

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

204677Orig1s000

MEDICAL REVIEW(S)

**Medical Officer Review
Amendment to Review of NDA 204-677**

Date:	01/31/2014
From	Brenda Ye
NDA # and Supplement #	NDA 204677 (sequence 031, 032), IND 78868
Date of Submissions	10/1/2013 (IND), 11/6/2013, 11/22/2013
Applicant	Piramal Life Sciences
Date of Original Submission	12/21/2012
Original PDUFA Goal Date	12/21/2013
Date of Major Amendment	11/22/2013
Proprietary Name / Established	Neuraceq/F-18 Florbetaben
Dosage forms / Strength	Solution for Injection /50 to 5000 MBq
Proposed Indication(s)	Detection of neuritic beta-amyloid plaques
Recommended:	Approval

1. Recommendation on Regulatory Action

The clinical reviewer recommends approval of the application.

The reviewer previously recommended Complete Response on the application due to lack of substantial evidence of effectiveness (particularly specificity). The reviewer also recommended that the applicant conduct another clinical study to demonstrate evidence of effectiveness (sensitivity and specificity) based on histopathology as the standard of truth.

The applicant subsequently conducted a clinical study (“Histopathology Read Study”, Protocol Number FBB-01_01_13) and submitted results of the study as a major amendment to the NDA. Sensitivity and specificity as demonstrated in this study both achieved prespecified threshold levels.

2. Study FBB-01_01_13 (“Histopathology Read Study”)

The new clinical study submitted in the major amendment dated 11/22/2013 is titled “A non-interventional study to assess the efficacy, reliability, and reproducibility of the florbetaben-F18 (FBB) β -amyloid Positron Emission Tomography (PET) scan visual assessment method as trained via an electronic training tool, using images from the histopathology study 14595”.

Study Subjects

All subjects in the “Histopathology Read Study” are from the Phase 3 Study 14595 (pivotal ‘Histopathology’ study), which finished subject enrollment, but continued to follow enrolled subjects to obtain post-mortem histopathology results on deceased subjects.

In this “Histopathology Read Study” (Study FBB-01_01_13), 82 subjects are autopsy subjects from Study 14595. Post-mortem brain specimens from these subjects underwent histopathological assessment by the Pathology Consensus Panel. The 82 autopsy subjects include both clinically demented and non-demented subjects.

An additional 10 healthy volunteers (HVs) are also included in the “Histopathology Read Study”. These 10 healthy volunteers serve as negative controls, and their brain histopathology results are presumed to be negative without autopsy.

Reviewer's comments: The applicant's primary efficacy analysis of the “Histopathology Read Study” included these 10 healthy volunteers. The FDA review team disagreed with the applicant on this approach, and the FDA review team's primary efficacy analysis of the study excluded these 10 healthy volunteers.

F-18 Florbetaben PET Image Evaluation

A total of 5 independent readers evaluated F-18 Florbetaben PET images. F-18 Florbetaben PET image evaluation algorithm is the same as that used in Study 16034 (pivotal ‘Pooled Read’ Study).

First Regional Cortical Tracer Uptake (RCTU) is obtained from 4 brain regions: frontal cortex, parietal cortex, lateral temporal cortex, and posterior cingulate. Then RCTU (regional assessment) is collapsed to render the overall subject level Brain Amyloid Plaque Load (BAPL):

- Normal: BAPL = 1 (negative or sparse brain amyloid deposition)
- Abnormal:
 - BAPL = 2 (moderate brain amyloid deposition)
 - BAPL = 3 (pronounced brain amyloid deposition)

Standard of Truth

Reviewer's comments: In previous pivotal Study 14595 ('Histopathology' Study), the histopathology standard of truth (SoT) included all three forms of brain amyloid deposition – neuritic plaques (amyloid deposition associated with neurons), diffuse amyloid plaques (intercellular amyloid deposition), and vascular amyloid (amyloid deposition associated with vessels). The FDA review team considered above SoT definition deficient because clinical significance of diffuse amyloid plaques and vascular amyloid are not well established in the medical community. The FDA review team recommended that the applicant use only neuritic plaques as the histopathology SoT.

In this “Histopathology Read Study”, only neuritic plaques are used for histopathology SoT. However two different methods for assessing neuritic plaques are included:

- **BSS(CERAD)/IHC** - neuritic plaques detected by Bielschowsky Silver Staining (BSS) according to CERAD criteria in combination with immunohistochemistry (IHC) for amyloid-beta staining
- **BSS(CERAD)** - neuritic plaques detected by Bielschowsky Silver Staining (BSS) according to CERAD scoring criteria

Reviewer's comments: Neuritic plaques are traditionally assessed by the Bielschowsky Silver Staining (BSS) according to CERAD criteria, and this method for assessing neuritic plaque is well established in the medical community. The FDA review team recommended that neuritic plaques as assessed by Bielschowsky Silver Staining (BSS) according to CERAD criteria be used as the histopathology SoT in primary efficacy analysis.

The applicant used neuritic plaques as assessed by Bielschowsky Silver Staining in combination with immunohistochemistry for β -amyloid staining (BSS/IHC) as the SoT in its primary analysis. The FDA review team used neuritic plaques as assessed by Bielschowsky Silver Staining (BSS) as the SoT in its primary efficacy analysis.

Efficacy Endpoints

In the applicant's efficacy analyses, primary efficacy endpoints are sensitivity and specificity of visual assessment F-18 florbetaben PET, compared to histopathology SOT of neuritic plaques as assessed by Bielschowsky Silver Staining in combination with immunohistochemistry [BSS(CERAD)/IHC].

Reviewer's comments: The FDA review team's primary efficacy analysis used histopathology SOT of neuritic plaques as assessed by Bielschowsky Silver Staining only [BSS(CERAD)].

The applicant's secondary efficacy endpoints include:

- sensitivity and specificity of visual assessment of F-18 Florbetaben PET, compared to histopathology SOT of BSS(CERAD)
- Inter-reader and intra-reader agreements

Win Criteria

Sensitivity and specificity of visual assessment of F-18 Florbetaben PET images are co-primary endpoints of the study. Prespecified sensitivity threshold is 0.6, and specificity threshold is 0.5. Three out of 5 blinded readers must win on both sensitivity and specificity for the study to be considered a win.

Specifically, the combined hypotheses were to be rejected if the lower limits of the 95% confidence intervals for sensitivity and specificity were higher than the thresholds of 0.6 and 0.5 respectively for at least 3 out of the 5 blinded readers.

3. Efficacy Results

Primary Efficacy

The FDA review team excluded 10 healthy volunteers from the primary efficacy analysis and used neuritic plaques detected by Bielschowsky Silver Staining (BSS) according to CERAD scoring criteria as the standard of truth. Results are shown in Table 1.

For sensitivity, the lower bounds of the 95% confidence interval are all above the 60% threshold level for all 5 readers.

For specificity, the lower bounds of the 95% confidence interval are above the 50% threshold level in Reader 1, 3, and 4. The lower bounds of the 95% confidence interval are 28.81% and 38.93% for Readers 2 and 5, respectively, both below the 50% threshold level.

Overall 3 out of 5 readers achieved prespecified sensitivity and specificity thresholds, and the combined null hypotheses can be rejected.

Table 1: Sensitivity and specificity (including normal approximated CI) of the visual assessment of FBB PET scans compared to histopathology (neuritic plaques detected by BSS(CERAD)) as SoT, excluding the healthy volunteers (FAS)

Blinded Reader	No. of TP	No. of TP + FN	Sensitivity [%]	Sensitivity 95% LCL [%]	Sensitivity 95% UCL [%]*	No. of TN	No. of TN + FP	Specificity estimate [%]	Specificity 95% LCL [%]	Specificity 95% UCL [%]*
Blinded Reader 1	49	52	94.23	87.89	100.00	24	30	80.00	65.69	94.31
Blinded Reader 2	51	52	98.08	94.34	100.00	14	30	46.67	28.81	64.52
Blinded Reader 3	47	52	90.38	82.37	98.40	24	30	80.00	65.69	94.31
Blinded Reader 4	50	52	96.15	90.93	100.00	23	30	76.67	61.53	91.80
Blinded Reader 5	52	52	100.00	93.15	100.00	17	30	56.67	38.93	74.40

Note: TP = True positive / FN = False negative / TN = True negative / FP = False positive; LCL = lower confidence limit; UCL = upper confidence limit; CI = confidence interval; SoT = Standard of Truth
 Note: * if the approximative confidence limit was >100% it was set to 100%

Secondary Efficacy

With healthy volunteers excluded, if using neuritic plaques detected by Bielschowsky Silver Staining (BSS) according to CERAD criteria in combination with immunohistochemistry (IHC) for amyloid-beta staining as the standard of truth, the same Readers 1, 3, 4 achieved both prespecified sensitivity and specificity thresholds (Table 2).

Table 2: Sensitivity and specificity (including normal approximated CI) of the visual assessment of FBB PET scans compared to histopathology (neuritic plaques detected by BSS(CERAD)/IHC) as SoT, excluding the healthy volunteers (FAS))

Blinded Reader	No. of TP	No. of TP + FN	Sensitivity [%]	Sensitivity 95% LCL [%]	Sensitivity 95% UCL [%]*	No. of TN	No. of TN + FP	Specificity estimate [%]	Specificity 95% LCL [%]	Specificity 95% UCL [%]*
Blinded Reader 1	52	56	92.86	86.11	99.60	23	26	88.46	76.18	100.00
Blinded Reader 2	55	56	98.21	94.75	100.00	14	26	53.85	34.68	73.01
Blinded Reader 3	51	56	91.07	83.60	98.54	24	26	92.31	82.06	100.00
Blinded Reader 4	54	56	96.43	91.57	100.00	23	26	88.46	76.18	100.00
Blinded Reader 5	56	56	100.00	93.62	100.00	17	26	65.38	47.10	83.67

Note: TP = True positive; FN = False negative; TN = True negative; FN = False negative; LCL = lower confidence limit; UCL = upper confidence limit; CI = confidence interval; SoT = Standard of Truth
 Note: * if the approximative confidence limit was >100% it was set to 100%

The applicant included 10 healthy volunteers as ‘true negatives’ in its efficacy analyses. As expected, these ‘true negatives’ somewhat inflated specificity results without significantly changing sensitivity results (Tables 3 and 4).

Table 3: Sensitivity and specificity (including normal approximated CI) of the visual assessment of FBB PET scans compared to histopathology (neuritic plaques detected by BSS(CERAD)) as SoT (FAS)

Blinded Reader	No. of TP	No. of TP + FN	Sensitivity [%]	Sensitivity 95% LCL [%]	Sensitivity 95% UCL [%]*	No. of TN	No. of TN + FP	Specificity estimate [%]	Specificity 95% LCL [%]	Specificity 95% UCL [%]*
Blinded Reader 1	49	52	94.23	87.89	100.00	34	40	85.00	73.93	96.07
Blinded Reader 2	51	52	98.08	94.34	100.00	19	40	47.50	32.02	62.98
Blinded Reader 3	47	52	90.38	82.37	98.40	34	40	85.00	73.93	96.07
Blinded Reader 4	50	52	96.15	90.93	100.00	31	40	77.50	64.56	90.44
Blinded Reader 5	52	52	100.00	93.15	100.00	22	40	55.00	39.58	70.42

Note: TP = True positive / FN = False negative / TN = True negative / FN = False negative; LCL = lower confidence limit; UCL = upper confidence limit; CI = confidence interval; SoT = Standard of Truth
 Note: * if the approximative confidence limit was >100% it was set to 100%

Table 4: Sensitivity and specificity (including normal approximated CI) of the visual assessment of FBB PET scans compared to histopathology (neuritic plaques detected by BSS(CERAD)/IHC) as SoT (FAS)

Blinded Reader	No. of TP	No. of TP + FN	Sensitivity [%]	Sensitivity 95% LCL [%]	Sensitivity 95% UCL [%]*	No. of TN	No. of TN + FP	Specificity estimate [%]	Specificity 95% LCL [%]	Specificity 95% UCL [%]*
Blinded Reader 1	52	56	92.86	86.11	99.60	33	36	91.67	82.64	100.00
Blinded Reader 2	55	56	98.21	94.75	100.00	19	36	52.78	36.47	69.09
Blinded Reader 3	51	56	91.07	83.60	98.54	34	36	94.44	86.96	100.00
Blinded Reader 4	54	56	96.43	91.57	100.00	31	36	86.11	74.81	97.41
Blinded Reader 5	56	56	100.00	93.62	100.00	22	36	61.11	45.19	77.04

Note: TP = True positive; FN = False negative; TN = True negative; FN = False negative; LCL = lower confidence limit; UCL = upper confidence limit; CI = confidence interval; SoT = Standard of Truth

Note: * if the approximative confidence limit was >100% it was set to 100%

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/s/

BRENDA Q YE
01/31/2014

ALEXANDER GOROVETS
01/31/2014

I agree with Dr. Ye's conclusions and recommendations based on the review of the major amendment.

Summary Review for Regulatory Action

Date	11/27/2013
From	Libero Marzella MD, PhD
Subject	Division Director Summary Review
NDA	204677
Applicant Name	Piramal Imaging
Date of Submission	12/21/2012
PDUFA Goal Date	12/21/2013
Proprietary Name / Established (USAN) Name	Neuraceq Florbetaben F 18
Dosage Forms / Strength	Solution for Injection/ 50 to 5000 MBq per mL
Indications	detection of beta amyloid in the brain in patients evaluated for Alzheimer's disease or other causes of cognitive decline
Action Recommended	Extend PDUFA goal date

INTRODUCTION

This memorandum is submitted in lieu of a complete Division Director NDA Summary review. The memorandum summarizes the rationale for recommending an extension of the PDUFA review goal date for this application.

On December 21, 2012 Piramal Imaging SA submitted an original 505(b)(1) New Drug Application (NDA 204677) for Neuraceq (florbetaben F 18 injection). Florbetaben is a radiopharmaceutical diagnostic agent proposed for use with positron emission tomography for detection of beta amyloid in the brain in patients evaluated for Alzheimer's disease or other causes of cognitive decline. The PDUFA review goal date for this application is December 21, 2013. A complete Response Action was anticipated because of the assessment by the clinical and statistical reviewers that the data in the original submission are not adequate to establish the effectiveness of florbetaben F 18 as an amyloid imaging agent.

