

Summary Minutes
Psychopharmacologic Drugs Advisory Committee Meeting
January 12, 2016

The following is the final report of the Psychopharmacologic Drugs Advisory Committee meeting held on January 12, 2016. A verbatim transcript will be available in approximately six weeks, sent to the Division of Anesthesia, Analgesic, and Addiction Products and posted on the FDA website at:

<http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PsychopharmacologicDrugsAdvisoryCommittee/ucm475314.htm>

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

The Psychopharmacologic Drugs Advisory Committee of the Food and Drug Administration, Center for Drug Evaluation and Research, met on January 12, 2016, at the FDA White Oak Campus, Building 31, The Great Room (Rm. 1503), White Oak Conference Center, Silver Spring, Maryland. Prior to the meeting, the members and temporary voting members were provided the background materials from the FDA, and from Braeburn Pharmaceuticals, Inc., on behalf of Titan Pharmaceuticals. The meeting was called to order by Judith M. Kramer, MD, MS (Acting Chairperson). The conflict of interest statement was read into the record by Jennifer Shepherd, RPh (Designated Federal Officer). There were approximately 100 people in attendance for the meeting. There were 18 Open Public Hearing speakers.

Issue: The committee discussed new drug application (NDA) 204442, PROBUPHINE (buprenorphine hydrochloride and ethylene vinyl acetate) subdermal implant, submitted by Braeburn Pharmaceuticals, Inc., on behalf of Titan Pharmaceuticals for the proposed indication of maintenance treatment of opioid dependence.

Attendance:

Psychopharmacologic Drugs Advisory Committee Members Present (Voting): Thomas A. Grieger, MD; David Pickar, MD

Psychopharmacologic Drugs Advisory Committee Members Not Present (Voting): David A. Brent, MD (Chairperson); Murray Stein, MD, MPH

Temporary Members (Voting): Warren K. Bickel, PhD; Kathleen T. Brady, MD, PhD; Melinda Campopiano, MD; Kathleen M. Carroll, PhD (via phone); Lori E. Dodd, PhD; Adam J. Gordon, MD, MPH, FACP, FASAM; Jennifer Higgins, PhD (Acting Consumer Representative); Dawn F. Ionescu, MD; Margaret Kotz, DO; Judith M. Kramer, MD, MS (Acting Chairperson); Laura F. McNicholas, MD, PhD; Rajesh Narendran, MD; Kenzie L. Preston, PhD; James Troendle, PhD; Michael Yesenko, MDiv (Patient Representative)

Acting Industry Representative to the Committee (Non- Voting):

Robert Russell Conley, MD (Industry Representative)

FDA Participants (Non-Voting): Sharon Hertz, MD; Rigoberto Roca, MD; Celia Winchell, MD; David Petullo, MS; Kimberly Lehrfeld, PharmD

Open Public Hearing Speakers: Sarah Wilson; Major General Arthur T. Dean, US Army, Retired (Community Anti-Drug Coalitions of America and Collaborative for Effective Prescription Opioid Policies); David Sheff (statement read by Susan Knade); Scott Jernigan; Shruti Kulkarni, JD (Center for Lawful Access and Abuse Deterrence); Shannon Ginnan, MD (Aimed Alliance); Amanda Wilson, MD (Clean Slate Centers) (statement ready by Shannon Ginnan, MD); Gary Mendell (Shatterproof); Wayne Campbell (Tyler's Light); Tracy Rupp, PharmD, MPH, RD (National Center for Health Research); Marc Harrold, Esq.; Afzar Malik, MD, MBA, DFAPA; Cynthia Moreno Tuohy (NAADAC, the Association for Addiction Professionals); David Emswiler; Amit Vijapura, MD (statement ready by Afzar Malik, MD); Joe R. Gay, PhD, LICDC (Health Recovery Services); Patrick Kennedy (former Congressman) (statement read by Gary Mendell); Tim Lepak (The National Alliance of Advocates for Buprenorphine Treatment) (statement read by Wayne Campbell)

The agenda was as follows:

Call to Order and Introduction of
Committee

Judith M. Kramer, MD
Acting Chairperson, PDAC

Conflict of Interest Statement

Jennifer Shepherd, RPh
Acting Designated Federal Officer, PDAC

FDA Opening Remarks

Celia Winchell, MD
Clinical Team Leader
Division of Anesthesia, Analgesia, and Addiction
Products (DAAAP)
Office of Drug Evaluation II (ODEII)
Office of New Drugs (OND), CDER, FDA

APPLICANT PRESENTATIONS

Braeburn Pharmaceuticals, Inc.

