

**Food and Drug Administration
Center for Drug Evaluation and Research**

**Summary Minutes of the Peripheral and Central Nervous System Drugs Advisory
Committee Meeting
September 28, 2017**

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

Topic: The committee discussed new drug application (NDA) 200896, ataluren for oral suspension, sponsored by PTC Therapeutics, Inc., for the treatment of patients with dystrophinopathy due to a nonsense mutation in the dystrophin gene.

These summary minutes for the September 28, 2017 meeting of the Peripheral and Central Nervous System Drugs Advisory Committee of the Food and Drug Administration were approved on October 11, 2017.

I certify that I attended the September 28, 2017 meeting of the Peripheral and Central Nervous System Drugs Advisory Committee of the Food and Drug Administration and that these minutes accurately reflect what transpired.

/s/
Moon Hee V. Choi, PharmD
Designated Federal Officer, PCNS

/s/
G. Caleb Alexander, MD, MS
Chairperson, PCNS

**Summary Minutes of the Peripheral and Central Nervous System Drugs
Advisory Committee Meeting
September 28, 2017**

The following is the final report of the Peripheral and Central Nervous System Drugs Advisory Committee meeting held on September 28, 2017. A verbatim transcript will be available in approximately six weeks, sent to the Division of Neurology Products and posted on the FDA website at:

<https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PeripheralandCentralNervousSystemDrugsAdvisoryCommittee/ucm573365.htm>.

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

The Peripheral and Central Nervous System Drugs Advisory Committee of the Food and Drug Administration, Center for Drug Evaluation and Research, met on September 28, 2017, at the Tommy Douglas Conference Center, 10000 New Hampshire Avenue, Silver Spring, Maryland 20903. Prior to the meeting, the members and temporary voting members were provided the briefing materials from the FDA and PTC Therapeutics, Inc. The meeting was called to order by G. Caleb Alexander, MD, MS (Chairperson). The conflict of interest statement was read into the record by Moon Hee V. Choi, PharmD (Designated Federal Officer). There were approximately 300 people in attendance. There were 28 Open Public Hearing (OPH) presentations.

Issue: The committee discussed new drug application (NDA) 200896, ataluren for oral suspension, sponsored by PTC Therapeutics, Inc., for the treatment of patients with dystrophinopathy due to a nonsense mutation in the dystrophin gene.

Attendance:

Peripheral and Central Nervous System Drugs Advisory Committee Members Present

(Voting): G. Caleb Alexander, MD, MS (Chairperson); Mark W. Green, MD, FAAN; Richard J. Kryscio, PhD; Chiadi U. Onyike, MD; Bruce I. Ovbiagele, MD, MSc, MAS; Joel S. Perlmutter, MD

Peripheral and Central Nervous System Drugs Advisory Committee Member Present

(Non-Voting): Mark Gordon, MD

Peripheral and Central Nervous System Drugs Advisory Committee Members Not Present

(Voting): Merit Cudkowicz, MD; Nicole R. Gonzales, MD

Temporary Members (Voting): Nathan B. Fountain, MD; Aaron S. Kesselheim, MD, JD, MPH; Wyatt Lison, Esq (Acting Consumer Representative); Michelle M. Mielke, PhD; Jeffrey Watkins (Patient Representative)

FDA Participants (Non-Voting): Robert Temple, MD; Ellis Unger, MD; Billy Dunn, MD; Eric Bastings, MD; Nicholas Kozauer, MD

Designated Federal Officer (Non-Voting): Moon Hee V. Choi, PharmD

Open Public Hearing Speakers: Teresa Wood and Matthew Harrison; Debra Miller (PTC Therapeutics, Inc.); Jacob and Cheri Gunvalson, MS, RN, PHN; Joanna Johnson; Azucena Lopez de Nava; Jonathan Piacentino; Joshua Wagner; Tamir Elnabarawy on behalf of Congressman Collin C. Peterson (MN-07); Diana and Christopher Rodriguez; Betty Vertin; Mark and Thomas Silverman; Jill Anne Castle, MEd and Joanne Wechsler; Stanley Nelson, MD; M. Carrie Miceli, PhD; Pat Furlong (Parent Project Muscular Dystrophy); Robert McFarland; Filippo Buccella (Parent Project Onlus Italia); Jack Mitchell on behalf of Megan Polanin, PhD (National Center for Health Research); Craig Campbell, MD, MSc, FRCPC; Jack, Terry and Maxx Kirley; Carolyn and Tim Monson; Charles Farwell; Ellen Wagner and Maria McDonnell; Laura Hagerty, PhD (Muscular Dystrophy Association); Rachel Salazar, PT, DPT; Susan Parzymieso, Michelle Barshay, Joseph and El'Freda Agboka and Deb Jenssen; Ronald Mueller, Angela Knight and Crissy Duran Blasingame; Daniel Karpekin

