

Summary Minutes of the meeting of the Psychopharmacologic Drugs Advisory Committee February 3, 2016

The following is the final report of the Psychopharmacologic Drugs Advisory Committee held on February 3, 2016. A verbatim transcript will be available in approximately six weeks, sent to the Division of Psychiatry Products and posted on the Food and Drug Administration (FDA) website at:

<http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PsychopharmacologicDrugsAdvisoryCommittee/ucm461701.htm>

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

The Psychopharmacologic Drugs Advisory Committee (PDAC) of the FDA, Center for Drug Evaluation and Research, met on February 3, 2016, 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 briefing materials from FDA and Takeda Development Center Americas, Inc. (afternoon session only). The meeting was called to order by David Pickar, MD (Acting Chairperson). The conflict of interest statement was read into the record by Kalyani Bhatt, BS, MS, (Designated Federal Officer). There were approximately 130 people in attendance for the morning session and 150 in attendance for the afternoon session. There were no Open Public Hearing (OPH) speakers registered for the morning session and seven OPH speakers for the afternoon session.

Issues: During the morning session, the committee discussed cognitive dysfunction in major depressive disorder (MDD). This is an evolving concept and experts in the field have not yet reached consensus as to whether cognitive dysfunction in MDD is a distinct entity. The committee considered the clinical presentation of cognitive dysfunction in MDD, as well as methods for assessing this condition.

During the afternoon session, the committee discussed new drug application 204447/supplemental new drug application 006, for the effectiveness of vortioxetine for the treatment of cognitive dysfunction in MDD, submitted by Takeda Development Center Americas, Inc.

Attendance:

Psychopharmacologic Drugs Advisory Committee Members Present (Voting): Thomas A. Grieger, MD; David Pickar, MD (Acting Chairperson); Murray Stein, MD, MPH

Psychopharmacologic Drugs Advisory Committee Member Not Present: David A. Brent, MD (Chairperson)

Temporary Members (Voting): Dwight Dickinson, PhD, JD; Jennifer Higgins, PhD (Acting Consumer Representative); Charles Hinkin, MD; Dawn Ionescu, MD; Francis J. McMahon, MD; Rajesh Narendran, MD; Natalie Compagni Portis, PsyD (Patient Representative)

Acting Industry Representative to the Committee (Non- Voting): Robert Russell Conley, MD

FDA Participants (Non-Voting): Robert Temple, MD; Mitchell Mathis, MD; Tiffany R. Farchione, MD; Aeva Gaymon-Doomes, MD; Wen-Hung Chen, PhD

Designated Federal Officer (Non-Voting): Kalyani Bhatt, BS, MS

Open Public Hearing Speakers for the Morning Session: *None*

Open Public Hearing Speakers for the Afternoon Session: Greg Mattingly, MD; Ray Bartholomew; David Bartley; Allen Doederlein (*President, Depression and Bipolar Support Alliance*); James North; Stephanie Fox-Rawlings, PhD (*Senior Fellow, National Center for Health Research*); Ken Dolan-Del Vecchio, LMFT (*Vice President, Health and Wellness*)

The agenda proceeded as follows:

Morning Session:

Call to Order and Introduction of Committee

David Pickar, MD
Acting Chair Chairperson, PDAC

Conflict of Interest Statement

Kalyani Bhatt, BS, MS
Designated Federal Officer, PDAC

FDA PRESENTATIONS

FDA Introductory Remarks

Mitchell Mathis, MD
Director
Division of Psychiatry Products (DPP)
Office of Drug Evaluation I (ODE-I)
Office of New Drugs (OND), CDER, FDA

Cognitive Dysfunction in Major Depressive Disorder: FDA's Perspective, Past and Present

Tiffany R. Farchione, MD
Deputy Director
DPP, ODE-I, OND, CDER, FDA

NATIONAL INSTITUTE OF MENTAL HEALTH (NIMH) PRESENTATION

Cognition and Neuroimaging in Depression

Carlos A. Zarate, Jr., MD
Chief, Experimental Therapeutics and Pathophysiology Branch
NIMH, Office of the Director
National Institutes of Health (NIH)

GUEST SPEAKER PRESENTATION

Cognitive Dysfunction and MDD

Madhukar Trivedi, MD
Director
Center for Depression Research Clinical Care
UT Southwestern Medical Center

NIMH PRESENTATION

Assessing Cognitive Function

Jenni Pacheco, PhD
Scientific Program Manager
NIMH, Office of the Director
NIH

Clarifying Questions

OPEN PUBLIC HEARING

Questions to the Committee/Committee Discussion

Afternoon Session:

Call to Order and Introduction of
Committee

David Pickar, MD
Acting Chairperson, PDAC

Conflict of Interest Statement

Kalyani Bhatt, BS, MS
Designated Federal Officer, PDAC

FDA Introductory Remarks

Tiffany R. Farchione, MD
Deputy Director
Division of Psychiatry Products (DPP)
Office of Drug Evaluation-I (ODE-I)
Office of New Drugs (OND), CDER, FDA

INDUSTRY PRESENTATIONS

Takeda Development Center Americas, Inc.

