee members as a fair and balanced representation of all advisory committees' outcomes.

Because FDA's memorandum to the PCNSDAC selectively presents only certain aspects of the record, PTC is providing the following materials to present the record in a fair and balanced manner:

1. **PTC's request to FDA for dispute resolution regarding the 2015 refusal to file the ataluren NDA (Sequence S0017, July 13, 2016).** This document presents PTC's arguments regarding the inconsistency of FDA's treatment of the filing decision of the ataluren NDA compared to other applications, which were taken to full review and/or approved.
2. **PTC's record of the Type A meeting on April 19, 2016 (Sequence S0016).** FDA created minutes of the Type A meeting which, in PTC's view, did not fully capture the matters discussed, and FDA has now provided these minutes to the PCNSDAC. Therefore, PTC is providing its own record of the meeting which was prepared and submitted to FDA prior to the filing of the dispute resolution request. Key differences between FDA's and PTC's records of the meeting are discussed in the body of PTC's dispute resolution request.
3. **A table of historical applications that were approved by FDA entirely based on retrospective analyses despite the failure of the clinical trials proposed as a basis for approval to meet their primary endpoints in the primary analysis.** This table below is presented to illustrate examples where an NDA has been approved despite the trials not having met their primary endpoint.

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Drug Name and Dosage Form	Type, Submission Date, Approval Date	Indication	Statistical Level for approval
Synribo (omacetaxine mepusuccinate) for Injection	NDA March 2012 October 2012	Treatment of adult patients with chronic or accelerated phase chronic myeloid leukemia (CML) with resistance and/or intolerance to two or more tyrosine kinase inhibitors (TKI). This indication is based upon response rate. There are no trials verifying an improvement in disease-related symptoms or increased survival with Synribo	Post-hoc analysis of a subset of patients in two single-arm studies without any pre-specified statistical considerations
Kalydeco (ivacaftor) Tablets	sNDA June 2014 December 2014	Treatment of cystic fibrosis in patients age 6 years and older who have an R117H mutation in the CFTR gene	Single controlled study p=0.198 (subgroup analysis p=0.0119)
Exjade (deferasirox) Tablets for Oral Suspension	NDA April 2005 November 2005	Treatment of chronic iron overload due to blood transfusions (transfusional hemosiderosis) in patients 2 years of age and older	Non-inferiority study failed to meet pre-specified criteria
Remodulin (treprostinil) Injection	NDA October 2000 (withdrawn July 2001 and resubmitted August 2001) March 2002	Treatment of pulmonary arterial hypertension in patients with NYHA Class II-IV symptoms to diminish symptoms associated with exercise	Pooled analysis (p=0.0064) of two studies: p=0.0607 and p=0.0550
Rilutek (riluzole) Tablets	NDA June 1995 December 1995	Treatment of patients with amyotrophic lateral sclerosis (ALS)	Two studies: p=0.12 and p=0.076 (p=0.05 and p=0.05 after post-hoc analysis)
Vasotec (enalapril maleate) Tablets	sNDA March 1993 November 1993	Treatment of Asymptomatic left ventricular dysfunction	Single controlled study p= 0.30 (statistically significant secondary endpoints)

Lastly, we also noted that the Division's memo to the committee does not provide a balanced reflection of the Statistical Review and Evaluation, including the observations that suggest a possible signal of treatment effect for ataluren. Most notably, the clinical review is silent on interpreting the data in light of the disease, its unmet need and natural history.

FORMAL DISPUTE RESOLUTION REQUEST

TRANSLARNA™
ATALUREN (PTC124)

NDA 200896

13 JULY 2016
PTC THERAPEUTICS, INC.
100 CORPORATE COURT
SOUTH PLAINFIELD, NJ 07080

TABLE OF CONTENTS

1 INTRODUCTION AND BACKGROUND

This is a formal dispute resolution request submitted by PTC Therapeutics, Inc. (PTC) regarding new drug application (NDA) 200896 for ataluren (PTC124), which was submitted under Section 505(b)(1) of the Federal Food, Drug and Cosmetic Act (FDCA) on 23 December 2015. The Division of Neurology Products (DNP) issued a refusal-to-file (RTF) letter on 22 February 2016 with respect to this NDA, which was upheld following a Type A meeting on 19 April 2016 with DNP Director Dr. William Dunn, representatives of senior leadership in the Office of Drug Evaluation I (ODE I), clinical team leaders and reviewers from DNP, as well as representatives of the Office of Clinical Pharmacology, the Controlled Substance Staff (CSS), and the Rare Diseases Program. *See* Letter from William Dunn, Deputy Director, ODE I, CDER, FDA, to Murad Husain, PTC Therapeutics, Inc. (22 February 2016) ("RTF Letter"). PTC requests reversal of the RTF decision to enable DNP to accept and engage in full, substantive review of NDA 200896, including the full range of benefits ordinarily made available as part of the review process for orphan drugs intended to treat serious or life-threatening conditions in areas of high unmet medical need. PTC also requests a meeting with Dr. Janet Woodcock, Director, Center for Drug Evaluation and Research, as the deciding officer for this appeal in accordance with the FDA guidance document on the formal dispute resolution process. *See* FDA, "Formal Dispute Resolution: Appeals Above the Division Level: Guidance for Industry and Review Staff" (Draft) 6 (September 2015) ("After a sponsor has decided to submit an FDRR, as part of the appeal, it can request a meeting with the deciding official for the appeal….This meeting is an opportunity for the sponsor to discuss the appeal issue(s) with the deciding official for the appeal.")

The proposed indication for ataluren is as follows: "Translarna™ (ataluren) is indicated for the treatment of patients with dystrophinopathy due to a nonsense mutation in the dystrophin gene. The presence of a nonsense mutation should be determined by genetic testing." Duchenne muscular dystrophy (DMD) is a rare genetic disorder characterized by a lack of functional dystrophin, a protein that is essential to the health of skeletal, pulmonary, and cardiac muscle tissue. DMD manifests during early childhood, and it is incurable and invariably fatal. Patients with DMD experience severe muscle degeneration and usually lose the ability to walk by their early teens. Loss of ambulatory function is followed by a loss of function in the upper extremities, and then by respiratory and cardiac failure. Patients typically require ventilation support in their late teens and usually die in their mid-twenties.

At present, drug treatment in the United States is limited to the unapproved use of a corticosteroid (prednisone). Another corticosteroid (deflazacort) recently was granted fast track status by FDA as a potential treatment for DMD. The use of either drug, however, is known to have serious side effects. Steroids slow the rate of muscle deterioration and may help improve muscle strength and delay the progression of DMD, but they do not treat the underlying cause of the disease. As current therapy for DMD is limited to these supportive measures, there is an urgent unmet need for new treatments for DMD that address the underlying cause of the disease.

Approximately 13% of DMD cases involve a nonsense mutation of the X-chromosome. In patients with this mutation, a defective gene causes premature stop codons to be transcribed into messenger RNA, which in turn results in the production of a truncated non-functional form of dystrophin. Nonsense mutation DMD (nmDMD) is an ultra-orphan condition, with an estimated 2,000 patients in the United States suffering from this form of the disease.

Beginning over a decade ago, PTC discovered and developed ataluren, a novel new drug that targets genetic disorders caused by nonsense mutations. In PTC's clinical studies in nmDMD, ataluren promoted the production of dystrophin and resulted in clinically meaningful changes to multiple clinical endpoints that are known to be prognostic for changes in the progression of this disease. PTC has been a pioneer in the development of approaches to treat nmDMD. Prior to PTC's Study 007, no registration-directed trials had been performed in DMD and the natural history of the disorder was not well understood. Conducting clinical trials while still learning about the disease has made for a difficult development program, as FDA itself has publicly recognized in its recent draft guidance on development of drugs for DMD, and PTC has worked closely with regulators, investigators, patients, and advocacy groups to develop clinically meaningful endpoints. *See* Janet Woodcock, FDAVoice, The More We Know About Rare Diseases, The More Likely We Are To Find Safe And Effective Treatments (23 October 2014), http://1.usa.gov/291FyY8 (noting that the natural histories of rare diseases are not "fully understood," and this "lack of knowledge limits researchers' ability to study rare diseases and develop new treatments"). Overall, 333 patients with nmDMD, 295 patients with other disorders, and 115 healthy volunteers have received ataluren in completed clinical trials, some for as long as 4.7 years. In addition, PTC has continued to provide access to ataluren to hundreds of patients worldwide through ongoing extension studies. In 2014, the European Medicines Agency granted conditional approval to ataluren (trade name Translarna), and it is now available in many countries outside the United States either commercially or via reimbursed early access programs.

2 DESCRIPTION OF SCIENTIFIC/MEDICAL MATTERS TO BE RESOLVED

The RTF letter provided two reasons for refusing to file NDA 200896:

1. DNP stated that the NDA "cannot be approved based on the data submitted" because the two pivotal trials were "negative" and "do not provide substantial evidence of effectiveness." *See* RTF Letter at 1.
2. DNP also asserted that the NDA contained "inadequate" information "regarding the abuse potential of ataluren" based on the ground that central nervous system (CNS) adverse events were "more commonly reported in ataluren-treated patients than in placebo-treated patients." *See* RTF Letter at 2.

PTC requests reversal of DNP's decision. The application contained all of the information required under section 505(b) of the FDCA and applicable regulations and therefore DNP was required to engage in a full review.

- With respect to DNP's concerns regarding approvability and substantial evidence of effectiveness:
    - The application contains extensive evidence of effectiveness that, upon review, could reasonably be determined to be substantial evidence of effectiveness for purposes of section 505(d) of the FDCA. This evidence includes the results of over a decade of clinical studies of ataluren, in hundreds of patients, including two of the largest placebo-controlled studies ever conducted in DMD.
    - DNP does not have the authority to refuse to file NDA 200896 based on concerns about the ultimate approvability of the application. Whether the

clinical trials included in the NDA for ataluren provide substantial evidence of effectiveness is a review question and cannot be used as the basis for a refusal to file.

- In the past year alone, DNP has accepted for filing and taken to full review two other applications for DMD with equal or less evidence of effectiveness, and DNP has allowed supplemental information to be provided in support of effectiveness in mid-review. Holding the ataluren application to a different standard is neither fair nor permissible under the law.

