Food and Drug Administration
Center for Drug Evaluation and Research

Summary Minutes of the Peripheral and Central Nervous System Drugs Advisory Committee Meeting November 24, 2015

Location: FDA White Oak Campus, Building 31 Conference Center, the Great Room (Rm. 1503), 10993 New Hampshire Avenue, Silver Spring, Maryland 20903

Topic: The committee discussed new drug application (NDA) 206031, drisapersen solution for injection, sponsored by BioMarin Pharmaceutical Inc., for the treatment of patients with Duchenne muscular dystrophy with mutations in the dystrophin gene that are amenable to treatment with exon 51 skipping as determined by genetic testing.

These summary minutes for November 24, 2015 meeting of the Peripheral and Central Nervous System Drugs Advisory Committee of the Food and Drug Administration were approved on December 15, 2015.

I certify that I attended the November 24, 2015 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/_____
Philip A. Bautista, PharmD
Acting 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
November 24, 2015

The following is the final report of the Peripheral and Central Nervous System Drugs Advisory Committee meeting held on November 24, 2015. A verbatim transcript will be available in approximately six weeks, sent to the Division of Neurology Products and posted on the FDA website at:
http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PeripheralandCentralNervousSystemDrugsAdvisoryCommittee/ucm467181.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 November 24, 2015, at the FDA White Oak Campus, Building 31 Conference Center, the Great Room (Rm. 1503), Silver Spring, Maryland. Prior to the meeting, the members and temporary voting members were provided the background materials from the FDA and BioMarin Pharmaceutical, 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 Philip Bautista, PharmD (Acting Designated Federal Officer). There were approximately 300 people in attendance. There were 24 Open Public Hearing (OPH) presentations.

Issue: The committee discussed new drug application (NDA) 206031, drisapersen solution for injection, sponsored by BioMarin Pharmaceutical Inc., for the treatment of patients with Duchenne muscular dystrophy with mutations in the dystrophin gene that are amenable to treatment with exon 51 skipping as determined by genetic testing.

Attendance:

Peripheral and Central Nervous System Drugs Advisory Committee Members Present (Voting): G. Caleb Alexander, MD, MS (Chairperson); Emilia Bagiella, PhD; Nicole R. Gonzales, MD; Richard P. Hoffman, PharmD; Michelle Mielke, PhD; Chiadu U. Onyike, MD, MHS; Bruce I. Ovbiagele, MD, MSc; Justin A. Zivin, MD

Peripheral and Central Nervous System Drugs Advisory Committee Members Not Present (Voting): Robert R. Clancy, MD

Temporary Members (Voting): Christopher M. Cassidy (Patient Representative); Michelle M. Estrella, MD, MHS; A. Reghan Foley, MD; Mark W. Green, MD, FAAN; Cheri Gunvalson, RN, MS (Patient Representative); Aaron S. Kesselheim, MD, JD; Rodney L. Levine, MD, PhD; Glen Nuckolls, PhD; Paul Romitti, PhD;

Acting Industry Representative to the Committee (Non-Voting): Mark Gordon, MD

FDA Participants (Non-Voting): Ellis Unger, MD; Robert Temple, MD; Billy Dunn, MD; Eric Bastings, MD; Ronald Farkas, MD, PhD

Open Public Hearing Speakers: Valerie Cwik (Muscular Dystrophy Association); Erica Muskopf; Michelle Gonzales; Tracy Rupp, PharmD, MPH, RD (National Center for Health Research); Jessica Rothe; Denise Taborski; Jessica and Benjamin Divin; Andrea Cleary and Simon Hogue; Laurie Burrack (statement read by Dr. Neera Gulati); Cam Penner; Pat Furlong (Parent Project Muscular Dystrophy); Tonya Carlone; Karen Jurack; Christine McSherry, RN; Brian Denger; Mary Herman, MD; Philip Arras; Traci Rico; Debra Miller (CureDuchenne); Maxime Arras; Todd Crawford; Charaine Woods; Roger Lopez (International Association of Fire Fighters); Tammy Cate

The agenda proceeded as follows:

Call to Order and Introduction of Committee	**G. Caleb Alexander, MD, MS** Chairperson, PCNS
Conflict of Interest Statement	**Philip A. Bautista, PharmD** Acting Designated Federal Officer, PCNS
FDA Introductory Remarks	**Billy Dunn, MD** Director Division of Neurology Products (DNP) Office of Drug Evaluation I (ODE I) Office of New Drugs (OND), CDER, FDA
SPONSOR PRESENTATIONS	**BioMarin Pharmaceutical, Inc.**
Introduction	**Camilla V. Simpson, MSc** Group Vice President, Regulatory Affairs and Pharmacovigilance BioMarin Pharmaceutical Inc.
Duchenne Muscular Dystrophy: Natural History and Clinical Trial Considerations	**Craig M. McDonald, MD** Professor and Chair, Department of Physical Medicine & Rehabilitation Director, Neuromuscular Disease Clinics University California, Davis
Efficacy of Drisapersen	**Henry J. Fuchs, MD** Chief Medical Officer BioMarin Pharmaceutical Inc.
Safety of Drisapersen and Risk Management	**Giles V. Campion, MD, PhD** Group Vice President, Clinical Science BioMarin Pharmaceutical Inc.
Summary of Benefit-Risk Clinical Perspective	**Craig M. McDonald, MD**

SPONSOR PRESENTATIONS (CONT.)

Conclusion	**Henry J. Fuchs, MD**
Clarifying Questions	

BREAK

FDA PRESENTATIONS

FDA Efficacy Review	**Veneeta Tandon, PhD** Clinical Reviewer DNP, ODE I, OND, CDER, FDA **Ashutosh Rao, PhD** Acting Chief Laboratory of Applied Biochemistry Division of Biotechnology Review & Research III Office of Biotechnology Products Office of Pharmaceutical Quality, CDER, FDA **Sharon Yan, PhD** Mathematical Statistician Division of Biometrics I, Office of Biostatistics Office of Translational Sciences, CDER, FDA
Drisapersen Safety	**Evelyn Mentari, MD, MS** Clinical Safety Reviewer DNP, ODE I, OND, CDER, FDA
Clarifying Questions	

LUNCH

Open Public Hearing

Questions to the Committee/Committee Discussion

BREAK

Questions to the Committee/Committee Discussion

ADJOURN

Questions to the Committee:

1. **DISCUSSION:** Discuss the strength of efficacy evidence provided by Study 1 with particular consideration of the following issues and any other issues that you think may be important:

a. Discrepant results of the two dosing regimens despite similar exposure to drisapersen

b. Lack of statistically significant results on secondary endpoints

Committee Discussion: *The committee discussed the strength of efficacy evidence provided by Study 1, the discrepant results of the two dosing regimens despite similar exposure to drisapersen, and the lack of statistically significant results on secondary endpoints. The committee agreed that the primary endpoint was positive for the continuous regimen, but found the lack of effectiveness of the intermittent arm was concerning, weakening the evidence from the continuous arm. Committee members also found that baseline differences between the Study 1 treatment arms were confounding factors. The committee discussed limitations in the ability of statistical adjustments for age and baseline walking distance to adjust for confounding. The committee agreed that the results of the analysis of the secondary endpoint were inconclusive. Please see the transcript for details of the committee discussion.*

2. **VOTE:** What overall impact do the issues discussed in question #1 have on the persuasiveness of Study 1

Vote Result: Strengthen = 1 Weaken= 9 No Effect= 7

Committee Discussion: *A slight majority of committee members (9 members) agreed that the issues surrounding the efficacy evidence discussed in Question #1 weakened the persuasiveness of Study 1 results. These members reiterated their concern regarding the baseline differences between treatment arms, and they attributed the favorable results in patients who received continuous drisapersen dosing vs. intermittent dosing to confounding factors, especially since the drisapersen plasma concentrations were similar in both dosing groups. These committee members also re-emphasized the lack of robust and statistically significant secondary endpoint results. The committee member who voted that the issues discussed in question #1 strengthened the persuasiveness of Study 1 data stated that the primary and secondary endpoints indicated that a clinically meaningful benefit might be present even though the study was not statistically persuasive. Seven committee members voted that the issues discussed in question #1 had no effect on the overall persuasiveness of Study 1. These members stated that the secondary endpoints results had little impact given the inherent limitations of this phase 2 study, in particular, its small sample size. One of the members who voted "No Effect" added that the discrepant results of the two dosing groups potentially weakened the impact of the results while the favorable trend in the secondary endpoints potentially strengthened the impact of the results. Please see the transcript for details of the committee discussion.*