Introduction

Behshad Sheldon
President & Chief Executive Officer
Braeburn Pharmaceuticals

Public Health Need

Frank Young, MD, PhD
Executive Vice President, Regulatory and Medical
Braeburn Pharmaceuticals

Medical Need

Michelle Lofwall, MD
Associate Professor, Depts of Behavioral Science
& Psychiatry
Center on Drug and Alcohol Research
University of Kentucky College of Medicine

APPLICANT PRESENTATIONS (CONT.)

Efficacy

Sonnie Kim, PharmD

Vice President, Clinical Development and Medical
Affairs
Braeburn Pharmaceuticals

Training Program & Safety

Steven Chavoustie, MD, FACOG

Principal Investigator
Segal Institute for Clinical Research
Volunteer Assistant Professor, University of
Miami Miller School of Medicine

Risk Management

Behshad Sheldon

Benefit/Risk

Michael Frost, MD, FACP, FASAM

Medical Director, Eagleville Hospital
President, Frost Medical Group

Clarifying Questions to Applicant

BREAK

FDA PRESENTATIONS

Efficacy and Safety of Probuphine for the
Maintenance Treatment of Opioid Dependence
in Clinically Stable Patients

Rachel Skeete, MD, MHS

Clinical Reviewer
DAAAP, ODEII, OND, CDER, FDA

James Travis, PhD

Statistics Reviewer
Division of Biostatistics II, Office of Biostatistics,
Office of Translational Sciences, CDER, FDA

Clarifying Questions to FDA

LUNCH

OPEN PUBLIC HEARING

BREAK

CHARGE TO THE COMMITTEE

Sharon Hertz, MD

Director
DAAAP, ODEII, OND, CDER, FDA

Questions to the Committee/Committee Discussion

ADJOURNMENT

Questions to the Committee:

1. Probuphine is a non-titratable product that provides a fixed plasma level of buprenorphine. The original studies raised concerns about the appropriateness of the dose for a broad population. The Applicant has specified a population, namely stable patients on a relatively low dose of sublingual buprenorphine, for whom they believe the dose provided by Probuphine is adequate.

DISCUSSION:

- a. Discuss whether there is a population that would benefit from the use of Probuphine and how to define this population.
- b. If there is a population that would benefit from Probuphine, discuss whether the study entry criteria adequately define this patient population.
- c. Discuss whether the population studied reflected this population.

Committee Discussion: *The committee discussed the importance of defining a stable population and stated that the definition used by the sponsor may need to be revised to more precisely identify the narrower subpopulation for whom Probuphine may be appropriate. Several committee members noted that the length of time that patients were considered stable for inclusion in the study should be longer. Committee members emphasized other indicators of stability beyond the dose of medication that the patient was using or the time in treatment. Several committee members expressed concern over missing data and ongoing and as needed use of supplemental buprenorphine. Please see the transcript for details of the committee discussion.*

2. In general, occasional dose adjustments for patients on sublingual buprenorphine can be expected over time. The sponsor chose not to include rescue medication as an element of the responder definition because there was an expectation that patients would require little to no rescue medication. However, that was not the case, as rescue medication was used by a number of patients, some throughout the 6-month treatment period.