- With respect to DNP's observations regarding abuse potential:
  - The application contained the information required by the applicable regulations to support a determination that ataluren does not exhibit potential for abuse. DNP referenced a draft guidance in the RTF letter, but draft guidances are not binding on applicants, and in any case PTC provided reformatted information from the NDA consistent with the draft guidance as a supplement to the materials for the Type A meeting.
  - Contrary to DNP's statement, and as further detailed in a document provided to DNP prior to the Type A meeting, there are no CNS signals from PTC's clinical trials (or any other studies) indicating abuse potential for ataluren.
  - In subsequent interactions with FDA, and at the Type A meeting, representatives of FDA not only refused to state the basis for the factual conclusion that ataluren exhibits abuse potential, but were evidently unfamiliar with the relevant parts of the application and the briefing materials provided by PTC. This alone suggests that an actual review of pertinent information in the application would be needed to determine whether PTC has adequately addressed abuse potential.

PTC's position that the ataluren NDA should be filed and taken to full review is presented in more detail in the following sections of this document.

2.1 Substantial evidence of effectiveness

2.1.1 Although PTC does not agree that this is the correct standard for an RTF decision, the ataluren NDA does contain substantial evidence of effectiveness

PTC's work on ataluren includes the most extensive clinical investigations ever conducted in DMD and the only clinical investigations specific to nmDMD. NDA 200896 reports the results of these investigations and provides substantial evidence for the effectiveness of ataluren, including the following:

- An analysis of a pre-specified subgroup of patients with baseline six-minute walk distance (6MWD) of 300-400 meters in Study 020 showing large and nominally statistically significant benefits as assessed by change in 6MWD, change in time to climb 4 stairs, time to descend 4 stairs, and change in North Star Ambulatory Assessment (NSAA).
- A retrospective analysis showing large and nominally statistically significant treatment effects for the baseline 6MWD 300-400 meters subgroup in Study 007 in the 6MWD and the time to descend 4 stairs.
- A pre-specified meta-analysis of two randomized controlled trials (Study 007 and Study 020) showing statistically significant benefits for efficacy endpoints that were

included in both trials. These endpoints include change in 6MWD, time to 10% worsening in 6MWD, change in time to run/walk 10 meters, change in time to climb 4 stairs, and change in time to descend 4 stairs.

- Documentation of a consistent pattern of differences favoring ataluren 10, 10, 20 mg/kg vs. placebo across primary and secondary outcome measures of physical functioning in the intent-to-treat (ITT) population of Study 020 and in the corrected ITT (cITT) population of Study 007. Notably, ataluren-treated patients were protected from loss of ambulation in both studies.

PTC included the baseline 6MWD 300-400 meters subgroup and the meta-analysis in the statistical analysis plan (SAP) for Study 020, which was provided to FDA for review and comment prior to database lock and unblinding of Study 020, but it did not specify either as the primary analysis. PTC also performed retrospective analyses, including a more conservative meta-analysis and analyses of several secondary endpoints. PTC provided a detailed rationale for reliance on the pre-specified baseline 6MWD 300-400 meters subgroup analyses, the pre-specified meta-analysis, and the new analyses in the NDA. At DNP's request, in connection with the NDA's use of the baseline 6MWD 300-400 meters subgroup analysis from Study 020, PTC proposed an adjustment for multiplicity at the Type A meeting which supported the significant effect seen in that subgroup. *See* PTC, Type A Meeting Briefing Document (23 March 2016) (PTC Briefing Package). These analyses and data meet the substantial evidence of efficacy standard. In particular, the NDA does contain "evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed." FDCA § 505(d). A full review of the NDA would allow experts in the DMD field to provide their views on the evidence in the ataluren NDA to FDA in support of its approvability.

According to DNP (and as stated in either the RTF letter or DNP's preliminary comments to or minutes of the Type A meeting):

- The baseline 6MWD 300-400 meters subgroup constituted "a post hoc adjustment of Study 020 that eliminates data from a majority of enrolled patients." *See* RTF Letter at 1.
- The meta-analysis combining data from Study 007 and Study 020 did not support the effectiveness of ataluren, primarily because it was "neither pre-specified nor planned." *See* FDA, Memorandum of Meeting Minutes, Type A Meeting at 6 (19 April 2016) ("FDA Type A Meeting Minutes").
- Most of the secondary endpoints in Study 020 were "nominally negative." *See* RTF Letter at 1.
- In spite of efforts to enrich the patient population from Study 007, the observed treatment effect in Study 020 was approximately half the size of the overall non-significant treatment effect in Study 007. *See* FDA Type A Meeting Minutes at 4.

PTC disagrees with DNP on these points. A detailed rebuttal of DNP's criticisms is provided below.

In addition to discussions about accepting the ataluren NDA for filing, the Type A meeting included discussions on the topic of approvability. *See* FDA Type A Meeting Minutes at 6-7.

Specifically, DNP stated that its conclusion that the ataluren application does not contain substantial evidence of effectiveness was based on significance testing that failed to reject the null hypothesis for the primary endpoint in the intent-to-treat (ITT) populations in Studies 007 and 020. *See* FDA Type A Meeting Minutes at 4. Therefore, in DNP's view, the robust treatment effects observed in subgroup analyses from those studies do not provide substantial evidence of effectiveness because those analyses do not adequately control for type I error. DNP commented that the Study 007 subgroup analyses are post hoc and the Study 020 analyses, although pre-specified, are considered merely hypothesis-generating in a trial with a negative primary analysis. *See* FDA Type A Meeting Minutes at 5. In its formal minutes of the Type A meeting, DNP did concede that the evidence from Study 007 and Study 020 could be viewed as supportive data if a single new adequate and well-controlled study were to be conducted. *See* FDA Type A Meeting Minutes at 7.

Baseline 6MWD 300-400 meters subgroup

With respect to the baseline 6MWD 300-400 meters subgroup, as PTC discussed in the NDA and at the Type A meeting, there are clinical and scientific reasons to believe that this is the population in which the six-minute walk test (6MWT) can best show drug effect in a one-year time frame. *See* PTC Briefing Package at 19. This information reflects the evolving understanding of the natural history of nmDMD, and it emerged only after PTC had designed and begun enrollment of Study 020. However, this subgroup was identified by PTC in revisions to the SAP for Study 020 made in May 2015 and shared with FDA at that time. *See* Draft Statistical Analysis Plan for ataluren Study 020 (submitted 4 May 2015). These revisions were finalized in an August 2015 submission to FDA prior to database lock and unblinding of Study 020. *See* Final Statistical Analysis Plan for ataluren Study 020 (submitted 20 August 2015). There is now evidence, from independent datasets, that patients with a baseline 6MWD between 300 and 400 meters are most likely to deteriorate in a reliably measurable way over the course of 48 weeks, while patients with a baseline 6MWD over 400 meters are unlikely to deteriorate in that time, and patients with baseline 6MWD below 300 meters are likely to deteriorate too rapidly to reliably measure. Based on this evidence, PTC included in the SAP for Study 020 an analysis of 6MWD for the subgroup of patients with baseline 6MWD of ≥300 to <400 meters as well as the complement subgroups (6MWD<300 meters and 6MWD≥400 meters). DNP itself has commented publicly on the difficulties of using the 6MWD as a clinical endpoint outside the 300-400 meter range, including the general pattern of patients below 300 meters 6MWD losing ambulation in a one to two year time frame, and the unlikelihood that patients walking more than 400 meters in the 6MWD will lose ambulation over a similar time period. *See* FDA, Memorandum from Dr. Farkas to Members and Invited Guests of the Peripheral and Central Nervous System Drugs Advisory Committee 29-30 (29 March 2016), *in* Briefing Document, Peripheral and Central Nervous System Drugs Advisory Committee Meeting (25 April 2016).

DNP representatives at the Type A meeting acknowledged that the baseline 6MWD 300-400 meters subgroup was identified in the SAP for Study 020. *See* FDA Type A Meeting Minutes at 5 (noting that PTC "chose to highlight the subgroup with baseline 6MWD of at least 300 meters but less than 400 meters . . . [that was] identified in the [SAP]"). However, DNP extended its critique of PTC's subgroup analysis by noting that the SAP defined 5 subgroups based on 6MWD and an additional 4 subgroups based on other characteristics at baseline, and that PTC did not pre-specify whether any of the subgroups would be included in the primary analyses with adjustments to control for Type-I error. *See* FDA Type A Meeting Minutes at 5. On this basis, DNP stated that any subgroup findings were exploratory and "cannot provide evidence of effectiveness." FDA Type A Meeting Minutes at 5. FDA representatives at the

Type A meeting also stated that it would be "a different conversation" if PTC had pre-specified the baseline 6MWD 300-400 meters subgroup as the primary analysis. *See* PTC Record of Meeting Discussion, Type A Meeting (19 April 2016) at 5 ("PTC Type A Meeting Record")

The mere fact that the selection of a different primary analysis is retrospective does not destroy its credibility, particularly where there is a rationale for the change and the relevant subgroup was identified in the SAP prior to data unblinding. DNP's comment that a retrospective analysis "cannot provide evidence of effectiveness" is not correct as a matter of law and regulation, and it is also not consistent with FDA's own historical precedents. As described in more detail below, FDA has taken to review, and has approved, NDAs for products that failed their original primary endpoint analysis and where retrospective analyses served as the primary evidence of effectiveness.

PTC does concur that some form of adjustment of the p-value (which was p=0.007 on an unadjusted basis) from the subgroup analysis is appropriate to account for multiplicity and minimize the chance of a Type I error. At the Type A meeting, based on consultations with outside statistical consults and a review of the statistical literature, PTC proposed an adjustment based on a permutation method, taking into account the most conservative approach of having 9 subgroups for multiplicity. *See* PTC, FDA Type A Meeting NDA 200896: Ataluren (PTC124), Presentation, Slide 55 (19 April 2016) ("PTC Meeting Presentation"). With no hierarchy among the subgroups, the adjusted p-value for the baseline 6MWD 300-400 meters subgroup using this method was p=0.036. This adjusted p-value provides additional statistical evidence that the treatment effect in these patients was not due to chance.