On November 22, 2013 the applicant submitted to the NDA the complete report of a new clinical study and requested that the submission be considered a major amendment. Subsequent to discussions and informal communications with the clinical and statistical reviewers, I concur that the new data submitted, if verified, will likely provide the confirmatory evidence of efficacy lacking in the original NDA submission.

ORIGINAL NDA REVIEWS

Clinical and statistical review issues

The original NDA submission relies on two phase 3 studies (denoted as the Histopathology study (14595) and the Pooled Read study (16043)) for evidence of safety and effectiveness of florbetaben F 18 for the proposed indication.

I concur with the Cross Discipline Team Leader (Dr Alex Gorovets) and the Clinical and Statistical reviewers (Drs. Brenda Ye and Lan Huang) that the data in the original NDA are insufficient for assessing the effectiveness of florbetaben as an amyloid imaging agent.

The Histopathology study was successful and provided adequate data for concept validation. However, the portion of the study using the practice applicable image interpretation method employed an inappropriate truth standard and those analyses are therefore considered exploratory. The Pooled Read study met its primary efficacy endpoint based on the practice applicable reading method and using web-based training, but failed to meet an important secondary endpoint raising concern about poor specificity.

Other discipline reviews

The CMC reviewer Dr. Anne Marie Russell recommends approval pending resolution of concerns about the adequacy of acceptance criteria for (b) (4) impurities in the (b) (4) drug substance. Facility inspections have been so far acceptable and some are still ongoing. The product microbiology reviewer, Dr. Erika Pfeiler, finds the product quality to be acceptable from the microbiologic perspective and recommends approval.

The pharmacology reviewer, Dr. Sunny Awe recommends approval. The review of non-clinical data has revealed no safety signals.

The clinical pharmacology reviewer Dr. Christy John, has found the dose finding and dosimetry studies to be acceptable. Dr. John recommends approval.

SUBMISSION OF NEW CLINICAL DATA

At the September 10, 2013 late-cycle meeting with Piramal, DMIP stated that the Histopathology study (14595) had achieved its co-primary efficacy endpoints and is acceptable as a method validation study. However, DMIP expressed concerns with the results of the Pooled Read study (16043). The study had met its primary efficacy endpoint of reader agreement but had failed to meet the important secondary endpoint of specificity of the reader's interpretations. DMIP stated that the applicant's secondary analyses of reader's performance from study 14595 and 16043 are considered to be exploratory. DMIP recommended that the applicant conduct a new reader study of all the cases in study 14595 for whom standard of truth data are available.

In response to these discussions on October 1, 2013 Piramal submitted to the florbetaben IND a new read study protocol (FBB-01-01-13) titled: "A non-interventional study to assess the efficacy, reliability, and reproducibility of the florbetaben-F18 (FBB) β -amyloid Positron Emission Tomography (PET) scan visual assessment method as trained via an electronic training tool, using images from the histopathology study 14595."

On October 18, 2013 DMIP sent a general advice letter to the applicant to recommend revisions to the study's primary efficacy analysis and to express some reservations about the inferences that can be drawn from a study based on the reinterpretation of images.

On November 6, 2013 the applicant submitted to the NDA a high level summary of the data and the datasets from the completed study. The study had met its prespecified efficacy endpoints. On

November 22, 2013, Piramal submitted the complete study report to the NDA. The applicant also requested the designation of the submission as a major amendment and the extension of the PDUFA review goal date to March 21, 2014.

On November 19, 2013 DMIP's CMC reviewers discussed with the applicant unresolved concerns regarding the acceptance criteria for impurities in the (b) (4) drug substance and requested a written justification of the safety of the proposed specifications. The CMC and Pharmacology/ Toxicology reviewers had internal discussions regarding the (b) (4) impurities and determined that qualification studies for these impurities would likely not be needed.

On November 25, 2013 the NDA review team (CMC, clinical, pharmacology/toxicology, and statistics) met to discuss the new clinical data and the outstanding (b) (4) impurity issues. The CMC team has determined that the outstanding (b) (4) issues do not rise to the level of a Complete Response action. The CMC team anticipates resolving the issues in the present review cycle. The Pharmacology Toxicology team concurs with the assessment that the issues will be addressed without the need for qualification studies. The clinical and statistical reviewers have determined that the study protocol, the study results and the data sets are reviewable and that if verified the results could address the clinical and statistical deficiencies in the original NDA.

Given this consensus DMIP anticipates designating Piramal's November 22, 2013 submission as a major amendment. This designation will extend the PDUFA review goal date.

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/s/

LIBERO L MARZELLA
11/27/2013

Cross-Discipline Team Leader Review

Date	October 28, 2013
From	Alex Gorovets, MD
Subject	Cross-Discipline Team Leader Review
NDA#	204677
Applicant	Piramal Imaging
Date of Submission	December 21, 2012
PDUFA Goal Date	December 21, 2013
Proprietary/Established names	Neuraceq / F18 Florbetaben
Dosage forms / Strength	Solution for Injection / 50 to 5000 MBq per mL
Proposed Indication	Florbetaben is indicated for the detection of β -amyloid in the brain, thereby assisting in the differential diagnosis in adult patients who are being evaluated for Alzheimer's disease and other causes of cognitive decline.
Recommended:	<i>Complete Response (based on data in the NDA to date)</i>

1. Introduction

The subject of this Cross Disciplinary Team Leader (CDTL) review is the New Drug Application (NDA) 204677 for Neuraceq, or F-18 Florbetaben, an amyloid imaging agent proposed for use with Positron Emission Tomography (PET) in patients being evaluated for possible Alzheimer's disease and other cognitive disorders.

The applicant is Piramal Imaging. The application is a 505(b)-(1) which relies on two Phase-3 studies for evidence of safety and effectiveness of F-18 Florbetaben in the proposed indication. The drug is similar in its clinical utility and in its mechanism of action to Amyvid which was approved over a year ago and to Vizamyl which is about to be approved.

The proposed indication is as follows:

(b) (4)

This review document addresses the evidence submitted by the applicant in support of the stated claim and concentrates mostly on the issue of whether the submitted data and analyses are sufficient for the drug approval. The document refers to analyses and review findings from multiple disciplines. During the review process, no significant disagreements have been encountered among the reviewers.

2. Background

Alzheimer's disease is the most common cause of dementia representing a major healthcare concern in this country and throughout the world. Although certain clinical scales have been proposed for the diagnostic evaluation of patients with suspected Alzheimer's dementia, a

definitive diagnosis can only be established by examining brain histopathology (i.e. post-mortem). One of the histologic hallmarks of the disease is the presence of extracellular β -amyloid deposits.

Amyloid imaging uses radioactive compounds with documented high in vitro amyloid affinity for in vivo, “pre-mortem” detection of amyloid deposits. One such compound is F18 Florbetaben which is also referred to as Florbetaben throughout this document. In addition to Florbetapir (Amyvid) and Flutemetamol (Vizamyl), both F18 radionuclides, the amyloid imaging agents also include the C11-PIB, or the “Pittsburgh Compound”, well known in the field of Alzheimer research but not usable clinically because of its very short half life.

The regulatory history of amyloid imaging involves two important Advisory Committee meetings. The first one in 2008 was dedicated to determining whether amyloid imaging is clinically useful and, if so, choosing an appropriate Standard of Truth for assessing an imaging drug’s performance. Florbetaben was one of the three F18 amyloid imaging drugs discussed at that meeting. The Committee advised the FDA that, with many cognitively intact elderly people known to have cerebral amyloid deposits, amyloid imaging would be only useful in ruling out the diagnosis of Alzheimer’s disease that is when the amyloid scan is negative. Of note, amyloid imaging is also often invoked in approaching a clinical trial of a therapeutic drug for Alzheimer’s disease aimed at affecting the process of amyloid deposition thought by many to be an important part of the disease’ pathogenesis. Although amyloid imaging agents could be used as this type of “biomarkers” in therapeutic drug development (i.e. for confirming amyloid presence before treating someone with an anti-amyloid drug), the clinical diagnostic use is for ruling out rather than confirming the presence of amyloid.

The second Advisory Committee meeting applicable to amyloid imaging was held in 2011 during the review of the Amyvid application by the FDA. At issue was the reading methodology and reader training. Interpretation of amyloid PET scans differs from a typical PET scan interpretation involving an identification of a “hot spot”. It involves a certain pattern recognition and differentiation, globally or region by region, of a tracer uptake between gray and white matter with a loss of clear border. From the Amyvid review, it was proposed that there would have to be a binary subject level image interpretation, positive vs. negative. There was also an expectation of a web-based training to be provided to the practitioners. The ability of multiple web-based trained readers to agree on an image interpretation would have to be validated by data. Because performance characteristics could not be measured in patients without histopathology (autopsy) as a standard of truth, one would have to show adequate reader agreement in different patient populations, especially in patients with Minimal Cognitive Impairment (MCI), the most likely intended use population for amyloid imaging.

Eventually, Amyvid approval was based on three sources of clinical data as described in the Clinical Studies section of the product labeling. The first was the study of correlation between amyloid imaging (without using a “practice applicable” reading method) and amyloid histopathology as a concept validation study. The second was the study of performance characteristics (sensitivity and specificity) by in-person trained readers, with histopathology as a Standard of Truth, and the third was the study of agreement (kappa-statistic) among five web-based-trained readers using images from different types of potential patient population

including MCI. The secondary endpoints in the reader agreement study measured the performance characteristics in patients with available histopathology. Both latter studies used a “practice applicable” reading methodology with binary outcome and the CERAD defined amyloid histopathology scale for a Standard of Truth (SOT).

CERAD stands for Consortium to Establish a Registry for Alzheimer’s disease. CERAD criteria use neuritic plaque counts on a histopathology slide as a necessary pathological feature of AD and use silver-stained (also known as “Bielschowsky”) tissue sections to count the plaques. According to these criteria, if counts are none or sparse the brain histopathology is considered to be negative for amyloid, if counts are moderate or frequent it is positive.

For Vizamyil, there were two sources of clinical data used in the approval process, with two studies being generally similar in design to the confirmatory studies two and three in the Amyvid development program. Both of the Vizamyil confirmatory studies used practice applicable reading methodology, the CERAD based SOT and a web based training in one of them. (With Vizamyil being an F18 labeled analogue of the well known “Pittsburgh Compound”, its label does not appear to include a histopathology based concept validation.)

For Florbetaben, the regulatory history of its development has been well documented by Dr. Brenda Ye in her primary clinical review. It should be noted that the review issues involving reading methodology, SOT definitions and reader performance, as well as various dataset clarification requirements, have been identified by Dr. Ye and Dr. Lan Huang, the primary statistical reviewer, early in the review process. These concerns, with different degrees of detail, have been communicated to the applicant at various times following the filing meeting, the midcycle meeting and in preparation to and during the late cycle meeting (LCM).

3. CMC/Device

The CMC reviewer, Dr. Ann Marie Russell has noted in her review that Florbetaben F 18 Injection is produced as a sterile solution for intravenous administration in a 30 mL multi-dose vial containing 50 MBq/mL (1.35 mCi/mL) to 5000 MBq/mL (135 mCi/mL) of F18 Florbetaben at End of Synthesis (EOS). The review goes on to list the excipients in the drug product and states that the unit dose is prepared by the radio-pharmacy and is 300 MBq (81 mCi) at time of calibration (time of patient injection). The unit dose is contained in a maximum volume of 10 mL maintaining the acceptable ratios of excipients. The concentration of drug substance in drug product is required to be from 50 MBq/mL to 5000 MBq/mL at EOS and is required to be no less than (b) (4) at expiry. The recommended single intravenous dose for Neuraceq is 300 MBq (81 mCi) of F18 Florbetaben in a dose volume of ≤10 mL. A 300 MBq maximum human dose of Florbetaben F 18 Injection contains not more than 30 mcg of Florbetaben. The Neuraceq dose is administered as a slow intravenous injection bolus.

Most of the CMC related data have been reviewed and found to be adequate for approval however some (b) (4) data and specifications are still pending. Facility inspections have been so far acceptable and some are still ongoing. The product microbiology reviewer, Dr. Erika Pfeiler recommends approval. There are no device issues in this application.

4. Nonclinical Pharmacology/Toxicology

Review of non-clinical data has revealed no safety signals for humans based on studies of safety pharmacology, single and repeated dose toxicity. Long-term toxicity studies have not been carried out, because this product is intended for short-term use only. The battery of genotoxicity tests did not show evidence of mutagenic potential and genotoxicity tests on key impurities proved negative. A waiver was granted for reproductive toxicology and carcinogenicity studies. The pharmacology reviewer, Dr. Sunny Awe has also reviewed the in vitro proof of concept studies showing how Florbetaben binds to amyloid fibrils and plaques. Dr. Awe recommends approval.

5. Clinical Pharmacology/Biopharmaceutics

The clinical pharmacology reviewer, Dr. Christy John, has found the dose finding and dosimetry studies to be acceptable with the selected radioactivity dose being 300MBq. Uptake of radioactivity in the brain is rapid occurring within 10 minutes post injection. Florbetaben is eliminated from plasma with a mean biologic half-life of about 1 hour (physical half-life of F 18 is about 2 hours). No radioactivity could be measured in blood at about 4 hours post injection. By 12 hours post-injection, up to approximately 30% of the injected radioactivity has been excreted in urine.

Dr. John has confirmed that no dose adjustment in patients with renal impairment is necessary. The effect of hepatic impairment was not studied. Dr. John also suggests that quantitative imaging with standard uptake value ratio (SUVr) measurements might improve reader performance, specificity in particular. As for a regulatory action, he recommends approval.

6. Clinical Microbiology

N/A

7. Clinical/Statistical- Efficacy

The primary clinical and statistical reviews have focused on the two Phase-3 studies submitted by the applicant in support of the proposed efficacy claim. These are the Histopathology study and the Pooled Read study.