3. **DISCUSSION:** Discuss the strength of efficacy evidence provided by Study 2 with particular consideration of the following issues and any other issues that you think may be important:

a. Lack of statistical significance of the primary outcome measure ($p = 0.07$ on ITT analysis, $p = 0.23$ on per protocol analysis)

b. 3 mg/kg group numerically inferior to placebo

c. 6 mg/kg group numerically inferior to placebo for most secondary endpoints

Committee Discussion: *The committee discussed the strength of the efficacy evidence provided by Study 2, with particular consideration of the lack of statistical significance of the primary outcome measure, the numerical inferiority of the 3mg/kg group vs. placebo, and the numerical inferiority of the 6mg/kg group vs. placebo for most secondary endpoints. Although some members of the committee noted the need for flexibility with regards to the interpretation of p-values close to 0.05, given the progressive nature of Duchenne muscular dystrophy, the committee highlighted that the removal of a single patient in the per protocol analysis resulted in a change in p-value from 0.07 (intention to treat analysis) to 0.23 (per protocol analysis). These members of the committee agreed that this change demonstrated the volatility of the data, to be expected in a phase 2 study of this small size. The committee also agreed that the 3 mg/kg dose is ineffective, as it was numerically inferior to placebo. Please see the transcript for details of the committee discussion.*

4. **VOTE:** What overall impact do the issues discussed in question #2 have on the persuasiveness of Study 2?

Vote Result: Strengthen = 0 Weaken = 5 No Effect = 12

Committee Discussion: *The majority of the committee (12 members) voted that the issues surrounding the efficacy evidence had no effect on the persuasiveness of Study 2. These members explained their vote by stating that Study 2 had already failed to meet the primary outcomes, and they re-expressed their concerns about the volatility of the data and the small sample size, which resulted in the results being highly influenced by the removal of a single patient (p = 0.07 on ITT analysis, p = 0.23 on per protocol analysis). Given this small sample size, these members agreed that they could not draw sound conclusions from the secondary endpoint data. The members of the committee (5 members) who voted that the issues weakened the persuasiveness emphasized that this study did not meet its primary outcomes. All members of the committee agreed that the 3mg/kg dose was ineffective. Please see the transcript for details of the committee discussion.*

5. **DISCUSSION:** Discuss the evidence provided by Study 3 with particular consideration of the following issues and any other issues that you think may be important:

a. Lack of statistical significance of the primary outcome measure (p = 0.42) in a well-powered Phase 3 study
b. Lack of nominally statistically significant results on all secondary endpoints

Committee Discussion*: The committee discussed the evidence provided by Study 3, and the lack of statistical significance of the primary and secondary outcome measures despite Study 3 being well-powered. The committee noted the difference of 10 meters in 6 minute walking distance (6MWD) between treatment and placebo group in favor of the drisapersen group*

was not statistically significant. The committee observed that both treatment arms had a decline in 6MWD from baseline, which is different than what was found in Study 1 and 2. Members of the committee agreed that more emphasis should be placed on the results of Study 3 because it had the largest sample size. One member of the committee added that this study likely predicts drisapersen's lack of effectiveness in the general Duchenne muscular dystrophy patient population amendable to treatment with drisapersen, given the broader inclusion criteria and the greater heterogeneity of the patient sample. Please see the transcript for details of the committee discussion.

6. **VOTE:** What is the impact of Study 3 results on the persuasiveness of findings in Study 1 and Study 2?