Despite PTC's proposed adjustment of the p-values for baseline 6MWD 300-400 meters subgroup, FDA representatives at the Type A meeting repeatedly expressed concern that the subgroup analyses reflected a chance finding. PTC addressed this in multiple ways. First, PTC showed that data from the matching subgroup from Study 007 was consistent with what was seen in Study 020. *See* PTC Meeting Presentation at 28. Second, PTC provided the results of sensitivity analyses showing that drug effect could be seen if the baseline definition of the subgroup was extended in either direction. *See* PTC Briefing Package at 11-12. Finally, PTC noted the trend for other placebo-controlled studies of drugs in development for DMD to focus on a baseline 6MWD range similar to the baseline 6MWD 300-400 meters subgroup in Study 020, supporting the emerging consensus on the importance of this range for sensitivity of the test. *See* PTC Briefing Package at 19. All of these considerations support the need for a full review of the NDA to address the complex data and results, rather than a summary decision not to accept the NDA for review.

Meta-analysis

The subgroup analyses presented by PTC represent only part of the substantial evidence of effectiveness provided by PTC. The NDA also included results of a meta-analysis that combined the ITT population of Study 020 with that subset of the Study 007 study population that would have met the entry criteria for Study 020. Contrary to the RTF letter and DNP's minutes of the Type A meeting, PTC did in fact plan and pre-specify a meta-analysis in the SAP provided to FDA prior to database lock in Study 020. *See* PTC Briefing Package at 11. PTC provided FDA with the draft SAP for review in May 2015, and the final SAP was submitted to the agency in August 2015. *See* Draft Statistical Analysis Plan for ataluren Study 020 (submitted 4 May 2015); Final Statistical Analysis Plan for ataluren Study 020 (submitted 20 August 2015). There is a compelling rationale for the use of meta-analyses to

estimate treatment effect in diseases such as DMD. In DMD, maximizing the sample size is important due to heterogeneity of disease progression, but is impractical in individual trials due to the rarity of the disease. Pooling of trial results is a valid way to overcome these limitations, and it can also mitigate the concerns about use of subgroups to show drug effect. The results of PTC's meta-analysis described in the SAP show statistically significant treatment effects on all efficacy endpoints that were included in both trials, for example, change in 6MWD (p=0.0193), time to 10% worsening in 6MWD (p=0.0232), change in time to run/walk 10 meters (p=0.0251), change in time to climb 4 stairs (p=0.0184), and time to descend 4 stairs (p=0.0044). *See* NDA 200896, Module 2.7.3, Table 14. To demonstrate that this was not a chance finding, PTC also presented to DNP a retrospective (but more conservative) meta-analysis including the entire Study 007 patient population at the same dose, which still gave a clinically meaningful and statistically significant result. *See* PTC Briefing Package at 11 (resulting in p-values, respectively, of 0.0152, 0.0195, 0.0262, 0.0041, and 0.0038).

In addition to the erroneous claim that the meta-analysis was neither planned nor pre-specified in the SAP for Study 020, DNP criticized the analysis on the grounds that the method was different from the pre-specified primary analysis in Study 007 and that omitting from the analysis the high-dose arm from Study 007 constituted "an additional post hoc adjustment." *See* FDA Type A Meeting Minutes at 6. Expecting PTC to have had perfect insight regarding the design and analysis of the first registration-directed trial ever conducted in DMD patients is not reasonable given the limitations of the natural history data and translational science in the DMD field at the time Study 007 was being planned. As PTC has repeatedly stated, and documented to FDA, events have since shown that the SAP for Study 007 was not suitable. *See* PTC Briefing Package at 8. Those events include the natural history data in DMD generated, for the first time, from the placebo arm of Study 007 itself. *See* PTC Briefing Package at 8. That the SAP for Study 020 incorporates learning from both Study 007 and other natural history data is both reasonable and unremarkable. Indeed, it is preferable for sponsors to use the latest data and methodology when developing each SAP, rather than preserve statistical analyses from prior trials that come to be known as inappropriate or suboptimal for the disease under study. *See* FDA "Guidance for Industry

E9: Statistical Principles for Clinical Trials," Section 5.1 (September 1998). With respect to omission of the high-dose arm, PTC did in fact incorporate the data from the high-dose arm in the model it used to determine the p-values for the meta-analysis presented in the NDA. *See, for example*, NDA 200896, Module 2.7.3 Table 14.2.1.36C. Furthermore, it was in Study 007 that PTC first learned of limitations on the effectiveness of ataluren at higher doses. PTC is not seeking approval of the high dose of ataluren in the NDA, and data with respect to that dose should not be used to negate the treatment effect seen with the dose for which approval is actually sought. FDA was provided with the draft SAP for Study 020 reflecting the proposed method for the meta-analysis and provided no comments with respect to the points it is now making (but FDA did provide comments on other aspects of the Study 020 SAP). *See* Draft Statistical Analysis Plan for ataluren Study 020 (submitted 4 May 2015); Final Statistical Analysis Plan for ataluren Study 020 (submitted 20 August 2015).

During the Type A meeting, when presented with a PTC slide showing a direct quote from the Study 020 SAP describing the meta-analysis, the representative from DNP's statistical team appeared to acknowledge DNP's factual error in stating that the meta-analysis was "neither planned nor pre-specified." Disappointingly, however, the meeting minutes prepared by DNP—which are nothing more than a verbatim repetition of the preliminary comments

with a few paragraphs of added text—failed to reflect that fact or correct DNP's erroneous statement.

Other endpoints

As PTC pointed out in the NDA and at the Type A meeting, data with respect to almost all efficacy endpoints in Studies 007 and 020 trended in favor of ataluren versus placebo. *See generally* PTC Briefing Package. DNP's comment that most of the secondary endpoints were "nominally negative" discounts the consistency of benefit shown for ataluren across endpoints in both trials. In particular, secondary outcome measures such as the 10-meter run/walk, 4-stair climb, 4-stair descend, favored ataluren versus placebo in the ITT population of Study 020 and cITT population of Study 007. Study 020 also added the NSAA and a measure of patient-reported physical functioning known as the Pediatrics Outcomes Data Collection Instrument (PODCI), both of which favored ataluren in the ITT population. In Study 007, a PedsQL measure of physical functioning also favored ataluren in the cITT population. In fact, in the ITT population of Study 020, ataluren showed a 31% increase in preservation of functions that are known to be important to improve the quality of life of DMD patients and their families. These effects on other endpoints were even more pronounced in the baseline 6MWD 300-400 meters subgroup. As FDA commented in its draft guidance concerning development of drugs for DMD, in this disease it is appropriate to include and consider multiple secondary and other endpoints to assess potential treatment effect. *See* FDA, Draft Guidance for Industry, Duchenne Muscular Dystrophy and Related Dystrophinopathies: Developing Drugs for Treatment 6 (June 2015) (noting that "multiple efficacy endpoints should be included when feasible") ("DMD Draft Guidance").

PTC addressed two secondary endpoints and one observational endpoint in detail at the Type A meeting: the NSAA, the timed function tests (TFTs), and loss of ambulation. All showed consistent benefits for the ataluren-treated population:

- NSAA: The NSAA is a composite endpoint evaluating physical function across 17 clinically meaningful motor tasks, which constitute DMD-specific measures of disease progression. In the ataluren NDA, PTC reported a nominally statistically significant benefit in the linear NSAA score the baseline 6MWD 300-400 meters subgroup. See NDA 200896, Module 2.7.3, Figure 40. At the Type A meeting, PTC also provided an analysis showing that across the individual results for the 17 motor tasks that make up the NSAA, ataluren-treated patients showed a benefit against placebo in 16 of the 17 motor tasks with a nominal p-value of 0.008. *See* PTC Meeting Presentation at 20. In the baseline 6MWD 300-400 meters subgroup, the robust effect seen in this analysis of the NSAA data was even greater. *See* PTC Meeting Presentation at 29.
- TFTs: PTC presented analyses showing preservation of stair-climbing and stair-descending abilities in the ataluren-treated ITT population in Study 020. The results for time to loss of 4-stair climbing ability in Study 020 occurred in 12/113 (11%) of ataluren-treated patients vs. 22/113 (19%) of placebo-treated patients in Study 020 (log-rank p= 0.0512). Stair climbing and descending is a clinically meaningful functional task and is always lost before long-distance ambulation (6MWT ability) or short-distance ambulation (10-meter run/walk ability). As Dr. Craig McDonald, a clinical investigator involved with multiple development programs for DMD, noted at the Type A meeting, preservation of this type of function is very important to the quality of life of patients with DMD. Dr. McDonald added that it took decades for the DMD field to appreciate the fact that steroids, which showed a benefit in the TFTs

similar in magnitude to ataluren's in early studies, had profound effects on time to loss of ambulation, upper limb function, and pulmonary function. *See* Henricson, E. et al., "The cooperative international neuromuscular research group Duchenne natural history study: Glucocorticoid treatment preserves clinically meaningful functional milestones and reduces rate of disease progression as measured by manual muscle testing and other commonly used clinical trial outcome measures," Muscle and Nerve 48:1 55-67 (July 2013). TFTs generally have been endorsed by FDA as a potential primary endpoint and some sponsors have begun using them in large, placebo-controlled trials. *See* DMD Draft Guidance at 7 (noting that TFTs "can be a useful measure of gross motor function"). For example, Pfizer's Phase 2 study of PF-06252616 in DMD, a randomized, 2-period, double-blind, placebo-controlled trial, employs change from baseline on the 4-stair climb test as its primary efficacy endpoint. *See* ClinicalTrials.gov, A Phase 2 Study to Evaluate the Safety, Efficacy, Pharmacokinetics and Pharmacodynamics of PF-06252616 in Duchenne Muscular Dystrophy, https://clinicaltrials.gov/ct2/show/NCT02310763.