DISCUSSION: Discuss whether use of rescue should be considered in defining a responder for a long-acting formulation of buprenorphine such as Probuphine, where the dose cannot be adjusted over time. If rescue should be part of the responder definition, should the use of rescue buprenorphine be differentiated based on the pattern or the frequency of rescue use over the 6-month treatment? Consider the following patterns of use:

- a. Use primarily after first initiating Probuphine
- b. Use throughout the 6-month period
- c. Use only at the end of the 6-month treatment period

Committee Discussion: *The committee discussed the issue of a non-responder versus a responder and suggested that supplemental buprenorphine use might not always constitute a treatment failure, particularly if use was at the beginning of a treatment*

cycle, when patients may be adjusting to the new dosage form, and at the end of treatment when buprenorphine plasma levels with the sustained delivery formulation may be waning. However, many committee members expressed concern over ongoing supplemental buprenorphine use throughout the treatment period. One committee member cautioned against allowing such a high non-inferiority margin when considering a potential pharmacotherapy for approval when compared to a standard of care. One committee member also stated that the frequent use of supplemental buprenorphine could still be a source of diversion of the buprenorphine. Please see the transcript for details of the committee discussion.

3. Customarily in opioid addiction treatment trials, there are many missing urine samples due to relapse and dropout from treatment. Because relapse is the most common reason for dropout, missing urine samples are assumed to be positive. However, in this study, the patients were stably abstinent from illicit drugs, and they were asked to provide only 10 samples over six months. Therefore, it was expected that there would be few missing samples, and that these could be missing for reasons other than relapse. Therefore, the strategy for imputation of missing data did not assume that all missing samples were positive. However, some situations arose in which it might be appropriate to assume that missed samples are indicators of illicit use.

DISCUSSION: Discuss how missing or incomplete urine toxicology results should be considered when defining a responder. Consider the following:

- a. Patients who were completely lost to follow-up immediately after receiving the Probuphine implant
- b. Samples that were not collected due to:
 1. Missed scheduled visit
 2. Missed random sample visit
 3. Refused by patient
- c. Samples that were collected on schedule but were not analyzed in a timely fashion (out of stability window for the test)

Committee Discussion: *Committee members agreed that the patients who were lost to follow-up just after study drug insertion should be included in the analysis as non-responders. Several committee members expressed concern over the missing urine toxicology data in the clinical studies and that there needs to be more analysis of these missing data. Committee members noted that missed visits for scheduled or random urine toxicology collections are likely indicators of return to illicit opioid use, even in a population deemed clinically stable. The Committee generally commented that samples that were collected on schedule did not need to be assumed to be positive if no other information supported that conclusion. Please see the transcript for details of the committee discussion.*

4. The protocol-specified responder definition did not take rescue use into account, and employed an optimistic imputation strategy for missing urine toxicology results, yielding a responder rate of 96% vs 88% for Probuphine and sublingual buprenorphine,

respectively. As you have seen, there are many different possible responder rates once these factors are taken into account.

DISCUSSION: Discuss which of the various approaches to expressing a responder rate you think is most appropriate.

***Committee Discussion:** One committee member recommended using an imputation model to explore predictors of missingness. Several committee members were concerned that the traditionally understood definition of an Intent to Treat (ITT) population was not really the ITT definition that was used by the Applicant. The committee recommended including the three patients the Applicant omitted from their defined ITT population, including the two patients who were lost to follow up and an additional patient who was incarcerated, in the analysis. In general, the Committee stated that approaches using the Agency's ITT definition, imputing missing samples as positive, and considering more than minimal use of supplemental dosing as indicative of inadequacy of the treatment were the most appropriate. Please see the transcript for details of the committee discussion.*

5. Patients managed with buprenorphine may require dose adjustment over time. However, in clinical practice, unlike patients on sublingual buprenorphine, Probuphine-treated patients would not necessarily be seen for regular visits with buprenorphine dose adjustments.

DISCUSSION:

- a. Discuss how the need for occasional supplemental doses will translate to clinical practice for patients treated with Probuphine. If patients need to have sublingual buprenorphine on hand in addition to Probuphine, discuss how these prescriptions will impact the product's ability to mitigate misuse, abuse, and accidental pediatric exposure.
- b. Some patients on Probuphine required supplemental sublingual buprenorphine only briefly after insertion of the implant, while others required it only at the end of the dosing period when plasma levels could have been falling. In contrast, some patients required ongoing supplemental dosing throughout the 6-month treatment period.

