Topic: The committee discussed new drug application (NDA) 202,008, Florbetapir F 18 Injection, sponsored by Avid Radiopharmaceuticals, proposed for use in Positron Emission Tomography (PET) imaging of β-amyloid (beta-amyloid) aggregates in the brain to help rule out Alzheimer's disease.

These summary minutes for the January 20, 2011 Peripheral and Central Nervous System Drugs Advisory Committee meeting were approved on February 4, 2011.

I certify that I attended the January 20, 2011 Peripheral and Central Nervous System Drugs Advisory Committee meeting and that these minutes accurately reflect what transpired.

-signed-
Diem-Kieu H. Ngo, Pharm.D., BCPS
(Designated Federal Official)

-signed-
Britt Anderson, M.D., Ph.D.
(Chair)
The following is the final report of the Peripheral and Central Nervous System Drugs Advisory Committee meeting held on January 20, 2011. A verbatim transcript will be available in approximately six weeks, sent to the Division and posted on the FDA website at http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PeripheralandCentralNervousSystemDrugsAdvisoryCommittee/ucm235850.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 January 20, 2011, at the FDA White Oak Campus, Building 31, the Great Room, White Oak Conference Center (Rm. 1503), 10903 New Hampshire Avenue, Silver Spring, Maryland. Prior to the meeting, the members and temporary voting members were provided the background materials from the FDA and Avid Radiopharmaceuticals. The meeting was called to order by Britt Anderson, M.D., Ph.D. (Chair). The conflict of interest statement was read into the record by Diem-Kieu H. Ngo, Pharm.D., BCPS (Designated Federal Official). There were approximately 200 people in attendance. There were eight Open Public Hearing (OPH) speakers.

**Issue:** The committee discussed new drug application (NDA) 202,008, Florbetapir F 18 Injection, sponsored by Avid Radiopharmaceuticals, proposed for use in Positron Emission Tomography (PET) imaging of \(\beta\)-amyloid (beta-amyloid) aggregates in the brain to help rule out Alzheimer's disease.

**Attendance:**

Peripheral and Central Nervous System Drugs Advisory Committee members present (voting):
Britt Anderson, M.D., Ph.D. (Chair); Jeffrey A. Cohen, M.D.; Nathan B. Fountain, M.D.; Mark W. Green, M.D.; Pooja Khatri, M.D.; Ying Lu, Ph.D.; Ellen J. Marder, M.D.; Jason W. Todd, M.D.

Peripheral and Central Nervous System Drugs Advisory Committee members not present (voting):
Samuel A. Frank, M.D. (Consumer Representative); Dean D. Kindler, M.D.

Peripheral and Central Nervous System Drugs Advisory Committee members not present (non-voting):
Roy Twyman, M.D. (Industry Representative)

Temporary Voting Members:
Vernon M. Chinchilli, Ph.D.; Lily Jung Henson, M.D., M.M.M., FAAN (Acting Consumer Representative); Peter Herscovitch, M.D., FRCP, FACP; Faiza Mahmoud, M.D.; Howard Mann, M.D.; Gianna McMillan (Patient Representative); Madhav Thambisetty, M.D., Ph.D.; Harvey A. Ziessman, M.D.; James L. Tatum, M.D., FCCP

Industry Representative present (non-voting): Enrico Veltri, M.D.

Guest Speaker (non-voting): G. William Rebeck, Ph.D.

FDA Participants (non-voting): Shaw T. Chen, M.D., Russell G. Katz, M.D.; CAPT Rafel D. Rieves, M.D.
**Open Public Hearing Speakers:** Peter T. Fox, M.D.; Michael W. Weiner, M.D.; David J Brooks M.D., D.Sc., FRCP, FMedSci; Norman L. Foster, M.D.; Joel S. Ross M.D., FACP, AGSF, CMD, CPI; Daniel Perry; Maria C. Carrillo, Ph.D.; Zaven S. Khachaturian, Ph.D.

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**The agenda was as follows:**

**Call to Order and Opening Remarks**  
**Britt Anderson, M.D., Ph.D.**  
Chair  
Peripheral and Central Nervous System Drugs  
Advisory Committee

**Introduction of Committee**

**Conflict of Interest Statement**  
**Diem-Kieu H. Ngo, Pharm.D., BCPS**  
Designated Federal Official

**FDA Introductory Remarks**  
**CAPT Rafel Dwaine Rieves, M.D.**  
Director, Division of Medical Imaging Products (DMIP)  
Office of Drug Evaluation (ODE) IV  
Office of New Drugs (OND), CDER, FDA

**FDA Presentation**

**Regulatory Considerations for Medical Imaging Agents**  
**Lucie Yang, M.D., Ph.D.**  
Medical Officer, DMIP, ODE IV, OND, CDER, FDA

**Guest Speaker Presentation**

**Presentation, Diagnosis and Management of Alzheimer’s Disease**  
**Madhav Thambisetty, M.D., Ph.D.**  
Staff Clinician (Neurology), Clinical Research Branch  
National Institute on Aging  
National Institutes of Health  
Adjunct Assistant Professor of Neurology  
Johns Hopkins University School of Medicine

**Amyloid and Amyloid Deposition in the Brain**  
**G. William Rebeck, Ph.D.**  
Professor, Department of Neuroscience  
Georgetown University Medical Center