- Ambulation: PTC also presented in the NDA and at the Type A meeting striking findings with respect to preservation of walking ability in boys treated with ataluren across the placebo-controlled trials. Loss of ambulation occurred in 7% of ataluren-treated patients in the cITT population of Study 007 (versus 11% of placebo-treated patients) and 8% of ataluren-treated patients in the ITT population of Study 020 (versus 12% of placebo-treated patients). *See* NDA 200896, Module 2.7.3, §§ 2.2.2.3, 3.1. Remarkably, in both studies, no ataluren-treated patients lost ambulation in the baseline 6MWD 300-400 meters subgroup, while 9% (Study 007) to 8% (Study 020) lost ambulation in placebo-treated patients in the same subgroup. *See* NDA 200896, Module 2.7.3, § 3.2. The preservation of ambulation in the baseline 6MWD 300-400 meters subgroup is meaningful not only in comparison to the placebo arms of PTC's trials, but also in comparison to external natural history data, which show a similar rate of loss of ambulation in this subgroup. In further support of the point that this is not a chance finding, PTC presented data at the Type A meeting showing that ataluren continued to preserve ambulation beyond one year in PTC's extension studies. *See* PTC Meeting Presentation at 32. As Dr. McDonald commented in his presentation at the Type A meeting, age at time of loss of ambulation has been shown to correlate with time to ventilation, an important milestone in the progression of DMD. See Humbertclaude, V. et al., "Motor and respiratory heterogeneity in Duchenne patients: Implication for clinical trials," European Journal of Paediatric Neurology 16:2, 149–160 (March 2012).

In acknowledging PTC's presentation of these analyses of multiple secondary and other endpoints, DNP noted 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." *See* FDA Type A Meeting Minutes at 5. While this may generally be true, in the case of PTC's analyses there is significant consistency across multiple endpoints and across two large, placebo-controlled trials. The likelihood that so many endpoints would trend in favor of ataluren across two separate placebo-controlled trials is extremely small, and when considered in light of the other data (including supportive data from other trials and extension studies) the findings in the secondary and other endpoints do support the effectiveness of ataluren in nmDMD.

Failure to Enrich

DNP commented, in support of its conclusion that the ataluren NDA did not contain substantial evidence of effectiveness, that the efforts to enrich the population from Study 007 in Study 020 did not produce the expected enhanced effect size. *See* FDA Type A Meeting Minutes at 4. However, as PTC explained at the Type A meeting, this is not due to lack of drug effect, but instead this came about because notwithstanding the revised enrollment criteria, the actual enrolled population of Study 020 largely mirrors the overall population of Study 007. In Study 020, patients had to be at no more than 80% of their predicted 6MWT distance to enroll. This was intended to keep individuals with walk distances over 400 meters from enrolling, but it did not have that effect in the context of a large, multi-center, global clinical trial. Instead, Study 020 enrolled proportionally more patients with walking distances greater than 400 meters than had Study 007. As the FDA's draft guidance concerning development of drugs for rare diseases acknowledges, it is important to recognize the differences between issues of drug effect and those pertaining to endpoint and assay sensitivity. *See* FDA, Draft Guidance for Industry, Rare Diseases: Common Issues in Drug Development Guidance for Industry 6 (August 2015). At the Type A meeting, PTC presented information showing the similarity between the populations of Study 007 and Study 020. *See* PTC Meeting Presentation at 17-19. Far from being a reason to discount the evidence of effectiveness of ataluren, this failure to enrich justifies further exploration of treatment effect in subgroup analyses to better show effect size in a relevant population.

2.1.2 DNP did not have the legal authority to refuse to file the ataluren NDA based on approvability concerns

PTC's submission of the results of two large, well-controlled trials, together with a rationale for relying on analyses that were planned and shared with FDA in advance of database lock and unblinding, meets the filing requirements of section 505(b) of the FDCA and the regulations at 21 C.F.R § 314.101. These legal authorities do not require that an NDA contain "substantial evidence of effectiveness" to be filed and taken to review. The decision to file and the decision to approve an NDA are distinct determinations, and DNP acted unlawfully when it merged the two issues with respect to ataluren.

2.1.2.1 DNP's refusal to file was inconsistent with section 505(b) of the FDCA

DNP premised its RTF decision on its determination that the NDA "[did] not contain information required under section 505(b) of the FDCA" because it "[did] not contain substantial evidence of effectiveness." *See* RTF Letter at 1. DNP's interpretation of the statute is incorrect. Section 505(b) does not require an NDA to contain "substantial evidence of effectiveness." Instead, section 505(b) of the FDCA provides that the NDA must contain "full reports of investigations which have been made to show . . . whether such drug is effective in use." 21 U.S.C. § 355(b)(1)(A) (emphasis added). By its plain terms, section 505(b) is met equally by positive or negative studies, so long as full reports are provided and no relevant studies are withheld. This meaning is confirmed by section 505(d), which makes it clear that determination of absence of substantial evidence of effectiveness is a review question: It requires FDA to refuse to approve an NDA if there is "a lack of substantial evidence of effectiveness." 21 U.S.C. § 355(d)(5); *see* 21 C.F.R. § 314.125(b)(5) (same). Contrary to the position taken by DNP, the approval standard for an NDA appears nowhere in section 505(b), which is relevant to the filing of NDAs. Indeed, the statute only defines the phrase "substantial evidence" for purposes of sections 505(d) and 505(e), not for section 505(b). *See* 21 U.S.C. § 355(d) ("As used in this subsection and subsection (e), the term 'substantial evidence' means….). These provisions indicate that Congress did not authorize

FDA to make substantive determinations about the sufficiency of evidence of efficacy at the threshold filing stage.

The ataluren NDA contained the results of Study 007 and Study 020, two double-blinded, placebo-controlled trials that are among the largest ever conducted in the Duchenne muscular dystrophy field. Any determination that the data from those studies do—or do not—provide substantial evidence of efficacy is to be made only at the conclusion of FDA's substantive review, as described in section 505(d) of the FDCA. By refusing to file the ataluren NDA on the ground that it "cannot be approved based on the data submitted," DNP exceeded the scope of its authority under the FDCA. *See* RTF Letter at 1.

2.1.2.2 DNP's refusal to file was inconsistent with 21 C.F.R. § 314.101

DNP based its decision on its views on ultimate approvability, as the RTF letter itself makes clear when it states that the ataluren NDA "cannot be approved based on the data submitted." *See* RTF Letter at 1. However, the applicable FDA regulation does not permit approvability determinations to be made at the filing stage. The regulation allows FDA's review divisions to make only a "threshold determination that the application is sufficiently complete to permit a substantive review." 21 C.F.R. § 314.101(a)(1) (emphasis added). To permit a substantive review, the NDA must "on its face contain information required under section 505(b) . . . and 314.50." 21 C.F.R. § 314.101(b)(3). As a threshold review designed to determine facial completeness, the RTF process does not and cannot include determinations as to whether substantial evidence of effectiveness has been shown. By making precisely that determination as to NDA 200896, DNP exceeded its authority under § 314.101. The regulation makes it clear that an NDA must be filed if it contains all of the "information required" to "permit a substantive review"—not all of the information required to permit a finding that the application is approvable.

Another FDA regulation and the administrative history of § 314.101 confirm that DNP acted outside the scope of its authority. The filing regulation for new animal drug applications (NADAs) states that an application may be refused for filing if it is "incomplete on its face." 21 C.F.R. § 514.110(b)(3). It also contains a separate provision stating that a NADA may be refused for filing if "the information concerning required matter is so inadequate that the [NADA] is clearly not approvable." 21 C.F.R. § 514.110(b)(4) (emphases added). Identical language used to be included in the NDA regulation. *See* 21 C.F.R. § 314.110(a)(4) (1980). When that language was deleted from the NDA regulation, FDA describe the change as an "important" improvement in how the Agency would process and review NDAs. 47 Fed. Reg. 46622, 46639 (Oct. 19, 1982). DNP's refusal to file the ataluren NDA is inconsistent with this thirty year old amendment to the NDA regulation.

2.1.2.3 DNP's refusal to file was inconsistent with FDA's guidance for industry

In connection with the Type A meeting, DNP stated that "FDA has long asserted that a study can be so clearly not supportive of effectiveness that it can be considered essentially absent." *See* FDA Type A Meeting Minutes at 3. As authority for this point, DNP cited the guidance regarding RTF decisions that was published by CDER in 1993. *Id*. (citing FDA, Guidance for Industry, New Drug Evaluation Guidance Document: Refusal to File (12 July 1993) ("RTF Guidance"). According to DNP, that guidance held that an "RTF could be based on advance judgment about what had been shown in a trial, e.g., lack of evidence of effectiveness." *See* RTF Guidance.

DNP's position is clearly incorrect. The RTF Guidance never stated, or even suggested, that an RTF could be based on an "advance judgment" that the trials included in an application

failed to provide evidence of effectiveness. To the contrary, the RTF Guidance clearly stated that such judgments could only be made in the approval context and were not permissible bases for RTF. The relevant passage provides:

> A not approvable action also could be based on an adverse judgment about what was done (e.g., the adequacy and comprehensiveness of the studies or the quality of the analyses of data), or what has been shown (e.g., lack of evidence of effectiveness or evidence that the benefits of the drug do not outweigh its risks). Such judgments would not, in contrast, be bases for RTF, unless based on facial incompleteness.

RTF Guidance at 2. The RTF Guidance also provides that an RTF must be based on "obvious" failures and cannot be "a matter of interpretation or judgment about the meaning of data submitted." *Id.* The RTF Guidance then goes on to state:

> The RTF is not an appropriate vehicle for dealing with complex and close judgments on such matters as balancing risks and benefits [or] magnitude of drug effect … Rejection of an application for these kinds of reasons should be effected through a not approvable action after full review.

Id. at 3. DNP's decision to refuse to file the NDA for ataluren obviously amounts to a complex evaluation of the magnitude of drug effect shown, based on its interpretation and judgment about the data submitted—all in direct contravention of the RTF Guidance.