In the Histopathology study, over two hundred end-of-life patients with a short life expectancy were enrolled and underwent a Florbetaben PET scan. The primary analysis population consisted of 31 patients who died and at autopsy contributed their brains to the histopathology based truth standard (SOT). In addition, images from 10 young healthy volunteers (YHV) for whom the “truth” was assumed to be negative for amyloid were included in the analyses. There were six brain regions for matching the imaging and histopathology results. Altogether there were 246 brain regions available for analyses. Three blinded readers read PET scan images region by region and the majority read was used in the primary analysis. Histopathology slides were evaluated by a central consensus panel (CP). The details of imaging and histopathology scoring systems have been thoroughly reviewed by D. Ye. The regional SOT in this part of the study evaluated different types of amyloid including neuritic and diffuse plaques as well as vascular amyloid using both the silver stain (BSS) and the

immunohistochemistry (IHC). As attested to by the applicant in later communications the BSS of the neuritic plaques was always looked at first.

The primary efficacy analyses in the Histopathology study included hypothesis testing which pre-specified that in order for the study to be successful the region based sensitivity of the majority read had to be over 60% and the region based specificity of the majority read had to be over 80%. The study was successful on both of these metrics as well as on each of the individual reads. The regional sensitivity of the majority read was 77% (95% CI: 65.5% - 89.4%) and the regional specificity of the majority read was 94% (95% CI: 88.6% to 99.8%).

There was a concern expressed by the primary reviewers about the design of the study involving approaches not applicable to clinical practice such as a majority read, broadly defined SOT and regionally based analyses. This reviewer has considered such approaches and analyses to be acceptable for this type of study where the goal is to demonstrate that the presence of amyloid deposits is matched between imaging and histopathologic assessments (concept validation).

As part of the Histopathology study, the applicant performed a variety of exploratory analyses aimed at developing and further refining a subject level, practice applicable reading methodology. The applicant also explored measurements of imaging performance against differently constructed truth standards. Predictably, a more broadly defined truth using all types of amyloid and both stains would result in higher test specificity as compared to a more narrowly defined truth such as only a silver stain of only neuritic plaques.

The applicant then performed a blinded read study using whole brain images of the same 31 patients and three independent readers who were in-person trained in the final version of the practice applicable reading method. The method has consisted of thoroughly reading four pre-defined brain regions and then providing a binary read outcome by calling a subject negative for amyloid only if all four regions are negative. The method is described in detail by Dr. Ye in her review. The analyses of reader performance in this part of the study have been carried out using locally obtained on-site histopathology assessments as an SOT. However, the review team has determined that this SOT has not been pre-specified or described in the protocol in terms of a nature of blinding or a number of histopathology readers, and has no relation to the CP assessments available for the same patients. Therefore, although the results of the analyses show high sensitivity and specificity for each of the readers, this reviewer agrees with the review team that these are exploratory analyses and are not appropriate for confirmatory efficacy evaluations.

The Pooled Read study involved brain images from 461 subjects including 54 patients with autopsy obtained histopathology (the same 31 as in the Histopathology study plus additional 23). The main purpose of this trial was to evaluate the practice applicable method of reading Florbetaben PET images in potential “future use” populations of patients. The images were chosen according to a pre-specified protocol from various earlier studies of Florbetaben and included patients with mild to moderate AD, frontotemporal lobe degeneration (FTLD),

vascular dementia, dementia with Lewy Bodies (DLB), subjects with MCI as well as young healthy volunteers (< 40 years) and older cognitively normal volunteers (> 55 years).

The study involved five readers who were trained using electronic media/web-based training tool which would be offered eventually to readers in practice. The primary efficacy endpoint of the study was an inter-reader subject-level agreement of the visual assessment results using kappa values across all 5 blinded readers. The pre-specified success criterion was kappa > 0.6. The important secondary endpoints were sensitivity and specificity in the cohort consisting of 54 patients with available histopathology results and including 10 healthy volunteers with the presumed to be negative truth standard (N=54+10=64). In order for the trial to be successful, the same three out of five readers had to achieve sensitivity greater than 60% (by lower bound of the 95% CI) and specificity greater than 70%. The SOT was a CP histopathology using CERAD terminology but inclusive of both neuritic and diffuse plaques and both BSS and IHC.

The trial succeeded on its primary efficacy endpoint with the inter-reader kappa statistic across five readers achieving the value of 0.79 (95% CI: 0.75 – 0.82). The inter-reader agreement was also found to be above the pre-specified threshold in all reader pairs, the highest being 0.87 (95% CI: 0.82 – 0.91) and the lowest being 0.68 (95% CI: 0.61 – 0.74). The kappa assessments in different patient populations were acceptable, with the inter-reader kappa of 0.82 (95% CI 0.73-0.92) across all five readers in the MCI patients being particularly reassuring.

The study did not do as well on its secondary endpoints which were designed to measure the performance characteristics of sensitivity and specificity that is to make sure that the readers while agreeing were agreeing on the right thing. The adapted Table 9 from Dr. Huang's review is presented here (YHVs stands for young healthy volunteer, pos for positive and neg for negative).

Reader	With YHVs, n=64=40 pos + 24 neg				Without YHVs, n=54 = 40 pos + 14 neg	
	Sensitivity	95% CI	Specificity	95% CI	Specificity	95% CI
1	90	(76, 97)	83	(63, 95)	71	(42,92)
2	90	(76, 97)	63	(41, 81)	64	(35, 87)
3	87.5	(73, 96)	75	(53, 90)	71	(42, 92)
4	87.5	(73, 96)	79	(58, 93)	64	(35, 87)
5	77.5	(62, 89)	92	(73, 99)	86	(57, 98)

As confirmed by Dr. Huang, all five readers succeeded on sensitivity with only one reader (the “worst” sensitivity reader) succeeding on both sensitivity and specificity. The other four readers all failed to achieve the pre-specified specificity threshold. The lower bounds of the 95% confidence interval ranged from 62% to 76% for sensitivity and from 41% to 73% for specificity. If one removes the YHVs from analyses, thus reducing the sample size of negative brains to only 14, the lower bounds for specificity drop to 35-57%.

Including YHVs in the efficacy analyses was considered unacceptable by both Dr. Huang and Dr. Ye. This reviewer tends to agree with such a determination. Whereas the inclusion of YHVs could be justified in the histopathology region-by-region concept validation analyses or in the reader agreement assessments it is not justified in the whole-brain reader performance

evaluations because a visual appreciation of an age-related normal structural anatomy in YHVs would bias the visual assessment of an amyloid image in favor of the latter being absent.

Dr. Huang also disagreed with the applicant's use of normal approximation to obtain the confidence intervals of sensitivity and specificity at subject-level noting that exact confidence intervals would be more proper in the case of the small sample sizes. Additional observation from the statistical review consisted of sub-group analyses based on race, gender and age revealing some differences but, given the limited numbers, not significant enough to reach any clinically applicable conclusions.

Overall, the Pooled Read study while succeeding on reader agreement and sensitivity has clearly failed on specificity. Even if we disregard the pre-specified lower bound threshold of 70% which could be considered arbitrary and not having particular clinical meaningfulness the specificity does not beat chance in four out of five readers unless the YHVs are also included. Of further note, these specificity values have all been obtained using a truth standard based on both neuritic and diffuse plaques counted with both BSS and IHC. As this further inflates specificity, if the applicant were to use the truth standard based strictly on CERAD (neuritic plaques by BSS only) as was done by the applicants of the other two amyloid products, the specificity would even be lower.

Having said this, one should also note that for the way this imaging drug is supposed to be used in diagnostic clinical practice, where a negative amyloid finding has a clinical meaning and a positive does not, a high false positive rate (low specificity) has a limited clinical significance. The successful demonstration of acceptable sensitivity levels (low false negative rate) could potentially provide a needed assurance in this drug's clinical utility even with performance levels as they are. While the reviewers considered that, given its certain complexity, the reading methodology itself might be problematic no particular deficiencies in the reading method have been identified. Poor specificity with wide confidence intervals appears most likely related to the small sample size of subjects with negative amyloid histopathology.

The main problem with the efficacy data submitted with the application is that the data are insufficient for providing substantial evidence of the drug's effectiveness. Only the first part of the Histopathology study was successful in that it has provided adequate data for concept validation. The second part of the study using the practice applicable reading method and in-person training, which would have been acceptable if used in one of the two confirmatory efficacy trials, employed an inappropriate on-site SOT and consisted of analyses considered to be only exploratory. This leaves only one efficacy trial, the Pooled Read study, providing efficacy data based on practice applicable reading method, here with web-trained readers, but resulting in poor specificity while using a central but still inappropriate SOT.

8. Safety

As cited by Dr. Ye in her clinical review, approximately 900 subjects have received F18 Florbetaben. There were no deaths or serious adverse reactions caused by the drug. Quoting from the review, the most common adverse reactions included injection site reactions (pain,

hematoma, erythema, irritation, etc), followed by headache. Overall safety results show that F18 Florbetaben at the proposed dose of 300 MBq per injection is safe and well tolerated.

9. Advisory Committee Meeting

No advisory committee meetings are being planned.

10. Pediatrics

Given the proposed use of this drug in patients with possible Alzheimer's disease the applicant has requested a waiver under PREA. Pediatric Research Committee (PeRC) has discussed the application and agreed with granting a full pediatric waiver.

11. Other Relevant Regulatory Issues

In relation to the GCP inspections of sponsor/CRO, histopathology laboratory and selected clinical sites no significant deficiencies were noted. A minor protocol deviation at a clinical site resulted in a single-item Form FDA 483.

There are no other relevant regulatory issues at this time.

12. Labeling

In view of the efficacy data deficiencies labeling discussions have not taken place. Label and Packaging review has been completed.

13. Recommendations/Risk Benefit Assessment

At this time based on data submitted to this NDA to date, this reviewer recommends issuing a Complete Response because these data are currently insufficient for assessing the effectiveness of Florbetaben as an amyloid imaging agent. Whereas benefit, if demonstrated, would easily outweigh this drug's risk, which is quite minimal, the fact that no benefit has yet been clearly demonstrated makes for an unfavorable benefit to risk assessment.

The review team most recently has communicated the efficacy related concerns to the applicant before and during the Late Cycle Meeting. As a result the applicant has conducted additional analyses. In particular, presenting here the results for one of the readers, using the in-person training and the SOT of neuritic plaques counted by both BSS + IHC, for the histopathology cohort of "54+10=64", sensitivity was 97% as a point estimate with [92%] as a lower bound of the 95% CI, and specificity was 93% [83%]. While the sensitivity numbers have virtually remained unchanged from analysis to analysis, specificity declined to 79% [63%] with the web-based training, as expected. In further analyses, using BSS only to count neuritic plaques (preferred by us "strict" CERAD) and in-person trained imaging readers, specificity was 84% [71%]. With web-based training, specificity dropped to 71% [55%].

The applicant also conducted analyses on the now expanded histopathology cohort of 82 autopsy patients (previous 54 + another 28) and the same 10 YHVs (N=82+10=92), with images having been read by the three in-person trained readers using the already established practice applicable reading methodology. With the SOT based on counting neuritic plaques by

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Alexander Gorovets, MD 102813

BSS + IHC, sensitivity again was essentially unchanged and specificity was now 92% [82% lower bound]. Using “strict” CERAD of BSS only, specificity was 83% [71%].

Based on these post hoc analyses the applicant has proposed and is apparently conducting a new read of images from this expanded cohort using five blinded readers with web-based training and the CERAD based SOT. The pre-specified success criteria are > 60% for sensitivity and > 50% for specificity which to this reviewer appear to be acceptable. The review team has communicated to the applicant that the same three out of five readers have to be successful on both sensitivity and specificity, that the primary analysis should include only 82 patients with histopathology and that the SOT should be consistently CERAD defined. The review team recognizes that such an approach might lead to a major amendment and an extension of the review clock.

It has also come to our attention that the applicant has submitted a marketing application for Florbetaben in Europe and that the EMA review appears to be favorable.

As for Postmarketing Risk Management Activities and Postmarketing Study Commitments none are being contemplated at this time.

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/s/

ALEXANDER GOROVETS
10/28/2013

CLINICAL REVIEW

Application Type	NDA (NME)
Application Number(s)	204677
Priority or Standard	Standard
Submit Date(s)	12/21/2012
Received Date(s)	Original NDA 12/21/2012, Amendments 2/1/2013, 2/15/2013 2/28/2013, 4/15/2013, 4/22/2013
PDUFA Goal Date	12/21/2013
Reviewer Name(s)	Brenda Ye, M.D.
Review Completion Date	08/23/2013
Established Name	F-18 Florbetaben
(Proposed) Trade Name	Neuraceq
Therapeutic Class	PET diagnostic agent
Applicant	Piramal Life Sciences
Formulation(s)	Intravenous Injection
Dosing Regimen	
Indication(s)	Florbetaben is indicated for the detection of β -amyloid in the brain, thereby assisting in the differential diagnosis in adult patients who are being evaluated for Alzheimer's disease and other causes of cognitive decline

Intended Population(s) Adult patients who are being evaluated for Alzheimer's disease and other causes of cognitive decline

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Overall there is lack of substantial evidence of effectiveness (particular specificity) from clinical data submitted in the NDA. The reviewer recommends Complete Response on the application.

The reviewer recommends that the applicant examine the differences between in-person training and regional brain PET reading methodology used in Study 14595 and the web-based training and global brain PET reading methodology used in Study 16034 and refine the global brain PET reading methodology and the web-based training.

Once the Florbetaben PET reading methodology and web-based training have been refined, the reviewer recommends another clinical study that utilizes the refined PET reading methodology and web-based training on brains with available autopsy results. The goal of the new clinical study would be to demonstrate evidence of effectiveness (sensitivity and specificity) of florbetaben based on histopathology as the standard of truth.

1.2 Risk Benefit Assessment

The product is a diagnostic radiopharmaceutical that does not offer direct therapeutic benefits. Since it is known that brain amyloid deposition occurs with normal aging, a positive florbetaben PET may not offer clinical benefits, but a negative florbetaben PET indicates the absence of brain β -amyloid deposition, which is inconsistent with Alzheimer's Disease.