**Clarifying Questions**

**Break**

**Industry Presentation**

**Introduction**  
**Daniel Skovronsky, M.D., Ph.D.**  
CEO, Avid Radiopharmaceuticals
Questions to the Committee:

1. (Discussion: New Considerations) In 2008, the PCNS Drugs Advisory Committee concluded that “a negative amyloid test could have clinical utility in ruling out a diagnosis of Alzheimer’s Disease.” Before turning to consider Amyvid™ specifically, discuss any new scientific and clinical developments since 2008 that bear on the clinical utility of a reliable imaging assessment “for the detection of cerebral amyloid.”
Committee Discussion: The committee members felt there have been major advances, especially in mild cognitive impairment (MCI) patients. There was a general consensus that there has been additional scientific research since 2008 which is supportive of the prior recommendations on the clinical utility of a negative scan for amyloid in patients with symptoms consistent with dementia. Additionally, the committee agreed that the new research offers a stronger evidentiary base for the recommendations from the 2008 advisory committee meeting. The committee was informed by the sponsor that the proposed indication had changed during the review cycle to state that, “Florbetapir F18 injection is a diagnostic radiopharmaceutical indicated for positron emission tomography (PET) imaging of beta-amyloid aggregates in the brain. A negative florbetapir-PET scan is clinically useful in ruling out the presence of pathologically significant levels of beta-amyloid in the brain.” Certain committee members expressed the opinion that a negative amyloid test may not necessarily rule out amyloid presence but simply make amyloid presence less likely.

2. (Discussion: Image Read Methods) Two Amyvid™ image reading methods were used in the phase 3 trial (A07): a semi-quantitative scoring method (0 – 4) in the “autopsy” cohort and a “binary” (positive/negative) method in the “specificity” cohort. Only the binary method is proposed for the clinical use of Amyvid™. Discuss the strengths and limitations of the A07 trial data. Consider the following questions:

a. To what extent would reinterpretation of the A07 “autopsy” cohort images help allay any concern about the lack of binary read results for patients with a histopathological measure of amyloid?

Committee Discussion: The committee members concurred that the reinterpretation of the A07 autopsy cohort images by a number of readers who use a binary read method would be important for addressing concerns regarding the lack of data and also help address concerns regarding consistency among readers, particularly if the readers use the clinically applicable training methods.

b. How important is the establishment of a clinically relevant histopathological “threshold” for determining whether an image is positive/negative?

Committee Discussion: The committee members agreed that a threshold must be chosen, but voiced concerns that the binary read method and the training in this method needs to minimize the potential for false positives and false negatives as well as inconsistency between image interpretations due to insufficient training. There was general consensus that there is a need for a clinically relevant histopathological “threshold” for determining whether an image is positive/negative.

c. How important is the establishment of a clinically-applicable reader training program?

Committee Discussion: The committee members agreed that it is essential for there to be a clinically-applicable reader training program. Multiple committee members emphasized the need to verify the sufficiency of the reader training methods. Members generally did not favor a certification-type approach to the training procedures.

d. How important is the establishment of acceptable reader-to-reader reproducibility for the binary read method, based upon readers trained according to a clinically-applicable training program?

Committee Discussion: The committee members agreed that it is essential for there to be acceptable reader-to-reader reproducibility for the binary read method, based upon readers trained according to a clinically-applicable training program.
3. (Discussion: Clinical Population) A phase 2 trial (A05) enrolled healthy control subjects as well as patients with a diagnosis of mild cognitive impairment or Alzheimer’s Disease. However, the phase 2 data raise questions about the reader-to-reader reproducibility of the binary read imaging results. Discuss the strengths and limitations of the A05 data. Consider the following questions:

a. To what extent does the A05 population exemplify patients who may ultimately undergo Amyvid™ imaging?

Committee Discussion: The committee members agreed that the A05 population better exemplifies patients who may ultimately undergo Amyvid imaging.

b. To what extent would reinterpretation of the A05 images provide useful information, especially if the reinterpretation was performed by readers trained according to a clinically-applicable reader training program?

Committee Discussion: There was a general consensus that reinterpretation of the A05 images will assess reproducibility of image interpretation among readers, and could increase confidence in the readings. The committee members agreed that there is important information to be gained in understanding the consistency of reads utilizing the scans of the A05 patients as a database.

4. (Vote) Do the available data support the approval of Amyvid™ at the present time? Discuss the basis for the vote, including any database deficiencies and ways to resolve these deficiencies (such as the collection of new premarketing or postmarketing data).

YES: 3  NO: 13  ABSTAIN: 0

Committee Discussion: The committee members agreed that Amyvid does what it purports to do: That is, it allows for amyloid imaging. However, they voiced concerns regarding the inconsistency in the PET scan readings and the other deficiencies as outlined above. Thus, the committee encouraged FDA to review additional data resulting from implementation and testing of a reader training program aimed at improving reader consistency.

5. (Vote) If there were implementation of a training program that demonstrated accurate diagnosis within the autopsy standard/population and a demonstration of a reader consistency in the population of intended application such as exemplified by A05, would the available data support the approval of Amyvid?

YES: 16  NO: 0  ABSTAIN: 0

Committee Discussion: The majority of the committee members requested the addition of this fifth question so that they may voice their desire to see Amyvid approved contingent upon additional data and resolution of the reader training method concerns. The committee unanimously agreed that the available data support the approval of Amyvid if there were implementation of a training program that demonstrated accurate diagnosis within the autopsy standard/population (A07) and a demonstration of reader consistency in the population of intended application as exemplified by A05. In particular, they recommended that the sponsor provide additional data on inter-rater reliability (re-reading of the A07 and A05 scans using the binary method) prior to approval.

The meeting was adjourned at approximately 4:30 p.m.