Introduction

Jonathon M. Parker, RPh, MS, PhD
Vice President, Global Regulatory Affairs
Takeda Pharmaceuticals

Measuring Change in Cognition with
Digit Symbol Substitution Test (DSST)

Judith Jaeger, MPA, PhD
Professor of Psychiatry and Behavioral Sciences
Albert Einstein College of Medicine
President and Principal Scientist
Cognition Metrics, LLC

Study Design and Results

Christina Kurre Olsen, PhD
Senior Specialist, Clinical Science
Lundbeck

Clinical Perspective

Maurizio Fava, MD

Executive Vice Chair, Department of Psychiatry
Massachusetts General Hospital
Executive Director, Clinical Trials Network and
Institute

Conclusion

Louis Mini, MD

Vice President, Global Medical Head, Medical
Affairs
Takeda Pharmaceuticals

Clarifying Questions

FDA PRESENTATIONS

Regulatory History of Vortioxetine for the
Treatment of Cognitive Dysfunction in
MDD

Tiffany R. Farchione, MD

Clinical Outcome Assessment Review of
Digit Symbol Substitution Test (DSST):
Vortioxetine for Cognitive Dysfunction in
MDD

Wen-Hung Chen, PhD

Acting Team Leader
Clinical Outcome Assessments Staff
Immediate Office
OND, CDER, FDA

Clinical, Safety, and Efficacy Data

Aeva Gaymon-Doomes, MD

Medical Officer
DPP, ODE-I, OND, CDER, FDA

Clarifying Questions

Open Public Hearing

Charge to the Committee

Tiffany R. Farchione, MD

Questions to the Committee/Committee Discussion

ADJOURNMENT

Questions to the Committee (Morning Session):

- 1. DISCUSSION:** Discuss whether cognitive dysfunction in MDD (Major Depressive Disorder) is an appropriate drug development target? If so, which cognitive domains are mainly affected by the cognitive dysfunction in MDD and what is the best method to assess these affected domains?

Committee Discussion: Overall, the committee agreed that cognitive dysfunction is an appropriate drug development target; however there are many questions and issues. The committee recognized the clinical significance of neuropsychological deficits in MDD. Discussion included whether the neuropsychological deficits were independent targets or overlapping with the syndrome of depression itself, i.e., “pseudospecific.” The committee was indecisive on the best method to assess the affected cognitive domain. Some examples stated included, processing speed and attentional processing. Please see the transcript for details of the committee’s discussion.

- 2. DISCUSSION:** What are the acceptable primary efficacy endpoints for a claim of the treatment of cognitive dysfunction in MDD?

Committee Discussion: The committee discussed relevance of specific neuropsychological measures. The Digit Symbol Substitution Test (DSST) emerged as the most sensitive neuropsychological measure; however, it was also recognized that while sensitive the DSST is non-specific. Other neuropsychological parameters including the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery were discussed. The committee also recognized the need for more data regarding neuropsychological testing and drug response in MDD. The committee members were open to recommendations to utilize tests focusing on working memory (e.g., Spatial Span Test), processing speed (e.g., DSST, Trail Making Part A) or verbal learning (e.g., Hopkins Verbal Learning Test). Please see the transcript for details of the committee’s discussion.

- 3. DISCUSSION:** Discuss whether a functional assessment is necessary as a co-primary endpoint?

Committee Discussion: The committee discussed the possibility of functional measures as a co-primary endpoint in MDD. It was noted that functional measures for neuropsychological deficits are already in place for schizophrenia and Alzheimer’s disease. However, the more severe cognitive deficits of Alzheimer’s disease and schizophrenia in comparison to MDD raised questions of utilizing functional assessment as an endpoint in depression. The committee agreed that functional measures must be workable in clinical trials. The committee also agreed that functional measures are not necessary as a co-primary endpoint with

neuropsychological measures. Please see the transcript for details of the committee's discussion.

Questions to the Committee (Afternoon Session):

1. **DISCUSSION:** Discuss whether the Digital Symbol Substitution Test (DSST) is an adequate measure of cognitive function in MDD?

Committee Discussion: The majority of the committee was in agreement that DSST is a useful measure of cognitive function, reflecting processing speed a variable recognized as important to day-to-day function, but not the only measure. The committee members further agreed while the DSST is highly sensitive – that is, it “recognizes” even modest levels of deficit - it is not specific to any one disorder. Consideration was given to the frequent complaint of depressed patients that function was not sufficiently restored despite mood improvement, including slowed cognition and lack of efficient function. In this regard, the DSST emerges as a useful measure. The panel members agreed that DSST is a measure, not necessarily an adequate measure, of cognitive dysfunction. Please see the transcript for details of the committee's discussion.

2. **DISCUSSION:** What, if any, additional data are needed pre- or post-approval to address outstanding issues? Please be clear whether you believe these data should be required prior to approval.

Committee Discussion: The committee was open to additional clinical data regarding neuropsychological measures and drug response, including symptoms that continue after clinical response. In addition, post-approval studies in more diverse populations were recommended. It was noted by the committee members that additional data were not necessary prior to approval. Please see the transcript for details of the committee's discussion.

3. **DISCUSSION:** Does a claim for an effect on cognitive function require showing of superiority to another antidepressant (or more than one) or is it sufficient to show an effect vs placebo on cognitive function?

Committee Discussion: The committee stated that data with regard to the relative effectiveness of vortioxetine in comparison to other antidepressants would be welcomed. The committee agreed, however, that it was not necessary to have such comparative data. There was discussion regarding how closely linked were neuropsychological deficits to other symptoms of depression. Please see the transcript for details of the committee's discussion.

4. **VOTE:** Has substantial evidence been presented by the applicant to support a claim of effectiveness for vortioxetine for treating cognitive dysfunction in MDD?

Yes: 8

No: 2

Abstain: 0

Committee Discussion: *The majority of the committee agreed that substantial evidence was presented by the applicant to support a claim of effectiveness for vortioxetine in treating cognitive dysfunction in MDD. It was stated that the two well-controlled trials demonstrated that DSST was statistically significantly reduced by vortioxetine in comparison with placebo. Those who voted “No” stated the evidence was not substantial and expressed concern whether DSST should stand alone as a drug target. The committee broadly both understood and shared this concern, although the majority felt that the data presented warranted a favorable response. Please see the transcript for details of the committee’s discussion.*

The meeting was adjourned at approximately 4:35 p.m.