There are two phase 3 studies submitted with the application. The first study, Study 14595 ('Histopathology Study') assessed sensitivity and specificity on a brain regional level. Although the study reached pre-specified thresholds for sensitivity and specificity, the study was not conducted in a setting representative of clinical practice (see section on Efficacy Summary for further detail)

The second study, Study 16034 is a pooled read study that assessed reader agreement and sensitivity and specificity of the product using web-based reader training that would be implemented in clinical practice. Although the study reached pre-specified threshold for inter-reader agreement as evaluated by kappa statistic, the study failed the other pre-specified hypothesis testing which is a combined hypothesis on the sensitivity and specificity of florbetaben PET based on histopathology. The combined hypotheses would be rejected if the lower limits of the 95% confidence intervals for sensitivity and specificity are higher than the thresholds of 0.6 and 0.7 respectively for at least 3 out of the 5 blinded readers. However, 4 out of 5 readers failed to reach the pre-specified threshold for specificity. Therefore the study failed to reject the combined null hypotheses and the study is a failed study.

Study 16034 indicates that the central readers agreed with each other, but they agreed on the wrong thing, particular with regard to specificity. Since brain amyloid deposition occurs with normal aging, specificity of the product is arguably more important than sensitivity, and the study failed with regard to specificity.

Overall, the lack of robust performance characteristics along with limited clinical benefits offered by the product does not lead to a favorable benefit-risk assessment.

1.3 Recommendations for Postmarket Risk Management Activities

None

1.4 Recommendations for Postmarket Studies/Clinical Trials

None

2 Introduction and Regulatory Background

2.1 Product Information

Definite diagnosis of Alzheimer's Disease (AD) and other dementia requires post-mortem histopathological examination of the brain. The neuropathological hallmarks of AD are: the presence of extracellular deposits of β -amyloid peptides, intra-neuronal neurofibrillary tangles, and the predominance of neocortical neuronal degeneration.

Florbetaben is an [^{18}F]-labeled polyethylene glycol stilbene derivative, which *in vitro* shows a high affinity and specificity for β -amyloid plaques.

Typical appearance of florbetaben PET images

In healthy volunteers cortical areas appeared of lower intensity when compared to the subcortical white matter areas. In abnormal images, cortical areas appeared with similar or higher intensity than the subcortical white matter areas. Figure 1 contrasts axial PET images from a healthy volunteer (top) and an AD patient (bottom) at three different sections of the brain (left - at the level of the cerebellum; middle – at the level of the ventricles; right – at a level superior to the ventricles).

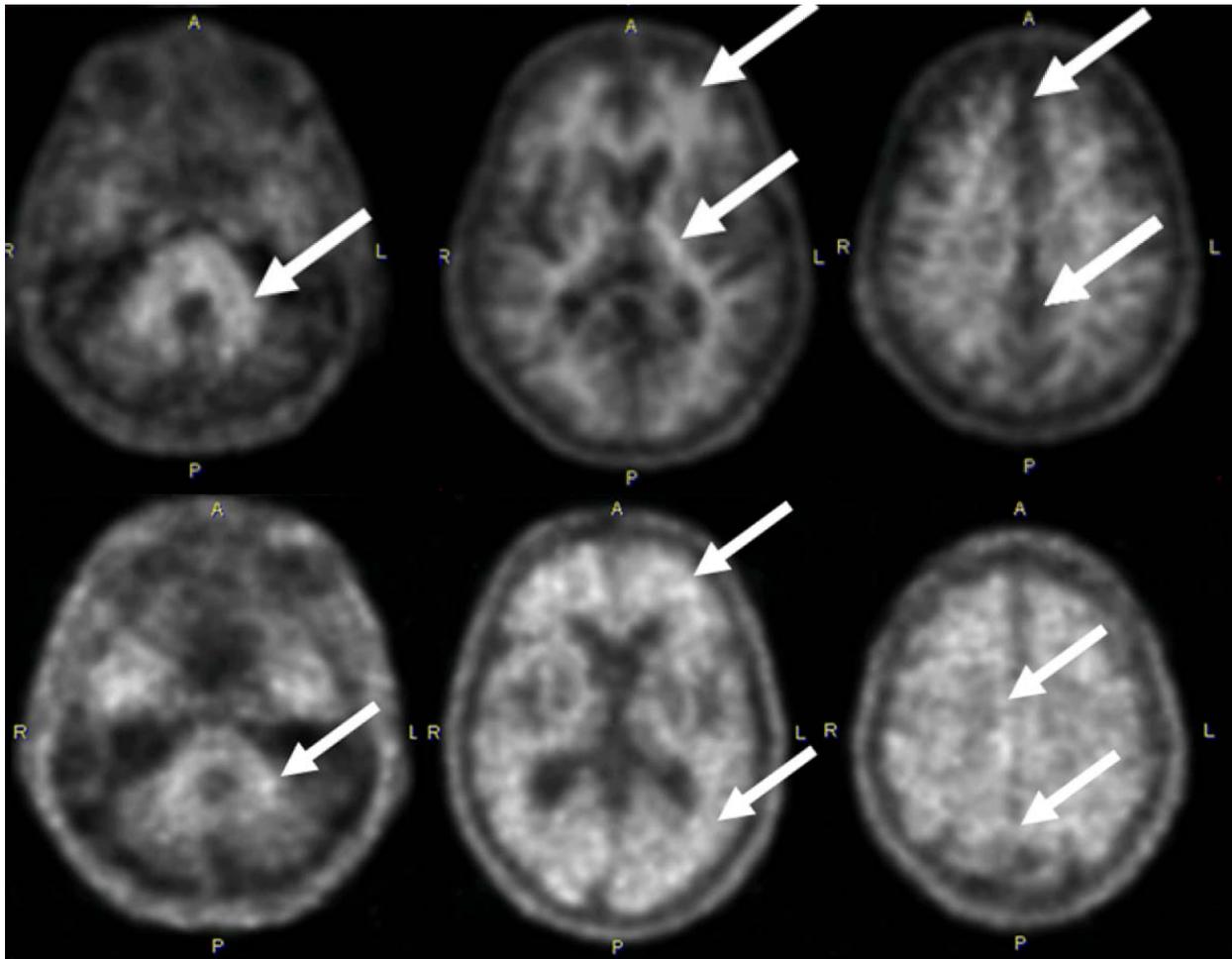


Figure 1: Florbetaben PET images from a healthy volunteer (top) and an AD subject (bottom)

The top 3 panels are from a negative (normal) PET in a healthy volunteer, the bottom 3 panels are from a positive (abnormal) PET in an AD patient. At the level of the cerebellum (left panels), note the cerebellum and cerebellar white matter (arrows). At the level of the ventricles (middle panels), contrast the white matter skeleton in the temporal region and the “spiky” appearance of the white matter in the frontal lobe in negative PET (arrows, upper middle panel), and the rounded “plumped” appearance of the frontal lobe and the disappearance of the “mountainous skeleton” in the temporal lobes (arrows, lower middle panel) in a positive PET. In the AD patient, both lobes demonstrate a uniform signal intensity equal to that seen in the “target” white matter. At the level above the ventricles (right panels), in a normal PET the mid-line is clearly visible and the posterior cingulate region imposes as a “photopenic hole” (arrows, top right panel). Contrast that with the barely noticeable mid-line and the disappearance of the “photopenic hole” in the region of the posterior cingulate in a positive PET (arrows, right lower panel).

Abnormal uptake of florbetaben can also be seen in other disorders as illustrated in the following figure.

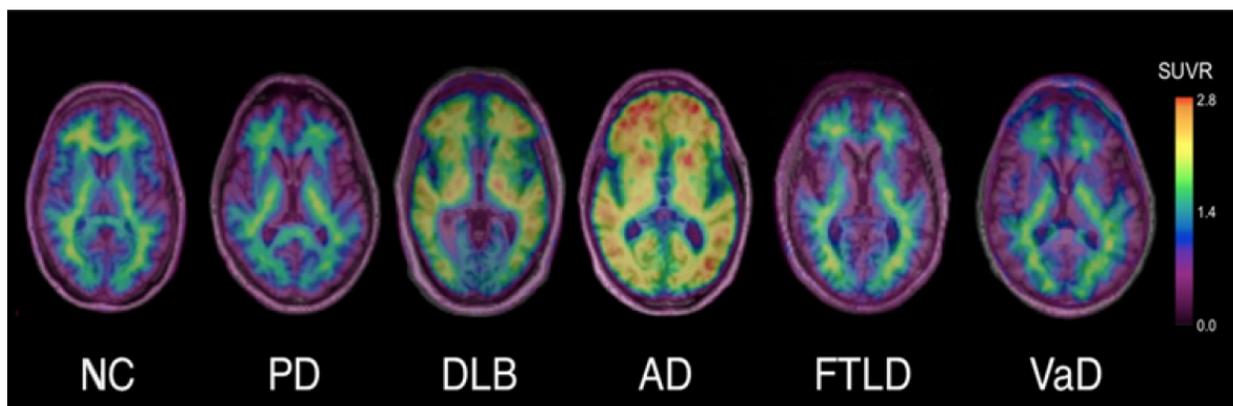


Figure 2: Examples of florbetaben PET transaxial images overlaid on co-registered MRI, rainbow scale (Study A42404)

NC = normal controls; PD = Parkinson’s disease; DLB = Diffuse Lewy body dementia; FTLD = frontotemporal lobe dementia; SUVR = standardized uptake value ratio; VaD = vascular dementia; PET = positron emission tomography; MRI magnetic resonance imaging.

Note: Images scan time window from 90 to 110 minutes post-injection. All images are scaled to the same SUVR maximum

2.2 Summary of Presubmission Regulatory Activity Related to Submission

Florbetaben was developed by Bayer HealthCare under IND 78,868. Piramal acquired the rights to this molecular entity from Bayer, effective May 2012. Based on a Piramal company statement, “core members of Bayer’s research and development team working on the portfolio will be joining Piramal Imaging, which will carry forward the development of florbetaben and take it through regulatory approval processes worldwide”..

Significant FDA/Sponsor meeting discussion points and outcomes regarding the florbetaben clinical development plan, specific corresponding communications, and related FDA Meeting highlights are listed below:

- 12/19/2007 Pre-IND teleconference - Discussion focused on the following:
 - Early phase of clinical development (Phase 1) and start of phase 2 study
 - Preclinical safety pharmacology studies
 - Specific pharmacology/toxicology questions posed to the Agency
 - Additional CMC comments provided by the FDA
- 10/23/2008 FDA Peripheral and Central Nervous System Drugs Advisory Committee (AC) Meeting - Discussion and advice on the development program for PET tracer to detect β -amyloid in the brain
 - In regards to the indication of detecting amyloid in the brain, the Committee overwhelmingly agreed that histopathological correlation should be the Standard of Truth (SoT) in Phase 3 clinical studies

- Clinical usefulness of the test was confirmed
- 11/3/2008 Teleconference follow-up to AC meeting –
 - The FDA confirmed histopathology as a standard of truth to evaluate the performance characteristics for the detection of amyloid plaques as recommended by the Advisory Committee.
- 3/18/2009 Type C meeting –
 - Discussion on revised development program to use histopathological verification as SoT for pivotal Phase 3 histopathology study
 - Additional discussion of proposed phase 2 studies
 - Agreement that safety will be evaluated separately due to the expected high number of SAEs
 - Agreement with FDA regarding the number of subjects in the safety database to support registration
- 8/11/2010 Type C meeting – Discussion and clarification of statistical analysis plan for Phase 3 histopathology study
- 6/1/2011 Type C meeting and 6/20/2011 follow-up teleconference – Discussion of clinical development program:
 - Phase 3 objectives
 - Phase 2/3 scan procedures
 - Impact of FDA Advisory Committee meeting, held January 20, 2011 (regarding a similar PET imaging product) on the florbetaben submission strategy including the discussion about image interpretation process to be used in the clinical setting
- 12/12/2011 Type B teleconference - Discussion of the Phase 3 “Pooled Image Read” study and training program on the visual assessment of PET images

Reviewer's comments: The following comments were sent to Bayer HealthCare on 11/2/2011:
“In the June 16, 2011 FDA Comment 2b, we stated “The acceptability of this less intense reader training process would need to be assessed in a premarket study...” We note in your response to the June 16, 2011 FDA Comments 2a and 3 that you plan to develop simplified web-based training material that does not require hands on training for the read of “pooled images” as well as the “post-approval setting during the re-read of the Phase 2 Part B images and the Phase 3 read.” We would like to emphasize that the validation of your “simplified training material” using the “pooled images” should be conducted as a premarket study, and this may be your intent. We look forward to discussing the composition of cases you plan to include (among other details of your study) to validate the web-based training program. We place a heavy emphasis on such a study for efficacy verification and for labeling/clinical implementation guidance”

The following comments were sent to Bayer Healthcare on 12/6/2011:
“We understand that the proposed “Pooled Read Study” involving an evaluation of 600 images taken from across a varied patient population is designed to explore an agreement on

a reading method among highly trained and tutored readers. We do not object to such an exploration as well as to other proposed analyses based on this reading method. However, please note that we would not accept such analyses as confirmatory of your drug's efficacy because the reading methodology (including the reader training) employed in all of these analyses does not appear to be the one you are proposing for use in clinical practice. We question the clinical applicability of an in-person training program and anticipate labeling implications if there is in person training of readers associated with the use of your drug.

We appreciate that you are also proposing a study to “validate” the yet to be developed “computer- (Web) based training program”. We recommend that, following the development of both a reading methodology applicable to clinical practice and a “computer- (Web) based training program”, you conduct a confirmatory clinical trial that would demonstrate an agreement among readers, who were trained using the program. Such a study would also have to demonstrate clinically meaningful performance characteristics (sensitivity/specificity within the subset of patients who have an amyloid truth standard based on pathology). We expect that the design of such a study would involve hypothesis testing for either reader agreement endpoints or performance characteristics endpoints, or both.”