The agenda was as follows:

Call to Order and Introduction of Committee	G. Caleb Alexander, MD, MS Chairperson, PCNS
Conflict of Interest Statement	Moon Hee V. Choi, PharmD Designated Federal Officer, PCNS
FDA Opening Remarks	Billy Dunn, MD Director, Division of Neurology Products (DNP) Office of Drug Evaluation I (ODE-I) Office of New Drugs (OND), CDER, FDA
APPLICANT PRESENTATIONS	PTC Therapeutics, Inc.
Introduction	Murad Husain, RPh, MS Senior Vice President, Global Regulatory Affairs PTC Therapeutics, Inc.
DMD Natural History and Clinical Endpoints	Kevin Flanigan, MD Director, Center for Gene Therapy Nationwide Children's Hospital
Ataluren Mechanism of Action	Ellen Welch, PhD Senior Vice President, Genetic Disorders PTC Therapeutics, Inc.
Ataluren Efficacy and Safety	Joe McIntosh, MD Senior Vice President, Head of Clinical Development PTC Therapeutics, Inc.

September 28, 2017

Peripheral and Central Nervous System Drugs Advisory Committee Meeting

**APPLICANT PRESENTATIONS
(CONT.)**

PTC Therapeutics, Inc.

Clinical Perspective

Craig McDonald, MD
Director, Neuromuscular Disease Clinics
University of California, Davis Children's Hospital
Study Chair, CINRG Duchenne Natural History Study

Clarifying Questions

BREAK

FDA PRESENTATIONS

Efficacy Considerations

Robert Temple, MD
Deputy Center Director for Clinical Science
CDER, FDA

Ataluren Efficacy - Overview

Veneeta Tandon, PhD
Clinical Reviewer
DNP, ODE-I, OND, CDER, FDA

Ataluren Efficacy Statistical Review

Xiang Ling, PhD
Senior Staff Fellow
Division of Biometrics I, Office of Biostatistics
Office of Translational Sciences (OTS), CDER, FDA

Ataluren Efficacy – Key
Considerations

Veneeta Tandon, PhD

Evaluation of the Hypothesis of an
“Inverted-U” Shaped Exposure-
Response Relationship of Ataluren

Venkatesh Atul Bhattaram, PhD
Senior Staff Fellow, Division of Pharmacometrics
Office of Clinical Pharmacology (OCP), OTS, CDER, FDA

Limitations of the Bioassays Used
for Dystrophin in Studies 004 and
007

Ashutosh Rao, PhD
Chief, Laboratory of Applied Biochemistry
Division of Biotechnology Review and Research III
Office of Biotechnology Products
Office of Pharmaceutical Quality, CDER, FDA

Nonclinical and In vitro Dystrophin
Models

James L. Weaver, PhD
Research Pharmacologist
Division of Applied Regulatory Science
OCP, OTS, CDER, FDA

FDA Summary

Nick Kozauer, MD
Clinical Team Leader
DNP, ODE-I, OND, CDER, FDA

Clarifying Questions

LUNCH

Open Public Hearing

Questions to the Committee/Committee Discussion

ADJOURNMENT

Questions to the Committee:

1. **VOTE:** The best interpretation of the information presented today regarding the use of ataluren for the treatment of dystrophinopathies resulting from nonsense mutations in the dystrophin gene is that:
 - A. The data suggest that ataluren is not effective
 - B. Although it is possible that ataluren may be effective, the data are inconclusive, and more work would be needed to establish whether ataluren is effective
 - C. The data are sufficient to conclude that ataluren is effective

Vote Result: A: 0 B: 10 C: 1

Committee Discussion: *The majority of the committee voted that the best interpretation of the information presented regarding the use of ataluren for the treatment of dystrophinopathies resulting from nonsense mutations in the dystrophin gene is that although it is possible that ataluren may be effective, the data are inconclusive, and more work would be needed to establish whether ataluren is effective. These members also generally agreed that the testimonies from the public appeared compelling and should encourage the applicant to continue working on the trials. The one committee member who voted that the data are sufficient to conclude that ataluren is effective stated that his vote was not based on the data presented by FDA and PTC Therapeutics, but on written statements by clinicians on their observations of patients who have shown positive results with ataluren and on the testimony provided by the public describing patients who experienced reversal of symptoms when ataluren was removed and improvement when it was reintroduced. Please see the transcript for details of the committee discussion.*

The meeting was adjourned at approximately 3:53 p.m.