In addition, the RTF Guidance provides three concrete examples of the types of failings that could amount to facial incompleteness regarding effectiveness. The guidance explains that an RTF might be appropriate if (1) the NDA lacks "any adequate and well-controlled studies"; (2) the NDA fails to justify reliance on a single study; or (3) the NDA relies on study designs that are "clearly inappropriate" as reflected "in regulations or well-established agency interpretation." *See* RTF Guidance. at 4-5. An identical list of examples can be found in the 2014 edition of the 21st Century Desk Reference. *See* CDER, 21st Century Review Process Desk Reference Guide, 58-59 (Sept. 2014), http://1.usa.gov/1LMWrsh.[1] None of them applies to the ataluren NDA, which contained the results of two adequate and well-controlled clinical trials.

2.1.2.4 DNP's refusal to file was inconsistent with FDA's operational policies

The RTF Guidance remains in force, according to CDER's current list of guidance for industry. *See* CDER, List of Guidance Documents, 49 (Oct. 27, 2014), *available at* FDA, Guidances (Drugs) (22 January 2016), http://1.usa.gov/1PQwe77.

However, CDER also has established certain "good review practices" that are to "be followed by review staff when conducting their application reviews." MAPP 6025.1, Good Review Practices, 4 (effective September 2006), http://1.usa.gov/1RxPYDX. One of those practices specifically addresses the RTF regulation. MAPP 6025.4, Good Review Practice: Refuse to File (effective October 2013), http://1.usa.gov/1Sgb9qO ("RTF MAPP"). Much like the RTF Guidance, the RTF MAPP carefully distinguishes between "review issues," which go to the approval decision, and "application deficiencies that serve as the basis for an RTF action."

[1] The desk reference is intended to be binding on CDER review staff. *See* MAPP 4180.4, NDAs/BLAs: Using the 21st Century Review Process Desk Reference Guide (effective 8 November 2010), http://1.usa.gov/1q696wG ("CDER review staff are responsible for following the procedures in the guide during NDA/BLA and efficacy supplement review.").

Id. at 2 & n.4. A refusal to file "should be based only on filing issues, not on review issues." *Id.* at 10. Concerns about the adequacy of statistical analyses are review issues that cannot support a refusal to file. *Id.* at 10-11.

PTC notes that an attachment to the recent RTF MAPP could be construed to support DNP's decision regarding the NDA for ataluren. The attachment asserts that reviewers may refuse to file an NDA if it 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." RTF MAPP at 20. That example was not contained in either the RTF Guidance or the more recent 2014 edition of the 21st Century Desk Reference. While PTC does not concede that an RTF based on the criteria in this example is consistent with FDA's statutory authority, the NDA for ataluren did in fact contain the type of "adequate explanation" to which the new example refers. The NDA explained that Study 007 was the first of its kind and that scientific understanding of the natural history of nmDMD developed significantly during Study 007, during the design of Study 020, and after the commencement of Study 020. NDA 200896, Module 2.7.3, § 1.3.1 . It also explained that post hoc adjustments to Study 007 show a statistically significant benefit, *id*. § 2.2.2.1, and that, while the primary endpoint of Study 020 "did not reach statistical significance" in the ITT population, *id*. § 2.3.2.1, it did show a statistically significant benefit in a key subgroup, *id*. § 2.3.2.2. The NDA also explained that analyses of secondary endpoint data in Study 020, *id*. § 2.3.3.1, and PTC's meta-analysis of the two studies, *id*. § 3.1, were positive. Finally, of course, an attachment to an internal FDA manual cannot change the clear meaning of the applicable law and regulations, which do not allow refusals to file based on review or approvability issues.

2.1.3 Ataluren should be provided the same opportunity for full review that DNP gave to two other recent applicants for products in development for Duchenne muscular dystrophy

The RTF regulation provides that FDA has discretion to accept an incomplete application for filing. *See* 21 C.F.R. § 314.101(d) ("FDA may refuse to file an application . . . if any of the following applies . . . ."). The RTF Guidance similarly states that the Agency "may" choose to not "use the RTF procedure, even where it could be invoked . . . if it believes that initiating the full review at the earliest possible time will better advance the public health." *See* RTF Guidance at 3. Moreover, CDER previously stated that it "will exercise" that "discretion . . . when the application is for a medically important drug." 58 Fed. Reg. 28983 (May 18, 1993); 58 Fed. Reg. 52497, 52498 (8 October 1993) (same). This commitment reflects the heightened need for substantive review when a drug has been designated a treatment for a life-threatening illness under the Subpart E regulations. *See* 21 C.F.R. §§ 312.80-312.84. As to those drugs, FDA has promised to "exercise the broadest flexibility." *Id.* § 312.80. In the DMD Draft Guidance, FDA reaffirmed that this was true for DMD, stating that "FDA has long stressed … that it is appropriate to exercise flexibility in applying the statutory standards to drugs for serious diseases with important unmet needs, while preserving appropriate guarantees for safety and effectiveness." *See* DMD Draft Guidance at 4. DNP's decision to refuse to file the NDA for ataluren is not in accord with any of these prior statements.

The RTF is all the more troubling because DNP has recently accepted for filing applications for other potential DMD treatments that relied solely on negative studies: drisapersen and eteplirsen. These investigational new drugs target a distinct and non-overlapping genetic subset of the overall DMD population from ataluren. Both applications were accepted for review and presented at advisory committee meetings, despite DNP's expressed opinion that they did not contain substantial evidence of efficacy. *See* FDA, Briefing Document, Peripheral and Central Nervous System Drugs Advisory Committee Meeting 22 (24

November 2015) (including the clinical review's conclusion that the drisapersen NDA does "not reach the level of substantial evidence"); FDA, Briefing Document, Peripheral and Central Nervous System Drugs Advisory Committee Meeting 89 (25 April 2016) (noting serious concerns with the data presented in support of approval). In the case of drisapersen, reliance on pooling of data from multiple clinical studies that failed their primary endpoint did not prevent DNP from accepting the NDA for review, and in the case of eteplirsen, the lack of any adequate and well-controlled studies did not prevent DNP from accepting the NDA for review. There is no principled basis allowing DNP to accept the drisapersen and eteplirsen NDAs for filing but refusing to file the ataluren NDA. FDA is legally required to "apply its scientific conclusions evenhandedly and . . . not grant to one person the right to do that which it denies to another similarly situated." *United States v. Diapulse Corp. of Am.*, 748 F.2d 56, 60 (2d Cir. 1984).

FDA has, on a number of occasions, not only taken to full review but approved other drugs despite similar concerns about the efficacy data contained in their applications.[2] These approvals demonstrate the inherent value of a full review under Section 505 of the FDCA—had the Agency allowed its reviewers to prejudge those applications at the filing stage, the drugs may never have been approved and patients may have been deprived of important treatment options.

FDA officials have also explicitly acknowledged the need to perform a careful review of data in the DMD field. In recent remarks by Dr. Janet Woodcock at the 25 April 2016 meeting of the Peripheral and Central Nervous System Drugs Advisory Committee to discuss Sarepta's NDA for eteplirsen for the treatment of DMD, she discussed the major challenges associated with assessing treatment effects in rare disease settings in which the translational science supporting drug development is inadequate. At that meeting, Dr. Woodcock observed that:

> [M]uch of the effort in evaluating a drug development program goes into avoiding a specific mistake, that is, erroneously approving a drug that is not effective. There often is little consideration of another error, which is failing to approve a drug that actually works. In devastating diseases, the consequences of this mistake can be extreme, but most of these consequences are borne by patients who traditionally have little say in how the standards are implemented.

[2] Examples include the following:

Drug Name	Indication	Type and Submission Date	Level of Statistical Significance Achieved
RILUTEK (riluzole)	Amyotrophic lateral sclerosis (ALS)	NDA 29 Jun 1995	Two studies: p=0.12 and p=0.076 (p=0.05 and p=0.05 after post-hoc analysis)
REMODULIN (treprostinil)	Pulmonary arterial hypertension	NDA 16 Oct 2000	Pooled analysis (p=0.0064) of two studies: p=0.0607 and p=0.0550
EXJADE (deferasirox)	Chronic overload due to blood transfusions	NDA 29 Apr 2005	Non-inferiority study failed to meet pre-specified criteria (no p-value)
VASOTEC (enalapril maleate)	Asymptomatic left ventricular dysfunction	sNDA 4 Nov 1993	Single controlled study p=.30 (statistically significant secondary endpoints)
KALYDECO (ivacaftor)	Cystic fibrosis (R117H mutation)	sNDA 20 Jun 2014	Single controlled study p=0.198 (subgroup analysis p=.0119)

Each of these drugs was taken to full review by FDA and approved even though the studies submitted in the application failed to achieve statistical significance on their primary endpoints.

See Transcript of the Peripheral and Central Nervous System Drugs Advisory Committee Meeting 158 (25 April 2016), http://bit.ly/29riVl1.

It is noteworthy that Dr. Woodcock's remarks were made in reference to the Advisory Committee's consideration of data from Sarepta's clinical trial comparing 12 treated DMD patients to external cohort data. There does not appear to be a plausible justification for why Dr. Woodcock's remarks would not also apply to consideration of ataluren data from two placebo-controlled trials that enrolled a total of 404 nmDMD patients and demonstrated robust treatment effects in large subgroups. In a disease setting in which translational science is lacking and the field's understanding of the natural history is incomplete and constantly evolving, PTC suggests there should be careful consideration of the only controlled clinical investigations specific to nmDMD to avoid failing to approve a drug that works.

Further, the threshold filing review under 21 C.F.R. § 314.101 is no substitute for a full review under Section 505. DNP's minutes of the Type A meeting concede that it engaged in only a "preliminary review" and "preliminary examination" of NDA 200896. *See* FDA Type A Meeting Minutes at 3, 8. Yet, the RTF letter explicitly opined that the data contained in the NDA could not support approval. *See* RTF Letter at 1 (noting that the application "cannot be approved based on the data submitted"). DNP cannot reasonably base an approvability determination on a preliminary review. Indeed, the record shows an obvious lack of familiarity with critical aspects of the application. By way of example, some staff at the Type A meeting seemed unfamiliar with the contents of the SAP for Study 020, having missed the fact that it contained PTC's meta-analysis. Agency staff also were not prepared to discuss issues related to abuse potential, including the data provided specifically for the meeting. FDA representatives at the meeting frequently shifted between discussion of whether the application was approvable (which as discussed above is not properly the subject of a Type A meeting on an RTF decision) or whether it should be filed.