- 4/20/2012 FDA Advice/Information Request –
 - FDA provided comments and recommendations to the Phase 3 “Pooled Image Read” protocol (Study No. 16034) submitted on March 9, 2012 to IND 78,868 including,
 - Primary and secondary endpoints
 - Statistical analysis of the primary target variable
 - Number of readers
- 8/24/2012 Pre-NDA meeting teleconference and 8/16/2012 FDA Advice and Information Request –
 - Agreement reached regarding the contents and formats of the NDA:
 - Placement of two pivotal studies would be in Module 5.3.5.1
 - Placement of ISE and ISS in Module 2
 - SAS datasets will be submitted for Phases 1, 2, 3 studies as well as the datasets necessary to verify analyses described within the ISS/ISE
 - FDA invited discussion on the Advice/Information Request dated August 16, 2012 for Study No. 16034.
 - FDA recommended not to include young healthy volunteers in sensitivity and specificity evaluation

Reviewer's comments: FDA again advised the sponsor not to include 10 young healthy volunteers in the efficacy analyses for sensitivity and specificity based on histopathology standard of truth in both the preliminary FDA comments sent before the Pre-NDA meeting and during the meeting discussion.

It should be noted that both pivotal studies, the Histopathology Study (14595) and the Pooled Read Study (16034), include 10 young healthy volunteers whose histopathology standard of truth

are presumed to be negative. The Histopathology Study (14595) includes 10 young healthy volunteers in the primary efficacy analysis of sensitivity and specificity at the brain regional level. The Pooled Read Study (16034) again includes 10 young healthy volunteers in the secondary efficacy evaluation for sensitivity and specificity using histopathology as the standard of truth.

The inclusion of young healthy volunteers artificially inflates the number of ‘true negative’ brains. Depending on the number of young healthy volunteers added and the relatively numbers of the pathology-positive and pathology-negative brains, the calculated performance characteristics (sensitivity and specificity, particularly specificity) also change accordingly. Therefore the FDA review team repeatedly advised Bayer Healthcare during the IND phase to not include young healthy volunteers in the efficacy analysis for sensitivity and specificity based on histopathology as the standard of truth.

2.3 Other Relevant Background Information

FDA held an Advisory Committee meeting on January 20, 2011 regarding a similar PET imaging product, Amyvid. The committee voted favorably toward the approval of Amyvid, but also raised concerns regarding PET image interpretation methodology. The difficulty in interpreting Amyvid brain PET images (and brain PET images from other similar amyloid detection agents) lies in the fact that brain gray matter deposition of amyloid proteins is abnormal, while white matter deposition of amyloid may be considered normal for older adults. Therefore a reader needs to have solid skills in distinguishing brain white matter from brain gray matter on brain PET images as a prerequisite. On top of this, the reader needs further training to fine tune reading skills of Amyvid brain PET images in order to reliably distinguish normal from abnormal. The committee recommended having a reader training program developed by the manufacturer.

3 Ethics and Good Clinical Practices

3.1 Compliance with Good Clinical Practices

The ‘Histopathology Study’ (Study 14595) was conducted in compliance with Good Clinical Practice (GCP). For the Pooled Read Study (Study 16034), the involvement of an Independent Ethics Committee(s) (IECs)/Institutional Review Board(s) (IRBs) was not appropriate in this non-interventional study which did not involve clinical investigators, or inclusion of subjects, and thus no informed consent or any other necessary subject involvement was necessary.

3.2 Financial Disclosures

The previous owner/sponsor of the product, Bayer Healthcare, signed financial certification which states that it did not enter into any financial arrangements with the investigators whereby the value of such compensation to the investigator could be affected by the outcome of the study. The certification is accompanied by tables listing every investigator involved in each submitted study, detailing whether the investigator has disclosable information as well as clarifying comments on the disclosable information from Bayer. The reviewer finds the financial disclosures acceptable.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Clinical Site Inspection Conducted by the Office of Scientific Investigation (OSI)

Final report of the OSI Scientific Investigation is pending at this time.

4.2 Clinical Pharmacology

The Clinical Pharmacology review team has no significant issues regarding the proposed dosing of Florbetaben. The Clinical Pharmacology reviewer recommends further exploration on the incorporation of SUVR (a quantitative efficacy endpoint) as a diagnostic aid to visual interpretation of florbetaben PET images by imaging physicians.

5 Sources of Clinical Data

The clinical development program contains data from 10 studies, including a pivotal phase 3 study (for histological confirmation) and a pooled read of mixed images, deriving from the different clinical studies.

5.1 Tables of Studies/Clinical Trials

A total of 10 clinical studies were conducted under the florbetaben clinical development program and are included in this NDA:

- Two proof-of-mechanism Clinical Phase 1 studies (Study Report A42404; Study 310863)
- Four additional Clinical Phase 1 studies (Studies 311722, 91790, 312161, 312043)
- Two supportive Clinical Phase 2 studies (Study 311741; Study 14311)
- One pivotal Phase 3 study
 - Study 14595: *“An open-label, non-randomized study to evaluate the efficacy and safety of BAY 94-9172 (ZK 6013443) positron emission tomography (PET)*

imaging for detection/exclusion of cerebral β -amyloid when compared to postmortem histopathology”

- One pivotal non-invasive Non-Interventional “Pooled Read Study”
 - Study 16034: *“A non-interventional study to assess the reliability, reproducibility and efficacy of the florbetaben β -amyloid PET scan visual assessment method as trained via a computer- (Web-) based training tool”.*

5.2 Review Strategy

The clinical review focused on the two pivotal Phase 3 clinical studies. In addition, since the FDA Advisory Committee meeting in October 2008 had concluded that histopathology would be the appropriate standard of truth for evaluation of amyloid detection agents, the clinical review focused on evaluating the performance characteristics (sensitivity and specificity) of florbetaben PET based on histopathology as the standard of truth.

5.3 Discussion of Individual Studies/Clinical Trials

5.3.1 Study 14595 – Pivotal ‘Histopathology’ Study

The safety population of the study is comprised of 216 subjects, including 137 subjects with Alzheimer’s Disease (AD), 31 subjects with other dementia, 5 subjects with Dementia with Lewy Body (DLB), 32 age-matched controls (“NDV”, i.e. non-demented volunteers), and 11 young healthy volunteers.

Postmortem specimens became available for 32 subjects, 31 of which were evaluable for efficacy (22 AD, 1 DLB, 2 other dementia, and 6 NDVs). [Later additional 24 subjects with autopsy data (total 55 subjects) became available for Pooled Read Study]

In addition to the 31 subjects with evaluable brain autopsy specimen, 10 healthy volunteers were included in efficacy analyses. The histopathology standard of truth of the 10 young healthy volunteers was presumed to be negative (no amyloid deposition).

1) Standard of Truth – Histopathology at the Brain Regional Level

Histopathology from brain autopsy specimens forms the basis of standard of truth (SOT) in Study 14595. A panel of 3 neuropathology experts forms the Pathology Consensus Panel for the central read of histopathology. Since the primary efficacy analysis is conducted at the brain regional level, the histopathology SOT from the Pathology Consensus Panel is given for each brain region, rather than the whole brain of a subject. Six brain regions are evaluated for histopathology and later for florbetaben PET visual assessment (Table 1).

Table 1: Brain regions for florbetaben PET regional visual assessment and subsequent comparison with corresponding histopathological specimen

Region number	Region name
1	Middle frontal gyrus (coronal plane)
2	Striate and parastriate areas of occipital cortex (coronal plane)
3	Hippocampus at the level of the lateral geniculate nucleus (coronal plane)
4	Anterior cingulate cortex (coronal plane)
5	Posterior cingulate cortex (coronal plane)
6	Cerebellar hemisphere directly adjacent to the cerebellar nuclei (sagittal plane)

For Region 3 and Region 5, related sub-regions were separately evaluated for histopathology, and the sub-regions were named Region 3A and Region 5A. Region 3A is parahippocampal gyrus/inferior temporal gyrus at the same level as Region 3 (level of the lateral geniculate nucleus), Region 5A precuneus at the same level as Region 5 or at the level of the posterior commissure. Region 3 and 3a as well as 5 and 5a were evaluated separately according to the study protocol “due to the distinct anatomy and different likelihood of pathology”. For final evaluation the results were collapsed in one data point for each region based on the following algorithm: in case any of the two parts (3 or 3a/5 or 5a) were assessed as “amyloid present” the whole region would be regarded as positive.

According to “Technical Manual for Pathology Related Procedures for CSP No. 14595” and “Consensus Panel Assessment Manual for SoT Evaluation” submitted as part of the Study 14595 protocol, for each brain regions, the following methods are applied:

- HE staining
- Silver stain according to Bielschowsky
- Immunohistochemistry for detection of
 - β -amyloid, MAB/clone 6E10 (former (b) (4), now (b) (4))
 - tau, MAB/clone AT8 (former (b) (4), now (b) (4))
 - α -synuclein, MAB/clone LB509 ((b) (4))

Each brain region has five slides - H&E, Bielschowsky silver stain, immunohistochemistry for β -amyloid, immunohistochemistry for tau protein, and immunohistochemistry for α -synuclein. Each autopsy subject has six brain regions, with 5 slides for each region, totaling 30 slides for each subject. The Pathology Consensus Panel evaluates each subject’s 30 slides together, usually proceeding from Region 1 to Region 6, but the panel can go back and forth as needed. For the Bielschowsky silver stain and immunohistochemistry for β -amyloid, the Consensus Panel grades *neuritic plaques* and *diffuse amyloid plaques* on the scale of none, sparse, moderate, and frequent. The Consensus Panel also grades *vascular amyloid* as none, sparse, moderate, or frequent on the immunohistochemistry for β -amyloid. For tau deposits and α -synuclein, the panel only grades as yes or no.

Therefore, there are five gradings – two for neuritic plaques (from Bielschowsky silver stain and immunohistochemistry for β -amyloid), two for diffuse plaques (from Bielschowsky silver stain and immunohistochemistry for β -amyloid), and one for vascular amyloid (from immunohistochemistry for β -amyloid). Each grading is given as none, or sparse, or moderate, or frequent.

For each brain region, the Pathology Consensus Panel takes into account all the pertinent information from the 5 stains and all the pertinent pathology parameters (two gradings for neuritic plaques, two gradings for diffuse amyloid plaques, and one grading for vascular amyloid) and give an overall binary grading for the region – yes or no for β -amyloid deposition. Gradings of none and sparse are condensed to “no” for β -amyloid deposition, and gradings of moderate and sparse are condensed to “yes” for β -amyloid. All three forms of amyloid deposition (neuritic plaques, diffuse amyloid plaques, and vascular amyloid) are treated equally, i.e. if any of the 5 gradings (neuritic plaques, diffuse amyloid plaques, and vascular amyloid) has a grading of moderate or above, the brain region is considered positive overall by the Pathology Consensus Panel.

Reviewer's comments: The Standard of Truth definition treats all three forms of amyloid deposition (neuritic plaques, diffuse amyloid plaques, and vascular amyloid) equally. The reviewer finds this approach reasonable. In discussion with the FDA Pharmacology and Toxicology reviewer and the Clinical Pharmacology reviewer, florbetaben does not appear to show preferential binding to amyloid in the neuritic plaques over the other two forms of amyloid deposition, at least the florbetaben NDA submission does not contain such preferential binding data. Even though medical community generally considers neuritic plaques more strongly associated with Alzheimer's Disease, while clinical meaningfulness of vascular amyloid remains unclear to the medical community, it should be noted that florbetaben PET as an imaging test is not expected to show difference between different forms of amyloid deposition. The reviewer therefore finds the Pathology Consensus Panel's decision to treat all three forms amyloid deposition (neuritic plaques, diffuse amyloid plaques, and vascular amyloid) equally in establishing the histopathology SOT is a reasonable approach.

The three Pathology Consensus Panel members review slides under a multi-head microscope, so that all 3 members can view the same microscopic findings together. The members first evaluate independently, and then discuss to give a consensus read on each stain and various pathology parameters (neuritic plaques, diffuse amyloid plaques, vascular amyloid). **Finally the panel gives an overall binary score of “yes” or “no” for β -amyloid deposition for a particular brain region, and this overall score of “yes” or “no” for the brain region from the Consensus Panel serves as the standard of truth for primary efficacy analysis of the study.**

As both methods, Bielschowsky silver staining and immunohistochemistry for β -amyloid have different sensitivity for the detection of β -amyloid, a discrepancy between the results of both methods may occur. Therefore, consensus panel members are asked to answer the question “Is β -amyloid present in this ROI - yes or no?” separately at the end of the evaluation. In answering this question they shall take into account the different methods, the different forms of amyloid

deposits and the different frequencies and their relative impact. **This answer is considered to be the overall consensus assessment of the SoT.**

2) Florbetaben PET Visual Interpretation

All patients had brain MRI, which were mandatory per protocol, and brain MRI images were forwarded to imaging core lab for central PET visual assessment. Before the blinded read, the PET and MRI image sets were co-registered by experts at the core lab using an automatic registration algorithm and the regional ROIs applied directly to the images. There was one image data set per ROI. Thus, there were 6 data sets per post mortem specimen and 6 for each of the young HVs.

During the subsequent blinded analysis for primary efficacy analysis, for each data set to be assessed, the blinded readers were presented both the MRI and the PET image data and could toggle back and forth between the two modalities. The 6 brain regions to be assessed are listed in Table 1. The 6 brain regions were chosen to include 5 regions with known high to moderate and 1 region (region 6) with known low probability of demonstrating significant gray matter (cortical) β -amyloid deposition in an AD patient as verified in the literature. Both the regional and the subject level visual assessment were performed by the same 3 independent blinded readers.

Reviewer's comments: Note that the blinded readers were not presented with whole brain co-registered PET-MR images. Rather, the imaging core lab 'cut out' specific brain regions of an MRI that matches the brain region and orientation of the regional brain pathology specimen. Then florbetaben PET images were 'cut out' to match the cropped MRI image. The cropped MRI image and the cropped florbetaben PET image of a specific brain region that match to a specific brain autopsy region were then co-registered, and the co-registered image would be presented to blinded readers.

It should be noted that such cropping of post-imaging procedure would not be practical for clinical practice. First of all, most clinical centers in the U.S. do not have MR-PET scanners to allow for co-registration of MRI and PET images. In current clinical practice, PET images are co-registered with non-contrast CT images (used to attenuation correction) rather than brain MRI. Furthermore, for those centers that do have MR-PET scanners, individual slices of whole brain PET and MRI images are co-registered, so imaging physicians read images of the whole brain rather than special 'cut-out' brain regions on display. Reading the whole brain images could arguably be more challenging, as readers need to pay attention to all the areas of the brain rather than just a few selected regions of the brain. This study is therefore not conducted in a setting that resembles clinical practice.