Discuss whether the pattern of supplemental sublingual buprenorphine should be taken into consideration when deciding if Probuphine is effective and should be continued for a given patient **in clinical practice**. Discuss whether there is a pattern of sublingual buprenorphine use that should result in the discontinuation of Probuphine.

***Committee Discussion:** The Committee felt strongly that it would be inappropriate to routinely prescribe medication for the patient to take home and use on an "as-needed" basis. The majority of the committee members agreed that regular visits would still be needed for patients treated with Probuphine and recommended at least monthly visits. One committee member stated that if patients required supplemental buprenorphine*

throughout the entire Probuphine 6-month treatment period, they would not consider Probuphine treatment for that patient again beyond that particular treatment period. Please see the transcript for details of the committee discussion.

6. The Sponsor has provided information on a training and certification program to ensure that practitioners can safely insert Probuphine. However, the procedure of removing Probuphine after six months of implantation is not readily modeled for the purposes of training because there is development of fibrotic tissue around the implants.

DISCUSSION: Discuss the steps the Sponsor should take to ensure that removals, including complicated removals, are performed appropriately.

***Committee Discussion:** A number of committee members expressed reservations about the training program being adequate to teach the procedure to providers who are not currently involved in performing procedures, such as psychiatrists. Several committee members stated that non-proceduralists should be initially observed by someone experienced in the removal of Probuphine. One committee member stated that the practice procedures should be done on humans. One committee member stated that non-proceduralists may have difficulty passing the certification program. Another committee member stated that the training program may be too cumbersome for many practitioners to be willing to undertake. They also expressed that volume is a key factor for procedural proficiency. Along those lines they suggested that availability of high volume trainers and high volume centers would be helpful for training purposes for non-proceduralists. Please see the transcript for details of the committee discussion.*

7. The Sponsor has proposed a Risk Evaluation and Mitigation Strategy (REMS) which consists of restricted distribution and a training/certification program for healthcare professionals who will insert and remove the product.

DISCUSSION: Discuss whether the REMS is adequate to address the risks of potential complications associated with the insertion and removal procedures, and abuse, misuse, and accidental overdose.

***Committee Discussion:** One committee member stated concerns that the paperwork required for providers to order and keep Probuphine in their offices may be cumbersome. Please see the transcript for details of the committee discussion.*

8. **VOTE:** Based on the data presented and discussed today, do the efficacy, safety, and risk-benefit profile of Probuphine support the approval of this application for a population of patients previously stable on a regimen of sublingual buprenorphine (as defined during prior discussion)?

YES: 12 NO: 5 Abstain: 0

Committee Discussion: *The majority of the committee agreed that the efficacy, safety, and risk-benefit profile of Probuphine supports the approval of this application for a population of patients previously stable on a regimen of sublingual buprenorphine. Those voting “Yes”, stated that the conservative and thorough analysis of the clinical trial data was appropriate, and they were satisfied that Probuphine was proven to be non-inferior. The committee recommended that the labeling be very clear in defining the appropriate treatment population and provide detailed information on the guidelines that should be followed for providing supplemental buprenorphine to patients on Probuphine. The committee stated that the benefit and safety profile of Probuphine was favorable for approval. Those committee members voting “No,” expressed concerns over missing data in the clinical trials and the lack of data on use beyond two years. Please see the transcript for details of the committee discussion*

9. **DISCUSSION:** Comment on any further development or explorations, e.g. higher doses, the Sponsor should undertake

Committee Discussion: *The committee provided many recommendations for further development including study of a more diverse populations, higher doses, treatment beyond two years and further exploration including data on need for supplemental doses, frequency of monitoring visits, urinalysis frequency, and tracking of improper implant removal, and the potential use of Probuphine for auto-taper. Please see the transcript for details of the committee discussion.*

The meeting was adjourned at approximately 5:00 p.m.