A full review would allow PTC to engage in a better dialogue regarding the ataluren NDA based on a thorough and detailed review of the data contained in the application. Indeed, in the context of a full review, DNP would have the ability to ask for additional data or analysis without the need for the application to be resubmitted, as DNP recently did in the case of Sarepta's eteplirsen NDA. PTC has such data from its extension studies which it would be prepared to provide, including the preservation of ambulation data presented at the Type A meeting as well as additional analyses showing a benefit in lung function in nonambulatory patients treated with ataluren.

2.2 Abuse potential

2.2.1 The application contained the information required by applicable regulation to support a determination that ataluren does not exhibit any potential for abuse

The RTF letter states:

> 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).

See RTF Letter at 2.

As discussed above, the applicable statutory and regulatory provisions do not allow FDA to refuse to file an NDA based on concerns about the adequacy or inadequacy of the information contained in the application. The only question at the filing stage is whether the application is sufficiently complete to permit a substantive review. Thus, this determination also constituted legal error.

In addition, however, the NDA for ataluren complied fully with the applicable regulatory requirements related to abuse potential. The NDA explained that the development program for ataluren generated no evidence suggesting that there is any potential for ataluren to be a CNS-active new molecular entity (NME). This conclusion was explained specifically in the Nonclinical Overview Module 2.4, Section 2.3.4, and the Summary of Clinical Safety Module 2.7.4, Sections 5.6 and 5.7. By explaining that ataluren does not present abuse potential, the NDA complied with the applicable regulation, 21 C.F.R. § 314.50(d)(5)(vii).

2.2.2 Neither PTC's clinical trials to date nor any other studies indicate that any abuse potential exists for ataluren

Based on the FDA's comment in the RTF letter, PTC supplemented its assessment of the abuse potential of ataluren in accordance with the FDA's draft guidance for industry on assessment of abuse potential. *See* FDA, Draft Guidance for Industry, Assessment of the Abuse Potential of Drugs (January 2010) ("Abuse Potential Guidance").[3] This supplemental assessment included further analysis of ataluren's chemical structure, class, and solubility profile; an assessment of any signals from PTC's extensive nonclinical safety testing; and a detailed review of clinical safety data for ataluren to detect the potential for abuse-related adverse events. Overall, the conclusion remained that ataluren does not have the chemical characteristics consistent with an NME with abuse potential, nor were any signals detected in nonclinical or clinical studies, and therefore neither a human abuse potential study nor scheduling under the Controlled Substances Act are warranted. PTC provided this more detailed assessment in connection with the briefing package for the Type A meeting. *See* PTC Briefing Package at 25-33.

2.2.3 Representatives of FDA have failed to provide any basis for the conclusion that ataluren exhibits abuse potential

The meeting minutes stated that PTC's submissions still lack "animal self-administration, drug discrimination and physical dependence studies." *See* FDA Type A Meeting Minutes at 8. But studies related to the abuse of a drug are only required in an NDA if the drug shows abuse potential in the first place. *See* 21 C.F.R. § 314.50(d)(5)(vii) ("If the drug has a potential for abuse . . . ."); *see also* Abuse Potential Guidance at 4 ("if the drug affects the central nervous system (CNS), is chemically or pharmacologically similar to other drugs with known abuse potential, or produces psychoactive effects"). PTC requested clarification of the basis for FDA's belief that ataluren has abuse potential in its Type A meeting request. Specifically, PTC asked for any analyses or queries FDA used to support the comment in the RTF letter regarding a possible imbalance in CNS adverse events suggestive of abuse potential. *See* FDA Type A Meeting Minutes at 8. In its preliminary response document for the Type A meeting, FDA responded that although the agency had "not performed any formal

[3] Because this guidance is still in draft form, it should not be implemented by FDA staff and cannot be used to impose obligations on PTC regarding the contents of NDA 200896. *See, e.g.* Letter from Thomas A. Kraus, Associate Commissioner, FDA to the Hon. Joseph R. Pitts, Chairman, Subcomm. on Health, Comm. on Energy and Commerce (12 November 2014), http://1.usa.gov/1W1ponh ("FDA should not implement [a draft] guidance document until it is finalized.") (citing 21 C.F.R. § 10.115(c)(1); 73 Fed. Reg. 40453, 40458 (15 July 2008) ("Industry is not obligated to implement draft guidance.")

analyses that we can share, a preliminary examination of the adverse events that you have submitted provided the basis for our comment." *Id*. But that preliminary examination has not been shared with PTC. Obviously, FDA cannot make a determination as important as an RTF decision without sharing its analyses with the affected company. *See, e.g.*, *Burlington Truck Lines v. United States*, 371 U.S. 156, 168 (1962) ("the agency . . . must disclose the basis of its order") (quotation marks omitted).

During the Type A meeting, PTC presented a slide taken from its briefing book showing adverse events and other data taken from the ataluren clinical trials. *See* PTC Meeting Presentation at 41. This slide provided the objective basis for PTC's conclusion that no abuse potential signal exists. The representative from the Controlled Substance Staff (CSS) stated that he was "not prepared to address the data at this time." PTC Type A Meeting Record at 4. This response is extremely disappointing and unfair to PTC. *See, e.g.*, *United States v. International Harvester Co.*, 387 F. Supp. 1338, 1342 (D.D.C. 1974) (fact that "the agency refused to discuss the matter" with the company violated basic procedural fairness). First, the main purpose of the Type A meeting was to address the reasons for the RTF letter, including the comments related to abuse potential. The CSS representative owed PTC the basic professional courtesy of reviewing the data and points presented in PTC's briefing book (which was provided well in advance of the meeting) and providing an answer to PTC's questions. To come to the Type A meeting unfamiliar with relevant materials and facts deprived PTC the opportunity for a timely science-based dialogue with the Agency on this issue. Second, the FDA's preliminary response document, presented to PTC the evening prior to the Type A meeting, suggested the need for expensive, time-consuming non-clinical studies regarding abuse potential. *See* FDA Type A Meeting Minutes at 8. To impose this requirement in the absence of any discussion of the underlying data—in fact, in the absence of any scientific support whatsoever for the position taken by CSS—is arbitrary, capricious and unfair to PTC.[4]

2.3 Conclusion

As multiple trials of investigational new drugs by many sponsors have shown, DMD is a difficult disorder to study in the clinical setting. PTC suggests that DNP, in refusing to accept the ataluren NDA for filing, has acted contrary to FDA's own comments in the DMD Draft Guidance. In that document, FDA stated "[w]hen making regulatory decisions regarding drugs for dystrophinopathies, FDA will consider patient and caregiver tolerance for risk, and the serious and life-threatening nature of these conditions." *See* DMD Draft Guidance at 11. Dr. Woodcock also supported this view when she stated her position that it is critical to also consider the possibility of Type II error in making regulatory decisions in the context of rare diseases with high unmet medical need. The RTF effectively forecloses any thoughtful consideration of these complex issues such as would occur in the context of a full review of the significant data in the NDA supporting ataluren's treatment effect in nmDMD (as well as the absence of any abuse potential). Based on the data and analyses PTC has presented to the agency, PTC asks for reversal of the RTF decision and a full review of the ataluren NDA,

[4] FDA's minutes of the meeting suggest that FDA representatives stated that in any request for a follow-up meeting with CSS, PTC should "submit specific questions so that an appropriate meeting format might be arranged." PTC representatives at the meeting do not recall this statement being made. In point of fact, PTC had already asked its specific questions concerning abuse potential in connection with the Type A meeting. Even if some evidence or signal of abuse potential supporting FDA's opinion is eventually produced by CSS, it remains PTC's position that FDA may legally not use that as a basis for a refuse-to-file decision. FDA may not use its unpreparedness at this meeting to require PTC to prepare and present at yet another meeting.

including all the benefits normally offered to sponsors of NDAs for rare diseases where high unmet medical need exists consistent with the PDUFA framework.

3 STEPS TAKEN TO RESOLVE DISPUTE

3.1 Background on Prior FDA Interactions

Ataluren was granted orphan drug designation for use in "the treatment of muscular dystrophy resulting from premature stop mutations in the dystrophin gene" *See* FDA, Orphan Drug Designation #04-1972 (10 January 2005). In addition, ataluren received Subpart E designation on 11 March 2006, for expedited development, evaluation, and marketing.

The protocol design for Study 007 of ataluren for the treatment on nmDMD was discussed with DNP on three occasions between June 2005 and August 2008, during which time the Division provided written recommendations (27 October 2007). The final SAP was submitted to the FDA on 14 January 2010. A pre- NDA meeting was held on 12 November 2009.

The initial NDA (200896) was submitted on 31 March 2011. On 26 May 2011, DNP refused to file the NDA on the ground that it "does not contain substantial evidence of effectiveness." A follow-up meeting between PTC and DNP occurred on 19 July 2011. A request for dispute resolution was then filed on 22 December 2011 to reconsider DNP's decision. A formal response essentially affirming the decision not to file the NDA was received on 20 January 2012 from the Office of Drug Evaluation I (ODE I).

The protocol design for Study 020 was discussed with DNP on 07 February 2012. *See* FDA, Type B Meeting Minutes (7 February 2012). At a Type C meeting with the FDA on 4 August 2014, it was agreed that an NDA for ataluren could be submitted under rolling review. *See* FDA, Type C Meeting Minutes (4 August 2014). Part 1 of the rolling NDA was submitted on 14 December 2014. The draft SAP for Study 020 was submitted to FDA (IND 68431) for review and comment on 4 May 2015 (SN0178). Comments from FDA on the draft SAP were received on 30 June 2015 (email from Fannie Choy). The final SAP was submitted to FDA on 20 August 2015 (SN0186). Part 2 of the rolling NDA was submitted on 23 December 2015, completing the NDA submission. On 22 February 2016, DNP refused to file the NDA. *See* RTF Letter.

3.2 Steps Taken to Resolve Dispute

On 23 March 2016, PTC requested a Type A meeting to discuss the RTF decision. Consistent with DNP's request in the RTF Letter, this meeting request included a meeting package and briefing book.