For each subject for whom a brain specimen has become available, six separate PET/MRI image data sets will be evaluated – but randomized amongst all regional level scans, hence avoiding bias associated with presenting all regional scans for a single subject together.

3) Primary Efficacy Analysis

Co-primary efficacy variables are Sensitivity and Specificity of PET Visual Assessment [Majority Read](#) at the [Brain Regional Level](#) Using [Binary PET Reading Methodology](#) Based on Histopathology as the Standard of Truth.

Primary efficacy analysis is conducted at the *brain regional level* based on the six brain regions listed in Table 1. Based on the PET images, a brain region (of a particular subject) was classified as “normal” or “abnormal” depending on the absence or presence of cortical tracer uptake in the respective brain region. “Normal” means absence of β -amyloid and “abnormal” presence of β -amyloid. (“Normal” and “Abnormal” were further defined for clarification via Amendment 5 of the study protocol for subject level assessment)

The co-primary efficacy variables of the study were evaluated using the *majority results* of the 3 independent blinded readers. This majority read value for the 3 readers is determined based on the match to the standard of truth, which is histopathology. If at least 2 readers match the standard of truth, the majority reader response will be considered a match. This majority read response is not a consensus read. The analysis based on the majority read is considered the relevant analysis of the co-primary efficacy variables. The 95% confidence interval is calculated for the majority read and for each blinded reader separately.

Majority read from 3 blinded readers was used for primary efficacy analysis. Majority read is defined as follows:

three independent assessments	→	majority read result
(normal, normal, normal)	→	normal
(normal, normal, abnormal)	→	normal
(normal, abnormal, abnormal)	→	abnormal
(abnormal, abnormal, abnormal)	→	abnormal
three independent assessments	→	majority read result
(normal, normal, unint/mis)	→	normal
(abnormal, abnormal, unint/mis)	→	abnormal
(normal, abnormal, unint/mis)	→	mismatch to SoT
three independent assessments	→	majority read result
(normal, unint/mis, unint/mis)	→	normal
(abnormal, unint/mis, unint/mis)	→	abnormal
three independent assessments	→	majority read result
(unint/mis, unint/mis, unint/mis)	→	mismatch to SoT

The following hypotheses were formulated:

$$H_{0,\text{sens}}: \text{sensitivity} \leq 0.6 \text{ vs. } H_{1,\text{sens}}: \text{sensitivity} > 0.6$$

$H_{0,spec}$: specificity ≤ 0.8 vs. $H_{1,spec}$: specificity > 0.8

$H_{0,sens}$ would be rejected if the lower bound of the two-sided 95% confidence is larger than 0.6.

$H_{0,spec}$ would be rejected if the lower bound of the two-sided 95% confidence is larger than 0.8.

4) Secondary Efficacy Analysis - Composite “Whole Brain” Regional Assessment

This is an exploratory secondary efficacy analysis based on the brain regional level assessment. The analysis evaluates the sensitivity and specificity of the composite “whole brain” regional PET visual assessment in detecting/excluding cerebral β -amyloid plaques based on the "whole brain" histopathological verification of the presence/absence of β -amyloid deposition as the standard of reference (SoR)

The composite “whole brain” regional assessment was derived from the assessment of the 6 brain regions in the following manner:

- The highest score across the 6 pre-defined brain regions in the PET scan determined the composite “whole brain” regional result. That is, if one region was scored "yes" for tracer uptake (i.e., β -amyloid deposition), this was the "composite score" for the entire brain. The scan was negative for tracer uptake (e.g., negative for β -amyloid) only if none of the 6 regions was scored "yes".
- the 'highest' score from the CP central pathology read of the 6 pre-defined brain regions determined the composite “whole brain” regional histology result for this subject: If in any of the 6 regions β -amyloid plaques were evaluated as being 'present' at a clinico-pathologically relevant level; (either moderate or frequent), the subject was determined as having clinico-pathologically relevant β -amyloid deposition in the brain. If in none of the regions the histopathological findings were assessed as being more than 'no' or 'sparse' β -amyloid plaques, the subject was scored as 'no β -amyloid present'.

Reviewer's comments: This is essentially a brain regional analysis, and the limitations of Study 14595 discussed in Section 6.3.1 of the review all apply – majority read of 3 PET readers, in person training, binary PET visual assessment scale which is not being proposed for future clinical practice, co-registration of PET-MRI which may not be practical for many centers in the U.S, six brain regions that are different from the 4 brain regions proposed as the florbetaben PET reading methodology for future clinical practice.

Overall the PET visual assessment was not conducted in settings representative of future clinical practice setting. If we compare this analysis with the subject level sensitivity and specificity analysis using histopathology as the standard of truth in Study 16034, one can see that the methodology for the establishment of the histopathology SOT (SoR) largely retained albeit there are differences in the impact of different stains and different forms of amyloid deposition as discussed in Section 5.3.2 of the review. However the PET visual assessment procedures/methodology used in this analysis (and the primary efficacy analysis) of Study 14595 was later abandoned and a new 4-region brain florbetaben PET visual assessment methodology more suitable for clinical practice was developed and introduced and tested in the next

exploratory secondary efficacy analysis of the study (further discussed in the next section of the review).

5) Secondary Efficacy Analysis - Subject Level Assessment of Sensitivity and Specificity of Florbetaben PET Visual Assessment Majority Read Compared to Onsite Neuropathological Diagnosis as the Standard of Reference

This is another exploratory secondary efficacy analysis of Study 14595. New in this analysis is the newly developed subject level florbetaben PET visual assessment methodology. Compared to the PET regional visual assessment methodology used in the primary efficacy analysis of the study, this newly developed PET reading methodology evaluates 4 brain regions instead of 6, and the 4 brain regions are largely different from the previous 6 regions as shown in Table 7 and discussed in Section 6.2.1 of the review. In addition to the difference in the brain regions evaluated for PET visual assessment, grading of F-18 florbetaben tracer uptake changed from a binary scale used in primary efficacy analysis of the study to a 3-level grading scale as shown in the following case-report form for the central blinded readers. The change in florbetaben PET visual assessment methodology reflects a major revision of the Study 14595 protocol albeit this change is only implemented in this exploratory secondary efficacy analysis of the study. These changes were introduced to the protocol via Amendment 5 of the protocol.

Table 2: Documentation of regional cortical tracer uptake scores – assessed by the independent blinded readers

Gray matter structures (cortical areas)	Enter RCTU (1, 2, 3) In case of side differences, document highest score	Region Interpretable (Yes/No)	Comments (eg, reason for non-interpretability)
1 Frontal cortex			
2 Posterior cingulate ^a			
3 Lateral temporal cortex			
4 Parietal cortex			

a The region “posterior cingulate” refers to two anatomical regions posterior cingulate and precuneus.

Reviewer's comments: this newly developed florbetaben PET visual assessment methodology is more applicable for clinical practice than the PET visual assessment procedures/methodology used in primary efficacy analysis of the study. However, these 4 brain regions may not be suitable for histopathology analysis, and that may be why the sponsor resorted to local onsite neurohistopathological diagnosis as the standard of reference in this exploratory secondary efficacy analysis.

The protocol for Study 14595 does not describe how the onsite histopathology SoR was determined in detail, and there is no dedicated histopathology charter as that developed for the central Pathology Consensus Panel. “A final onsite neuropathological diagnosis was established according to international guidelines” and “Sites were responsible for establishing the detailed neuropathology diagnosis”.

To establish this diagnosis, the onsite pathologist uses the following international guidelines:

- AD had to be diagnosed according to the CERAD criteria and the Braak & Braak classification for tau-deposits.
- DLB had to be diagnosed according to the Consensus guidelines for the clinical and pathologic diagnosis of dementia with Lewy bodies (DLB)
- Parkinson's disease had to be diagnosed according to the Diagnostic criteria for Parkinson Disease
- Frontal temporal dementia had to be diagnosed according to the Consensus of the Consortium for Frontotemporal Lobar Degeneration

Reviewer's comments: Based on above guidelines and the "Local pathology data" case report form copied on the next pages (Table 3), it appears that the goal of the onsite histopathology evaluation is to establish a neuropathology diagnosis rather than to determine whether amyloid deposition is present or not. This is different from the Consensus Panel SOT, which determines whether amyloid deposition is present.

*No protocol was submitted for the methodology used for establishing SOR (presence or absence of amyloid deposition) based on the various neuropathology diagnoses. For example, it is not clear at all how various stages of the Braak and Braak criteria for neurofibrillary tangle (NFT) is 'collapsed' to subject level SOR of whether amyloid is present or absent in the subject. It is entirely unclear how the local pathologists determined the standard of reference for this analysis. **The reviewer does not regard this analysis capable of providing any confirmatory clinical data for demonstrating the effectiveness of florbetaben PET in detecting brain amyloid deposition.***

Table 3: Local Pathology Case Report Form (Study 14595)

Local pathology data		203
Study no. 1 4 5 9 5	Subject no. _____	
● Local diagnosis		
Neuropathological diagnosis	
NIA-Reagan criteria for AD	82 <input type="checkbox"/> no evidence 83 <input type="checkbox"/> low likelihood 84 <input type="checkbox"/> intermediate likelihood 85 <input type="checkbox"/> high likelihood	
CERAD criteria for AD (Mirra et al. 1991)	103 <input type="checkbox"/> 0 (no evidence of AD) 86 <input type="checkbox"/> A (histological findings are uncertain evidence of AD) 87 <input type="checkbox"/> B (histological findings suggest the diagnosis of AD) 88 <input type="checkbox"/> C (histological findings indicate the diagnosis of AD)	
Braak and Braak criteria for NFT (1991)	89 <input type="checkbox"/> Stage I 90 <input type="checkbox"/> Stage II 91 <input type="checkbox"/> Stage III 92 <input type="checkbox"/> Stage IV 93 <input type="checkbox"/> Stage V 94 <input type="checkbox"/> Stage VI	
Presence of any other tau pathology (e.g. CBD, CSP)	1 <input type="checkbox"/> no 2 <input type="checkbox"/> yes	
if yes, please specify	
McKeith criteria for DLB (2005)	82 <input type="checkbox"/> no evidence 95 <input type="checkbox"/> brainstem-predominant type 96 <input type="checkbox"/> limbic type 97 <input type="checkbox"/> diffuse neocortical type	
Evidence for MSA	1 <input type="checkbox"/> no 2 <input type="checkbox"/> yes	
if yes, please specify	
Gelb criteria for PD (1999)		
Clinical diagnosis of PD provided	1 <input type="checkbox"/> no 2 <input type="checkbox"/> yes	
if yes, are the Gelb criteria (1999) for PD diagnosis fulfilled	1 <input type="checkbox"/> no 2 <input type="checkbox"/> yes	

Local pathology data		204
Study no. 1 4 5 9 5	Subject no. _____	
● Local diagnosis (continued)		
FTD according to Cairns (2007)		
Is there any evidence for frontal or temporal lobe degeneration	1 <input type="checkbox"/> no 2 <input type="checkbox"/> yes	
If yes, please specify	_____	
kind of evidence	2 <input type="checkbox"/> macroscopic 2 <input type="checkbox"/> histological	
criteria according to Cairns	
● Other relevant pathology		
Evidence for any other neurodegenerative disorder	1 <input type="checkbox"/> no 2 <input type="checkbox"/> yes	
if yes, please specify	
Any other evidence for neurological diseases?	1 <input type="checkbox"/> no 2 <input type="checkbox"/> yes	
if yes, please specify	
Evidence for vascular disorders?	1 <input type="checkbox"/> no 2 <input type="checkbox"/> yes, please specify below	
vascular pathology predominantly present in -please select only one-	100 <input type="checkbox"/> small vessels 101 <input type="checkbox"/> middle vessels 102 <input type="checkbox"/> large vessels	
evidence for stroke?	1 <input type="checkbox"/> no 2 <input type="checkbox"/> yes	
if yes, please specify	
any other evidence	1 <input type="checkbox"/> no 2 <input type="checkbox"/> yes	
if yes, please specify	
Evidence for mass lesions (e.g. evidence for tumor, metastasis, skull base pathology incl. meningioma, infarct, hemorrhage, abscess)	1 <input type="checkbox"/> no 2 <input type="checkbox"/> yes	
if yes, please specify type and location	

The use of local histopathology results as standard of reference has a number of other limitations:

a) The Central Histopathology Consensus Panel is comprised of a panel of 3 neuropathologists, with the Panel's consensus read as the SOT. The local histopathology evaluation appears to be performed by a single pathologist as the local pathology case report form for each subject does not contain spaces for a panel of 3 pathologists.

b) The central pathology Consensus Panel is comprised of 3 renowned neuropathologists. The single onsite pathologist is of unclear qualification, and it is unclear whether this pathologist is an expert in neuropathology

c) Since there is no clear local histopathology evaluation protocol submitted in the NDA, the reviewer suspects that such a standard protocol/charter for local histopathology evaluation was not developed for the study. Therefore it is unclear if various local sites followed the same procedures and used same criteria in their onsite histopathology evaluation

d) The Consensus Panel SOT manual specifies that the 3 panel members will first undergo training together before evaluating trial subjects. It is not practical for the various onsite pathologists to be trained together first before evaluating trial subjects' autopsy specimens. This further introduces site-to-site variations.

Overall onsite histopathology is not acceptable as a standard of truth in providing confirmatory data to demonstrate the effectiveness of florbetaben.

5.3.2 Study 16034 – Pivotal ‘Pooled Read’ Study

Study 16034 is entitled “A non-interventional study to assess the reliability, reproducibility and efficacy of the florbetaben β -amyloid PET scan visual assessment method as trained via a computer-(Web)-based training tool”. The main purpose of this “pooled” read Study (Study 16034) was to assess the reliability, reproducibility and efficacy of the florbetaben β -amyloid PET scan visual assessment method in a cohort that was as close to the “future use” population as possible, and was trained via a computer (web)-based training tool.

The primary efficacy endpoint of the study is:

- Inter-reader agreement of the visual assessment results assessed on the subject level using kappa values across all 5 blinded readers. This assesses the reproducibility of the visual assessment of PET scans from a patient population that closely represents the “future use” population comprised of 461 florbetaben PET scans pooled from various florbetaben clinical studies.