   Vote Result: Strengthen = 0 Weaken = 15 No Effect = 2

   Committee Discussion: *The majority of the committee (15 members) agreed that the Study 3 results greatly weakened the persuasiveness of findings in Study 1 and Study 2. These members stated that Study 3, the phase 3 study, was larger in size and well-powered to detect an effect of drisapersen if it had been present. Some members of the committee highlighted the need to explore the utility of drisapersen loading doses and explore whether efficacy might be present in specific patient subpopulations. Two members of the committee voted that Study 3 had no impact on the persuasiveness of Study 1 and 2 results. One of these two members stated that the broader inclusion criteria likely skewed the treatment effect. Please see the transcript for details of the committee discussion.*

7. **DISCUSSION:** Drisapersen was designed to increase production of dystrophin. Discuss the evidence presented about dystrophin production, including the following:

   a. Similar number of patients with skipped band of mRNA detected by PCR in the placebo group and drisapersen group

   b. Similar number of patients with dystrophin increase from baseline in the placebo group and drisapersen group on immunofluorescence testing

   c. Lack of notable increase in dystrophin with drisapersen treatment on western blot analysis (pre-treatment levels <1% and post-treatment levels <1%)

   Committee Discussion*: The committee expressed their concerns about the lack of notable increase in dystrophin levels in patients who received drisapersen treatment vs. placebo despite drisapersen's proposed mechanism of action. The committee agreed, however, that this lack of increase could have been the result of the chosen muscle biopsy site (tibialis anterior muscle) and/or the current issues surrounding dystrophin measurement methods, including lack of a reference standard and inability to distinguish between revertant and drug-induced dystrophin. Some members questioned the credibility and representativeness of the dystrophin data given that a low percentage of patients had viable samples (74% of patients in Study 2 and 48% of patients in Study 3). Please see the transcript for details of the committee discussion.*

8. **VOTE:** What is the impact of the dystrophin results on the interpretation of the clinical results?

   Vote Result: Strengthen = 0 Weaken = 6 No Effect = 10 No Vote = 1

   Committee Discussion: *The majority of the committee (10 members) agreed that the evidence presented about dystrophin production in the studies had little effect on the interpretation of the clinical results. These members highlighted the complexities of measuring dystrophin and other biomarkers, and the lack of understanding of the relationship between dystrophin levels and clinical outcomes. These members agreed that the data were inconclusive and voiced concern regarding missing data and poor quality biopsies. The six members who voted that the evidence weakened the interpretation of the clinical results expressed the concerns that drisapersen appeared to have failed to increase dystrophin levels, its proposed mechanism of action. The committee agreed that this lack of effect on dystrophin levels may be a reflection of the lack of efficacy demonstrated in Study 3. One member of the committee left the meeting early and did not vote on this question. Please see the transcript for details of the committee discussion*

9. **DISCUSSION:** In light of today's discussions, please discuss the overall strengths and weaknesses of the data supporting the efficacy of drisapersen and the acceptability of its safety profile for the treatment of Duchenne muscular dystrophy amenable to exon 51 skipping.

   Committee Discussion: *In general, the committee agreed that the efficacy of drisapersen as a treatment for patients with Duchenne muscular dystrophy with mutations in the dystrophin gene that are amenable to treatment with exon 51 skipping (as determined by genetic testing) has not been demonstrated by the data obtained so far from the clinical program. Based on the progressive nature of this fatal disease and the open public hearing testimonies, the committee also agreed that many members of this patient population would likely be willing to accept the safety risks. However, members of the committee noted that these patients and their parents should only accept these safety risks if drisapersen is efficacious. Members of the committee also noted that although there were no deaths in the studies, many of the adverse effects could lead to mortality. The committee agreed that the sponsor should explore the use of drisapersen in a narrower patient population, including younger patients and those who are not under rapid decline in order to determine whether there is a subset of patients in whom the drug might be effective. Some members of the committee highlighted that this drug may only be effective during a narrow period of a patient's lifetime. Please see the transcript for details of the committee discussion.*

The meeting was adjourned at approximately 5:31 p.m.