The briefing book posed four questions. PTC asked:

1. Whether DNP would reconsider its RTF decision and accept the NDA, either under the general NDA pathway or pursuant to FDA's accelerated approval regulations;
2. Why DNP had described the analyses of Study 020 and meta-analysis of the two studies as post hoc adjustments, given that those analyses had been pre-specified in the SAP for Study 020 and the company's selection of the 300-400m baseline 6MWD subgroup was consistent with the most up-to-date understanding of the natural history of DMD;
3. Whether DNP could share an analysis demonstrating that there exists a possible imbalance in CNS adverse events; and

4. When and how DNP would provide a response to PTC's request for reconsideration.

In its briefing book, PTC also provided supplementary information, consistent with the draft Abuse Potential Guidance, that the company believed would provide sufficient information for the review division to conduct an abuse potential assessment. *See generally* PTC Briefing Package.

At approximately 5:30 pm on the day before the Type A meeting, DNP provided preliminary answers to the questions from PTC.

The Type A meeting occurred on 19 April 2016. Attendees included DNP Director Dr. William Dunn, Dr. Robert Temple, and Dr. Ellis Unger from ODE I, clinical team leaders and reviewers from DNP, as well as representatives of the Office of Clinical Pharmacology, CSS, and the Rare Diseases Program. PTC gave a slide presentation, during which PTC presented its study results, including data from an ongoing open-label extension study (Study 020e). *See* FDA Type A Meeting Minutes.

PTC received DNP's minutes of the Type A meeting on 19 May 2016. The minutes largely replicated (word for word) the "preliminary" answers provided prior to the Type A meeting, with a few added paragraphs indicating that DNP had rejected PTC's request for reconsideration of the RTF decision. *See* FDA Type A Meeting Minutes. Because the DNP minutes do not contain the full record of the meeting and also continue to contain material misstatements of fact, PTC provided its own record of the meeting to the agency on 8 July 2016. *See* PTC Type A Meeting Record.

4 PROPOSED SOLUTIONS/OUTCOMES

PTC is requesting reversal of DNP's decision to refuse to file NDA 200896 for ataluren. Specifically, PTC requests that NDA 200896 be taken to full review, be accorded the full benefits of the PDUFA framework, be the subject of an advisory committee meeting on approvability, and be treated in a fair and equitable manner similar to the precedent applications for Duchenne muscular dystrophy recently taken to full review by DNP. PTC believes this proposed outcome would find strong support among experts in the field of DMD as well representatives in the patient and caregiver community, and would recognize the urgent need for new treatments for patients with nmDMD.

In connection with the Type A meeting, PTC proposed a potential path forward using the Subpart H framework. This would involve using the analysis of the baseline 6MWD 300-400 meters subgroup as an intermediate clinical endpoint. PTC offered to work with DNP in the design of a post-marketing confirmatory trial to verify the anticipated clinical benefit of ataluren. DNP rejected this approach on the grounds that the level of evidence necessary to demonstrate an effect on such an endpoint is the same as that for a clinical endpoint that would support regular approval, and that in the context of the current application, the 6MWD was a clinically meaningful endpoint presumably capable of supporting a full approval.

In suggesting the Subpart H framework, PTC relied in part on a letter sent by DNP to Prosensa (at that time the applicant for the drisapersen NDA), in which the review division had proposed using 6MWD as an intermediate endpoint. In that document, which was subsequently made public by Prosensa, FDA stated: "The basis for accelerated approval might be a conclusion that drisapersen has some effect on the rate of decline of walking performance, a relatively short-term clinical benefit, that may be reasonably likely to predict a long-term beneficial effect on irreversible morbidity or mortality." *See* Letter from Billy

Dunn, DNP, FDA, to Larry Bell, Prosensa Therapeutics B.V. (provided as an attachment to PTC Briefing Package) PTC suggested in materials prepared for the Type A meeting and at that meeting that the same approach would be viable for ataluren. During the Type A meeting, in denying PTC's suggestion, DNP staff stated that differences in the two companies' use of, and results from, the 6MWD endpoint justified the differential treatment. In fact, Prosensa used the same implementation of the 6MWD as PTC, even consulting with PTC on clinical trial design and receiving sample materials on the 6MWD from PTC. PTC continues to believe that accelerated approval using the 6MWD as an intermediate endpoint would be a viable approach to review and ultimately approve the ataluren NDA, and PTC continues to stand ready to work with DNP on the design of a new trial in support of accelerated approval. PTC believes it is likely that this trial would involve endpoints other than 6MWD, for example the TFTs or NSAA.

Relevant to the discussion of potential endpoints for accelerated approval under Subpart H, FDA has made it clear in public communications that dystrophin quantification is not a valid surrogate endpoint due to technical limitations of the assay and lack of correlation with clinical endpoints. This lack of correlation between dystrophin and clinical benefit makes it difficult to use as a predictive surrogate endpoint.

If the agency has changed its position on use of dystrophin as a surrogate endpoint for Subpart H purposes, as the recent public communications from Sarepta suggest, PTC would note that in an open-label, proof-of-concept study in 38 patients with nmDMD (Study 004) comparing pre- and post-treatment muscle biopsies clearly demonstrated that ataluren promoted dystrophin production. Post-treatment increases in dystrophin were observed in 61% of the patients in 28 days of treatment, with mean changes in dystrophin expression from baseline of 11.0% (p=0.008). To overcome the difficulties associated with quantifying dystrophin expression from human biopsies, PTC took the additional step of using myotubes derived from pre-treatment muscle biopsies and culturing them in vitro in the presence of ataluren. In this experiment, 100% of the patient-derived myotubes demonstrated increases in dystrophin expression. This clearly indicates that even patients who were considered non-responders in the clinical trial had the potential to respond to ataluren. All these data are incorporated in the ataluren NDA, and PTC continues to be open to a resolution of this dispute that incorporates an accelerated approval approach based on dystrophin as a surrogate biomarker.

Finally, PTC notes that the ability to request that DNP file the ataluren NDA "over protest" under 21 C.F.R. § 314.101(a)(3) is not an adequate form of relief because the NDA would not receive the same quality of review. FDA has made it clear that an application filed over protest will automatically be downgraded to standard review, regardless of the clinical need for the product. See MAPP 6020.3, Review Designation Policy: Priority (P) and Standard (S), 4 (effective 25 June 25 2013), http://1.usa.gov/21L1J9j ("If the application receives a refuse-to-file decision, applications filed over protest will be designated a standard review."). Further, FDA will not establish target dates for its review of an application filed over protest. See MAPP 6010.8, NDAs and BLAs: Communication to Applicants of Planned Review Timelines (effective 25 August 2014), http://1.usa.gov/1UqeozX ("No timeline will be communicated for applications that are filed over protest in response to a refuse-to-file decision by the FDA."). In addition, FDA will not allow any application filed over protest to participate in The Program for Enhanced Review Transparency and Communication for NME NDAs and Original BLAs (The Program). See RTF MAPP at 6; 2014 Desk Reference at 18, 20. The Program involves additional commitments by FDA to communicate with the sponsor while the application is being reviewed, through a Day 74 Letter, Discipline Review

Letters, a Mid-Cycle teleconference, and a Late-Cycle meeting. See FDA, PDUFA Reauthorization Performance Goals And Procedures Fiscal Years 2013 Through 2017, § II(A), http://1.usa.gov/1obRRIx. The central goal of The Program is to "increase[e] the likelihood of first-cycle approval," and, according to FDA's interim assessment, it has resulted in a "statistically significant" increase in the rate of first cycle approvals. Eastern Research Group, Inc., Assessment of the Program for Enhanced Review Transparency and Communication for NME NDAs and Original BLAs in PDUFA V, ES-2 (27 March 2015), http://1.usa.gov/1MFi25q. Given these consequences, filing "over protest" does not represent an adequate resolution of the dispute over DNP's refusal to file the NDA for ataluren.

5 DIVISION/OFFICE THAT ISSUED DECISION DISPUTED MATTER

The RTF Letter was issued by the Division of Neurology Products and signed by Dr. William Dunn.

6 MEETING WITH THE DECIDING OFFICIAL

As discussed above, a Type A meeting was held on 19 April 2016 with DNP Director Dr. Dunn, representatives of senior leadership in ODE I, clinical team leaders and reviewers from DNP, as well as representatives of the Office of Clinical Pharmacology, CSS, and the Rare Diseases Program. In connection with its request for reconsideration and reversal of the RTF decision, PTC provided a briefing package in advance of the meeting and gave a slide presentation. Following the meeting, DNP prepared minutes indicating their rejection of PTC's request for reconsideration, and PTC prepared and submitted a separate record of the meeting. PTC is requesting a meeting with Dr. Janet Woodcock, Director, Center for Drug Evaluation and Research, as the deciding officer for this formal dispute resolution request.

7 REQUEST FOR ADVISORY COMMITTEE REVIEW

PTC is not requesting a public advisory committee meeting on the RTF decision. However, as noted above, PTC is requesting a meeting with Dr. Janet Woodcock, Director, Center for Drug Evaluation and Research, as the deciding officer for this formal dispute resolution request.

8 LIST OF PREVIOUSLY SUBMITTED DOCUMENTS NECESSARY FOR RESOLUTION (WITH REFERENCE TO SUBMISSION DATES)

1. NDA 200896 for ataluren (PTC124), final submission on 23 December 2015
2. Draft Statistical Analysis Plan for ataluren Study 020, submitted (IND 68431) for review and comment on 4 May 2015
3. Final Statistical Analysis Plan for ataluren Study 020, submitted (IND 68431) 20 August 2015
4. PTC briefing package for Type A meeting regarding 2016 RTF letter, submitted 23 March 2016

5. PTC slides for Type A meeting regarding 2016 RTF letter, submitted 19 April 2016
6. PTC record of Type A meeting regarding 2016 RTF letter, submitted 8 July 2016

9 STATEMENT CONCERNING NEW INFORMATION

Information contained in this formal dispute resolution request was previously provided to DNP in NDA 200896 (or IND 68431) or in connection with the Type A meeting at which reconsideration of the RTF decision was requested.