The kappa value κ_{inter} across the 5 blinded readers for the [binary assessment normal / abnormal](#) on the subject level will be calculated over all images read. The confidence interval will be calculated based on an asymptotic variance estimate. The hypothesis to be tested is

$$H_{0, \text{inter}}: \kappa_{\text{inter}} \leq 0.6 \text{ vs. } H_{1, \text{inter}}: \kappa_{\text{inter}} > 0.6$$

The hypothesis will be rejected, when the lower bound of the confidence interval for κ_{inter} is larger than 0.6.

Secondary efficacy endpoints include:

- To assess the intra-reader variability of the visual assessment results based on a 10% re-read of the above image data set.
- To assess the reliability of the visual assessment of florbetaben PET scans via determination of sensitivity and specificity to detect β - amyloid on a subject level with histopathology as standard of truth (SoT) using the images from the 55 autopsy cases enriched with the images of 10 healthy volunteers (HVs) from the pivotal Phase 3 study (Study 14595).
- To assess the reliability of the visual assessment of florbetaben PET scans via determination of sensitivity and specificity of florbetaben PET scans with the Consensus Panel (CP) clinical diagnosis as Standard of Reference (SoR) using the images from 237 subjects from Part B of the Global Phase 2 study (Study 311741).

The sensitivity and specificity will be assessed for each of the 5 readers in the 55 post mortem subjects from Study 14595 with available histopathology as SoT, enriched by the results from 10 HVs without autopsy for whom amyloid pathology in the brain is assumed negative by default. Corresponding 95% confidence intervals will be calculated. The following combined hypotheses will be tested:

$$H_{0, \text{sens}}: \text{sensitivity} \leq 0.6 \text{ vs. } H_{1, \text{sens}}: \text{sensitivity} > 0.6$$

$$H_{0, \text{spec}}: \text{specificity} \leq 0.7 \text{ vs. } H_{1, \text{spec}}: \text{specificity} > 0.7$$

The combined hypotheses will be rejected if the lower limits of the 95% confidence intervals for sensitivity and specificity are higher than the thresholds of 0.6 and 0.7 respectively for at least 3 out of the 5 blinded readers. A descriptive sub-analysis will be performed excluding the 10 HVs.

Definition of the Histopathology Standard of Truth in Study 16034

1) Definition of the regional Standard of Truth:

A brain region will be considered to have ‘relevant β -amyloid present’, if the CP of neuropathology experts judged it as having a final rating of “moderate” or higher for neuritic or diffuse β -amyloid plaques based on the Bielschowsky silver staining.

2) Definition of the subject based Standard of Truth for this analysis:

The regional SOT obtained in these 6 small brain regions will be collapsed into a subject based SOT as described below.

The 'highest' score from the CP histopathological evaluation of the 6 pre-defined brain regions will determine the composite “whole brain” regional histology result for this subject: If in any of the 6 regions β -amyloid plaques were evaluated as being 'present' at a clinico-pathologically

relevant level (either moderate or frequent), the subject is determined as having clinico-pathologically relevant β -amyloid deposition in the brain. If in none of the regions the histopathological findings were assessed as being more than 'no' or 'sparse' β -amyloid plaques, the subject is scored as 'no β -amyloid present'. It may occur that the CP histopathological evaluation of some regions was/is not possible. A subject will be included in this analysis if a CP diagnosis is available for at least 5 regions.

Reviewer's comments: Note the definition of the regional standard of truth in this Pooled Read Study (16034) is different from that in the Histopathology Study (14595), for the same brain regions. The Pathology Consensus Panel in Study 14595 considers 5 individual gradings for each brain region – neuritic plaques by the Bielschowsky silver staining, neuritic plaques by immunohistochemistry for β -amyloid, diffuse amyloid plaques by the Bielschowsky silver staining, diffuse amyloid plaques by immunohistochemistry for β -amyloid, and vascular amyloid. However, the definition for the same brain regional histopathology standard of truth in the Pooled Read Study (16034) considers only 2 gradings – neuritic plaques by the Bielschowsky silver staining and diffuse amyloid plaques by the Bielschowsky silver staining, leaving out the other 3 gradings considered by the Pathology Consensus Panel. Furthermore, the 'revised' brain regional standard of truth rejects the Pathology Consensus Panel's final overall binary grading (presence or absence of amyloid deposition) for a particular brain region, which is used as the standard of truth in Study 14595. The reviewer considers the approach taken by the Pathology Consensus Panel more appropriate, as we do not have evidence for preferential binding of florbetaben to one form of amyloid deposition over another form, i.e. florbetaben PET would not have the capability to distinguish amongst different forms of amyloid deposition – neuritic plaques, diffuse amyloid plaques, and vascular amyloid. Florbetaben PET simply detects the presence of amyloid regardless of its forms.

Because the change in the definition of the brain regional standard of truth between Study 14595 and Study 16034, the same brain regions from the same 31 autopsy brains from Study 14595 now have a different standard of truth in the Pooled Read Study (16034). Subject based standard of truth in Study 16034 derives from this 'revised' brain regional histopathology SOT.

The reviewer compared the brain regional SOT from Study 14595 (and s the composite 'whole brain' SOR collapsed from the 6 regional SOT) and subject level SOT used for Study 16034 for the same 31 autopsy brains from Study 14595. The differences are small. Out of the 31 autopsy brains that are evaluable, two subjects' (Subject ID: 200010006 and 200040004) SOT changed from composite 'whole brain' positive for amyloid in Study 14595 to subject level negative for amyloid in Study 16034, representing ~6% of the 31 subjects.

A total of 507 images, which include 461 subject images plus 46 (10%) repeat images for a re-read, were selected from the images provided in four Phase 1 studies, the Phase 2 Study 311741 Part B, and the pivotal Phase 3 Study 14595. These PET scan images were pooled, and randomly assigned for consecutive, blinded visual assessment by 5 independent readers. To reflect the future study population, the pooled images included cases with various forms of clinically diagnosed dementia such as probable/possible mild to moderate AD, FTLN, VaD, and DLB as well as cases from clinically non-demented subjects, e.g., MCI, young (< 40 years) and elderly

(> 55 years) cognitively normal HVs, as well as from subjects from the Phase 3 histopathology study. The latter included 54 subjects (including clinically demented and non-demented subjects) who died and were autopsied by 19 MAY 2012, and had an evaluable PET scan. The data were enriched with scans from 10 young HVs who served as negative controls (without autopsy).

A total of 55 autopsied and evaluable brain specimens became available from the pivotal Study 14595 (from the last data cut-off date of 04 Nov 2011 for the interim CSR A47592 up to the cut-off date of 19 May 2012 for the present study report). Thus, the PET scans from the additional 24 subjects for whom brain specimens became available during this period went into the Pooled Read study (Study 16034) to be read by the five blinded readers.

Table 4: Clinical studies from which images were drawn for analysis in Study 16034

Diagnosis/Studies	A42402	311722	91790	312043	311741	14595	Total
Alzheimer's dementia ¹	10 (2) ⁵	-	-	-	131 (17)	41 (2)	182 (21)
HV ²	10 (2)	17	18 (1)		125 (11)	18 (1)	188 (15)
MCI ³	-	-	-	45 (5)	6	-	51 (5)
DLB ⁴	6 (1)	-	-	-	2	2 (1)	10 (2)
FTLD	11	-	-	-	1	-	12
PD	5	-	-	-	-	-	5
VaD	4	-	-	-	-	-	4
DEM	-	-	-	-	-	3	3
Other ⁶	-	-	-	-	3 (2)	-	3 (2)
CP diagnosis not available ⁶	-	-	-	-	3 (1)	-	3 (1)
	46 (5)	17	18 (1)	45 (5)	271 (31)	64 (4)	461 (46) ⁵

AD = Alzheimer's dementia; HV = healthy volunteers; MCI = mild cognitive impairment; DLB = dementia with Levy bodies; FTLD = fronto-temporal lobe dementia; PD = Parkinson's disease; VaD = vascular dementia; DEM = other dementia; Other = clinical Consensus Panel (CP) established a diagnosis other than dementia; not available = the clinical CP could not establish a diagnosis.

¹AD = combination of probable AD + possible AD; ²HV = combination of HV = non-demented volunteers + Healthy negative controls; ³MCI = combination of MCI + amnesic MCI + non-amnesic MCI; ⁴DLB = combined DLB + possible DLB; ⁵Numbers in parenthesis indicate repeat image re-reads (total 46); ⁶"other" and "not available" = these scans were used only for the primary and intra-reader endpoints, but not for the secondary endpoint analysis.

Reviewer's comments: The inclusion/exclusion criteria of the study are not clear. Bayer HealthCare (b) (4) available image sets from phase 1, phase 2, and phase 3 studies based on Dr. Kress's clinical review in DARRTS dated 3/21/2012 and FDA pre-meeting preliminary comments on 12/6/2011. Why finally only 460

image sets were chosen for the ‘pooled read’ study is unknown, but raises questions of selection bias.

For Phase 1 studies A42402, 311722, and 91790, it appears that the non-selected subjects were healthy volunteers in these studies, while all subjects with pathology were included. However the Phase 2 study (#311741) enrolled 422 subjects, why only 271 subjects were chosen for the pooled read study is unknown and raises questions of selection bias. The pivotal ‘histopathology’ study (#14595) evaluated 216 subjects, and why only 64 subjects were chosen for the ‘pooled read’ study is unknown and again raises questions for selection bias. It further puzzles the reviewer why progressively larger proportions of subjects were excluded from the ‘pooled read’ study going from Phase 1, to Phase 2, to Phase 3 studies.

Overall the selection process of the 460 image sets out of the 1000 available image sets was unclear.

6 Review of Efficacy

Efficacy Summary

There are two Phase 3 studies submitted in the application: Studies 14595 and 16034

Histopathology Study (14595)

Primary Efficacy - Sensitivity and Specificity of PET Visual Assessment [Majority Read](#) at the [Brain Regional Level](#) Using [Binary PET Reading Methodology](#) Based on Histopathology as the Standard of Truth

The co-primary efficacy variables are sensitivity and specificity of regional tracer brain uptake of florbetaben based on the majority read of the visual assessment by the three blinded readers of PET images obtained 90 to 110 minutes post-injection over the 6 brain regions (of a particular subject).

Based on the PET images, a brain region (of a particular subject) is classified as “normal” or “abnormal” depending on the presence or absence of cortical tracer uptake in the respective brain region. “Normal” means absence of β -amyloid and “Abnormal” presence of β -amyloid.

The co-primary efficacy variables of the study were evaluated using the majority results of the 3 independent blinded readers. This majority read value for the 3 readers is determined based on the match to the standard of truth, which is histopathology. If at least 2 readers match the standard of truth, the majority reader response will be considered a match. This majority read response is not a consensus read. The analysis based on the majority read is considered the relevant analysis of the co-primary efficacy variables. The 95% confidence interval is calculated for the majority read and for each blinded reader separately.

The sensitivity P_{sens} is defined as the true proportion of brain regions classified as abnormal from all brain regions (from all subjects) where a standard of truth is available and the standard of truth is ‘ β -amyloid present’. One subject could contribute with 0 to 6 brain regions where β -amyloid is present according to the standard of truth.

The specificity P_{spec} is defined as the true proportion of brain regions classified as normal from all brain regions (from all subjects) where a standard of truth is available and the standard of truth is ‘ β -amyloid not present’. One subject may contribute with 0 to 6 brain regions where β -amyloid is not present according to the standard of truth.

The following hypotheses were formulated:

$H_{0,sens}$: sensitivity ≤ 0.6 vs. $H_{1,sens}$: sensitivity > 0.6

$H_{0,spec}$: specificity ≤ 0.8 vs. $H_{1,spec}$: specificity > 0.8

$H_{0,sens}$ would be rejected if the lower bound of the two-sided 95% confidence is larger than 0.6.

$H_{0,spec}$ would be rejected if the lower bound of the two-sided 95% confidence is larger than 0.8.

For the 6 brain regions of interest, the sensitivity for the majority read was 77.36% (95% CI: 65.35% – 89.37%) and the specificity was 94.20% (95% CI: 88.57% – 99.84%). Therefore, the combined null hypotheses for this study that sensitivity is $\leq 60\%$ and specificity is $\leq 80\%$ were rejected.

Although the study is a win based on its pre-specified co-primary efficacy endpoints, it should be noted that:

- 1) The study used the majority read of 3 independent readers in its primary efficacy analysis. In clinical practice, each Florbetaben PET is likely to be read by only one reader, and relying on the majority read of 3 readers would not be practical. So if one reader is wrong, and the other two readers are right, the majority read is still right and would not reflect the one wrong.
- 2) The primary efficacy analysis was conducted at the brain regional level. The clinical significance of brain regional β -amyloid deposition is not clear to the medical community. Furthermore, only special cut-out PET image of the brain regions that were evaluated for histopathology were displayed to the blinded readers, i.e. the readers were not presented with the whole brain PET images that would be normally read by imaging physicians in clinical practice.
- 3) Binary Florbetaben PET reading methodology was used for primary efficacy analysis, however, this binary reading methodology is not being proposed for clinical practice by the applicant.
- 4) PET-MRI co-registration is used for the images displayed to the blinded readers. Since many centers in the U.S. may not have PET-MR co-registration capability, the co-registration of PET-MR used in the blinded read is not representative of current real world clinical practice.

- 5) The study population is mostly end-of-life patients artificially enriched with 10 young healthy volunteers as additional ‘true negatives’, neither population is the intended patient population of the product in future clinical practice

Because the majority read is not practice for clinical practice, the brain regional analysis of amyloid deposition is of unclear clinical significance, and the binary PET reading methodology is not being proposed for clinical practice by the applicant, and the study population does not truly reflect the intended patient population of the product, Study 14595 did not assess the product’s performance characteristics in settings resembling future clinical practice. The study therefore does not bear as much clinical significance as the ‘Pooled Read Study’, which assesses the product’s performance characteristics in settings resembling future clinical practice.