10 SPONSOR CONTACT FOR APPEAL

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NDA 200896
Ataluren (PTC124) for the Treatment of Nonsense Mutation Dystrophinopathy
PTC Record of Meeting Discussion
FDA Type A Meeting
Meeting Date: 19 April 2016

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

Sponsor 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)

RECORD OF MEETING DISCUSSION

Presentation and Data Discussion

Following introductions, PTC proceeded with a slide presentation (attached). FDA asked questions during the presentation prompting discussion as outlined below.

The first question from FDA (R. Farkas) was regarding Slide 5, dystrophin data, concerning the availability of the data from the Western blots. PTC responded that these data were available in the literature, noting that even low levels have an effect. R. Farkas indicated this was an important point, and that FDA would like to see these data. PTC agreed to provide references to these publications. In addition, PTC noted that Phase 2a data showing that ataluren causes the expression of dystrophin have been previously discussed with the Division and provided in the NDA as evidence for proof of concept.

The next question from R. Temple for Slide 20 regarded North Star Ambulatory Assessment (NSAA) loss of function analysis. He requested clarification if these data were for patients with change in score of 2 or 1 to 0, and are based on the intent to treat (ITT) population from Study 020. PTC confirmed his understanding.

Regarding Slide 27, S. Peltz commented that the timed function test (TFT) effect is on top of steroids, where it has been shown that a 1 second improvement due to steroid treatment results in preservation of ambulation for 2 years.

A further discussion between FDA and PTC on the efficacy results followed, with key discussion points as noted below:

- Discussion on primary analysis and 6 minute walk distance (6MWD) subgroups:
    - For the 300–400 m range, FDA (R. Farkas) stated he understood PTC's argument, but suggested also looking at data from patients below 300 m. He wanted to know why the agency should trust the 300–400 m group and not also use the data from the <300 m group. He expressed concern about the possibility of a chance finding.
      C. McDonald (for PTC) responded that effects were also seen in <300 m group, but patients lose walking ability and other functions rapidly in this decline phase.
      R. Farkas indicated it was not clear where those lines are drawn and that it would be helpful if PTC can look at other groups.
    - R. Temple asked why the Study 020 statistical analysis plan (SAP) included the 300-400 m subgroup, and what PTC's plan was for analysis with respect to that subgroup.
      R. Spiegel acknowledged PTC didn't amend the protocol to make 300–400 m the primary analysis or propose allocation of alpha spend because the intention remained to meet the primary objective, however the 300–400 m group was certainly 'pre-specified' in that sense that it was pre-specified and included in the SAP, which was reviewed by the FDA. The final SAP, based on the FDA comments, was submitted to the IND (68,431) prior to database lock and data unblinding. An FDA representative then read from the SAP concerning the subgroups and requested clarification on the number of subgroups. J. McIntosh referenced a slide showing a permutation method adjusting the p-value for the 300–400 m subgroup based on a conservative assumption that there were 9 subgroups in the trial, and noted that after adjustment the p-value was still significant as reflected on the relevant slide (p=0.036, Slide 55).
      S. Peltz asked what the agency's main concern was with respect to PTC's focus on the 300-400 m subgroup, noting that loss of ambulation blurs the drug effect in the <300 m group and that patients over 400 m tend to remain stable over a one year period. FDA stated that it was reasonable to pre-specify, but R. Temple wanted to know why PTC didn't spend alpha on that group. S. Peltz stated that in a rare disease setting such as this, PTC was learning about the disease as the company worked through the development process, and that there should not be a penalty for updating the SAP with additional subgroup analyses based on natural history data that emerged only after the trial commenced. S. Peltz noted that in PTC's view this set of data shows a clinical benefit in the treated population.

- Discussion on other endpoints and additional, supportive data:
    - Moving beyond 6 minute walk test (6MWT), S. Peltz pointed out assessments of benefit across multiple endpoints, including a time to event analysis of loss of ambulation (Slide 32). Overall, he stated that ataluren shows a clear and consistent benefit across multiple assessments.
    - A representative of FDA inquired about the open-label data from Study 020e and how long patients have been treated; M. Souza responded that about 100 patients have completed the 2nd year, with patients still in the study being evaluated.
    - R. Farkas asked how PTC defined loss of ambulation and C. McDonald noted that it was a rigorous assessment of 2 parameters: loss of ability to perform 10 m run/walk in >30 seconds as well as the NSAA Question 2 walking ability being a 'no' (score of zero). S. Peltz pointed out that these differences have been observed in a 1 year study.

- The FDA clinical pharmacologist asked about patients being on steroids and if steroids work in patients in the <300 m 6MWD subgroup. C. McDonald responded that the ataluren benefit is seen on top of prednisone and deflazacort. Steroids may preserve upper limb and pulmonary function in the lower functioning patients. S. Peltz added that even in these patients, preservation of function is extremely important, with loss of 1 milestone predicting for loss of later milestones.

R. Spiegel then presented slides to address some of FDA's preliminary meeting comments, and clarified that the meta-analysis was both planned and pre-specified in the SAP, quoting directly from the SAP. FDA representatives appeared surprised at this point. However, B. Dunn commented that meta-analysis still could not be accepted in light of the failure of the primary analysis in each trial. M. Boulding noted again that the meta-analysis was in the SAP and that there are regulatory precedents on the acceptance of this approach in rare diseases with small patient populations.

R. Spiegel then asked for clarification as to specifically what signal in the adverse event profile was seen to justify the Agency's position regarding abuse potential. The FDA Controlled Substance Staff (CSS) representative (M. Rusinowitz) stated that he was "not prepared" to address the data previously provided by PTC and presented at the Type A meeting or to discuss what signals of abuse potential were seen, but stated that there is a difference of opinion with respect to abuse potential. Dr. Peltz expressed concern about the best way to quickly resolve this difference of opinion, and inquired whether direct communications with CSS were possible. B. Dunn stated that PTC should reach out directly to the CSS.

Closing Discussion

Following PTC's presentation, R. Temple started the discussion regarding PTC's request to be considered for Subpart H / accelerated approval, and why PTC believes 6MWT is an intermediate endpoint. B. Dunn added that this endpoint is not really intermediate and could be the basis for full approval. R. Temple added that FDA has a growing impression that if data are not good enough for approval then companies go for accelerated approval, which does not change the efficacy standard for approval. R. Temple did acknowledge that he understands that PTC is asking if the totality of the data is worth a full review. S. Peltz responded that there exists language offering accelerated approval as a path for approval for another DMD drug, from an FDA communication in a letter from R. Temple to another sponsor (Prosensa).

B. Dunn stated that they cannot comment on another company's letter, and that the situation related to the Prosensa letter was very complicated, given that they had a short effect and thus the certainty on long term benefit might not be clear. He stated that it was a very fact-specific setting in which the letter was issued, and only relevant to a that set of circumstances.

M. Boulding stated that this was highlighted as an example of regulatory flexibility that the agency has shown to other DMD applicants, and that what PTC is looking for is similar regulatory flexibility with respect to the ataluren NDA filing in the context of a rare disease.

C. McDonald stated that the company applied 6MWT to broad populations but that this endpoint has limitations with certain segments, and therefore it is important to consider a new way of looking at efficacy by applying NSAA to ITT population.

B. Dunn commented that the company is characterizing this information as new/emerging, but it is not that new to FDA, and that the agency has been looking at data in this way for a while. He

added that FDA understands the points the company is making, and that if PTC had applied this knowledge prior to initiation of Study 020 it could have resulted in approval, but FDA are not convinced the study achieved its goals. B. Dunn commented that there appeared to be a layering of multiple aspects of what happened vs a prospective evaluation.

R. Temple added that FDA is 'for' generic enrichment designs. R. Farkas stated that if PTC has new data to show them how dystrophin levels correlate to clinical benefit it would be of great interest to the agency.

S. Peltz asked if the agency agrees that the 300–400 m subgroup is the best group in which to show an effect, and R. Temple responded that FDA doesn't know if patients who are worse off can't be stabilized. C. McDonald stated that if a confirmatory trial was to be designed there is a feasibility issue that would make a placebo control difficult, other approaches and other endpoints would need to be considered.

B. Dunn stated that the use of the term "confirmatory" is not the proper word, and recognized the pragmatic considerations for a new trial. R. Spiegel asked if there is another way to move forward in lieu of another trial, for example, follow up data from the extension study. B. Dunn commented that the agency is concerned about the methods of analysis and degree of persuasiveness for the existing data and that if another trial were to be conducted FDA would rely on PTC to propose the trial design. C. McDonald stated that from a clinical perspective it seems implausible that these results would be due to chance alone and warned FDA to avoid a Type II error with respect to efficacy, and emphasized his belief that the drug is safe.

E. Unger commented that if PTC had selected the 300-400 m subgroup as the primary analysis, then PTC and the FDA would be having a "very different conversation," S. Peltz stated that if there was a biological justification for the subgroup, then this was just semantics.

R. Farkas commented on FDA's concern that the high dose group (in Study 007) was ignored in the overall analysis.

S. Peltz stated that there is a strong biological justification for the dose-response relationship.

B. Dunn then explained to PTC that DNP's decision to not accept the application doesn't mean that no review was done, when actually a substantial review was undertaken.

B. Dunn also stated that EMA are well aware of FDA's position and they have heard the details – commenting that they (FDA and EMA) have had a lot of exchange and interchange about issues, which he stated are well understood by all involved.

He added that FDA believes data are supportive but insufficient standing alone, and they have serious reservations about accepting PTC's conclusions, rooted largely in PTC's methods of analysis.

R. Temple then stated again that they understand that PTC want FDA to talk about the totality of the data, that they 'always talk about things, and they will go away and talk about this.'

S. Peltz asked if they [FDA] were willing to rethink their position, and FDA responded that if they need more information, they will ask for it.

R. Temple again noted that FDA needs additional thinking and communication and discussion on whether there is a change in stance, and it will be communicated to PTC as part of the minutes. He understands that PTC's position is that the data deserve a review, and that PTC wants a chance to present the full data as part of that review.

R. Temple closed the meeting noting that FDA will talk again, and as efficiently as possible, to understand if and how to get to the next step, and communicate any decisions in supplemental language in the minutes.