Pooled Read Study (16034)

Primary Efficacy

The primary efficacy endpoint of the study is:

- Inter-reader agreement of the visual assessment results assessed on the subject level using kappa values across all 5 blinded readers. This assesses the reproducibility of the visual assessment of PET scans from a patient population that closely represents the “future use” population comprised of 461 florbetaben PET scans pooled from various florbetaben clinical studies.

The kappa value κ_{inter} across the 5 blinded readers for the [binary assessment normal / abnormal](#) on the subject level will be calculated over all images read. The confidence interval will be calculated based on an asymptotic variance estimate. The hypothesis to be tested is

$$H_{0, \text{inter}}: \kappa_{\text{inter}} \leq 0.6 \text{ vs. } H_{1, \text{inter}}: \kappa_{\text{inter}} > 0.6$$

The hypothesis will be rejected, when the lower bound of the confidence interval for κ_{inter} is larger than 0.6.

Kappa statistic across 5 readers was 0.787, with 95% confidence interval ranged 0.750 - 0.824. Therefore the primary endpoint of inter-reader agreement exceeded the pre-specified kappa value threshold of 0.6 (for the lower bound of the two sided 95% CI).

Secondary Efficacy

Secondary efficacy endpoints include:

- To assess the intra-reader variability of the visual assessment results based on a 10% re-read of the above image data set.
- To assess the reliability of the visual assessment of florbetaben PET scans via determination of sensitivity and specificity to detect β - amyloid on a subject level with histopathology as standard of truth (SoT) using the images from the 55 autopsy cases enriched with the images of 10 healthy volunteers (HVs) from the pivotal Phase 3 study (Study 14595).
- To assess the reliability of the visual assessment of florbetaben PET scans via determination of sensitivity and specificity of florbetaben PET scans with the Consensus

Panel (CP) clinical diagnosis as Standard of Reference (SoR) using the images from 237 subjects from Part B of the Global Phase 2 study (Study 311741).

The sensitivity and specificity were assessed for each of the 5 readers in the 55 post mortem subjects from Study 14595 with available histopathology as SoT, enriched by the results from 10 HVs without autopsy for whom amyloid pathology in the brain is assumed negative by default. Corresponding 95% confidence intervals was calculated. The following combined hypotheses were tested:

$$H_{0, \text{sens}}: \text{sensitivity} \leq 0.6 \text{ vs. } H_{1, \text{sens}}: \text{sensitivity} > 0.6$$

$$H_{0, \text{spec}}: \text{specificity} \leq 0.7 \text{ vs. } H_{1, \text{spec}}: \text{specificity} > 0.7$$

The combined hypotheses would be rejected if the lower limits of the 95% confidence intervals for sensitivity and specificity are higher than the thresholds of 0.6 and 0.7 respectively for at least 3 out of the 5 blinded readers.

The sensitivity for the Blinded Readers 1 and 2 was 90% (95% CI: 80.70 – 99.30) and that for blinded readers 3 and 4 was 87.5% (95% CI: 77.25 – 97.75). Blinded Reader 5 provided a value of 77.50% (95% CI: 64.56 – 90.44). The lower bound of the 95% confidence intervals for sensitivity was above the 60% threshold level for all 5 readers.

The specificity ranged from 62.5% (95% CI: 43.13 – 81.87) for Blinded Reader 3 to 91.67% (95% CI: 80.61 – 100.00) for Blinded Reader 5. The lower bound of the 95% confidence interval ranged 43.13 – 80.61, with 4 out of 5 readers below the pre-specified 70% threshold, i.e. only 1 out of 5 readers reached the pre-specified specificity threshold of 70%. Therefore the study failed to reject the combined null hypotheses that the lower limits of the 95% confidence intervals for sensitivity is ≤ 0.6 and for specificity is ≤ 0.7 for at least 3 out of the 5 blinded readers. The study is a failed study based on this failure.

A descriptive sub-analysis was performed excluding the 10 HVs (Table 4). Point estimates for specificity decreased even further. The applicant argues that the low specificity is due to the small sample size when the 10 healthy volunteers were excluded. However the decrease in sample size would affect the 95% confidence interval, but should not substantially affect the point estimates. Therefore the reviewer disagrees with the applicant that the low specificity is due to small sample size.

Overall Study 16034 failed because the pre-specified combined null hypotheses for sensitivity and specificity were not rejected, even though the null hypothesis for primary efficacy on reader agreement was rejected. In clinical sense, the 5 readers agreed with each other, but they agreed on the wrong thing – particularly for specificity!

The fact that the 5 readers agreed with each other but they were agreeing on the wrong thing suggests a systematic error in the proposed Florbetaben PET reading methodology (which changed multiple times during the Florbetaben product development) and/or the web-based reader training module.

Efficacy Conclusion

There are two Phase 3 studies submitted with the application – the ‘Histopathology Study’ (Study 14595) and the ‘Pooled Read Study (Study 16034). The Histopathology Study achieved its pre-specified co-primary objectives of assessing sensitivity and specificity based on histopathology as the standard of truth. However the study did not evaluate the product’s sensitivity and specificity in settings representative of future clinical practice by using the majority read of 3 readers, conducting analyses on the brain regional level, and using binary PET reading methodology that is not proposed by the applicant to be used for future clinical practice. The study therefore does not bear as much clinical significance as the Pooled Read Study, which assesses the product’s performance characteristics in settings resembling future clinical practice.

The Pooled Read Study failed to reject the pre-specified combined null hypotheses of sensitivity $\leq 60\%$ and specificity $\leq 70\%$ in 3 out of 5 readers, based on histopathology as the standard of truth. Even though the study achieved its pre-specified primary efficacy objective of demonstrating inter-reader agreement by rejecting the null hypothesis of kappa statistic ≤ 0.6 , the readers were agreeing on the wrong thing with regard to specificity.

In terms of clinical significance, specificity is more important than sensitivity for the product. This is based on conclusions reached by the FDA Advisory Committee that the presence of β -amyloid deposition in the brain has limited clinical meaningfulness, but the absence of β -amyloid deposition in the brain helps exclude Alzheimer’s Disease.

The Pooled Read Study, which assesses the product’s performance characteristics in settings representative of future clinical practice, failed with regard to specificity, which is the most important performance characteristic of the product in future clinical practice.

Overall there is lack of substantial evidence of effectiveness (particular specificity) from clinical data submitted with the NDA. The reviewer recommends the applicant refine the Florbetaben PET reading methodology and web-based reader training module.

6.1 Indication

The applicant proposed the following labeling indication:

 (b) (4)

6.2 The PET Reading Methodology Developed and Proposed by the Applicant

Table 5: Definitions of regional cortical tracer uptake (RCTU)

RCTU*	Condition for assessment
1 No tracer uptake	Tracer uptake (ie, signal intensity) in gray matter in the region is lower than in white matter
2 Moderate tracer uptake	Smaller area(s) of tracer uptake equal to or higher than that present in white matter: - extending beyond the white matter rim to the outer cortical margin - involving the majority of the slices within the respective region
3 Pronounced tracer uptake	A large confluent area of tracer uptake equal to or higher than that present in white matter: - extending beyond the white matter rim to the outer cortical margin - and involving the entire region including the majority of the slices within the respective region

*in bold: major changes to former RCTB

The BAPL was assessed using a scoring system which intended to collapse the RCTB in 4 of cortical regions (Table 5) into a single 3-grade scoring system, as a means to assess β -amyloid burden of the brain globally. This BAPL score was assessed as follows:

- 1 = Without β -amyloid plaque load
- 2 = Scan with minor β -amyloid plaque load
- 3 = Scan with significant β -amyloid plaque load

Table 6: Definitions of brain amyloid plaque load (BAPL)

BAPL score	Rule for assessment
1 Scan without β -amyloid deposition	RCTU score 1 in each of the 4 brain regions 1, 2, 3, and 4
2 Scan with moderate β -amyloid deposition	RCTU score 2 in any or all of the 4 brain regions 1, 2, 3, and 4 and no score 3 in these 4 regions
3 Scan with pronounced β -amyloid deposition	RCTU score 3 at least in one of the brain regions 1, 2, 3, and 4

6.2.1 Brain Regions Included in the Histopathology Analysis and Visual Assessment

The clinical reviewer noticed that histopathology analysis used 6 other brain regions, mostly different from the brain regions included in the proposed PET visual assessment method. The following information request was sent to the applicant as part of the FDA General Advice Letter dated January 18, 2013 in preparation for the Applicant Orientation Meeting:

The primary efficacy analysis of the 'Histopathology' study (#14595) was based on

regional analysis of 6 brain regions. The proposed Florbetaben PET reading methodology assesses 4 brain regions, most of which appear different from the 6 brain regions used for the primary efficacy analysis of the 'Histopathology' study. Please explain the difference in the selection of brain regions for these two studies, and present justifications for the 4 brain regions chosen for the PET reading methodology.

The applicant responded in NDA Amendment dated February 15, 2013 that the 6 brain regions for histopathology analysis were primarily selected based on two considerations:

- 1) **Feasibility:** Could identical brain regions for histology comparison be matched between the PET image and the processed histological specimen? (coronal slices with MR overlay, photo documentation and thereafter analysis of small areas in the PET image were necessary)
- 2) **Statistical considerations:** In order to assess sensitivity and specificity, it was necessary to have both brain regions with high likelihood to be positive as well as regions which are more likely to be negative within one subject. Therefore, the six histopathology brain regions were selected on the basis of expected amyloid burden ranging from low (e.g., cerebellum) to high likelihood (e.g., frontal cortex).

The Applicant further responded that the four brain regions for the subject-based visual assessment were evaluated in the histopathology study as secondary efficacy analysis.

If the six brain regions for the histology comparison used for the primary efficacy analysis are compared to the four regions (five regions if counting cerebellum, which is also included in the six brain regions for histopathology) to be used for the subject-based visual assessment (Table 7), two regions are anatomically matched (cerebellar cortex and posterior cingulate/precuneus). Another two regions are related - middle frontal gyrus used for histopathology is a part of the frontal cortex used for PET visual assessment; hippocampus used for histopathology is adjacent to lateral temporal cortex used in PET visual assessment. Two other brain regions used for histopathology analysis (striate and parastriate areas of occipital cortex; anterior cingulate cortex) are not included in PET visual assessment for efficacy assessment. One other region from the PET visual assessment, the parietal cortex, was not included in the histopathology assessment. Table 7 summarizes the overlap and differences between the brain regions.

Table 7: Brain regions for histopathological assessment, and subject-based assessment

Brain regions for histopathological assessment	Brain regions for subject-based assessment	Anatomical match	Comment
Middle frontal gyrus	Frontal cortex	Yes, middle frontal gyrus is part of frontal cortex	
Striate and parastriate areas of occipital cortex	-	-	Was assessed in phase 2, but excluded during the development of the visual assessment methodology (no additional diagnostic information gained and to reduce complexity)
Hippocampus	Lateral temporal cortex	Hippocampus is adjacent to the lateral temporal cortex	Hippocampus is more relevant for pathological evaluation while lateral temporal cortex is the corresponding region for visual assessment
Anterior cingulate cortex	-	-	Was assessed in phase 2, but excluded during the development of the visual assessment methodology (no additional diagnostic information gained and to reduce complexity)
Posterior cingulate / Precuneus	Posterior cingulate cortex / Precuneus	Yes	
-	Parietal cortex	-	
Cerebellar cortex	Cerebellar cortex	Yes	Reference region for histopathology and white matter uptake, not used for visual assessment

6.2.2 PET Image Display for Visual Assessment

The clinical reviewer noticed that the Florbetaben PET imaging display was changed from mix of color rainbow display and grayscale display to grayscale display only during the product development. A request was sent to the company as part of the FDA General Advice Letter dated January 18, 2013 in preparation for the Applicant Orientation Meeting on February 4, 2013:

“Rainbow color display was used in Phase 1 and Phase 2 studies, while gray scale display was used in Phase 3 studies and appears to be proposed for future clinical use as well. Please discuss the rationale of your transition from rainbow color display to gray scale display. If helpful, you may use case presentations to illustrate your points.”

The applicant replied in NDA amendment dated 2/15/2013 and also during the Applicant Orientation Meeting that the use of a rainbow color scale tends to downgrade BAPL scores, biasing results towards findings of no tracer uptake. Gray scales preserve more information in the image than color scales, which are designed to artificially enhance contrasts. In addition, linear gray scale is available on all nuclear medicine workstations. The change from color to gray scale is further supported by the fact that evaluation of signal detection performance in test systems had shown up to 30% poorer performance when rainbow color scales are used, compared to linear gray scale. (Hong Li and Arthur E. Burgess; SPIE Proceedings Vol. 3036; Medical Imaging 1997: Image Perception, pp.143-149).

6.3 Analysis of Primary Endpoint(s)

6.3.1 Sensitivity and Specificity of PET Visual Assessment Majority Read At the Brain Regional Level Using Binary PET Reading Methodology Based on Histopathology as the Standard of Truth (Histopathology Study #14595)

There are 32 autopsy brains, with one brain (subject 400010011) not assessable, leaving 31 brains assessable for primary efficacy analysis. Ten young healthy volunteers were also included in the primary efficacy analysis, and their standard of truth is presumed to be negative. So altogether

Each brain has 6 brain regions for analysis. For 41 subjects (including 31 patients and 10 young healthy volunteers included in the primary efficacy analysis), there should be 246 brain regions for analysis.

Reviewer's comments: According to the study's clinical study report, there were 244 evaluable brain regions, including 186 brain regions from autopsy, and 60 presumed negative brain regions from the 10 young healthy volunteers.

The reviewer independently examined histopathology results from Module 5 Section 16.2.6 Individual Efficacy Response Data Tabulations, and noticed there were 4 brain regions given the overall not assessable rating from the Consensus Panel for the SOT in addition to Subject 400010011, for whom all 6 brain regions were not assessable according to the Consensus Panel for SOT. Therefore there were 242 evaluable brain regions. The reviewer compiled brain regional SOT from Module 5 Section 16.2.6 Individual Efficacy Response Data Tabulations as Table 8 below.

From Table 8 we can see that for each subject, brain regional variation is small, and different regions of a brain mostly have concordant histopathology results.

Table 8: Consensus Panel Brain Regional Histopathology SOT (32 autopsy brains from Study 14595)

Subject ID	Region 1	Region 2	Region 3	Region 3a	Region 4	Region 5	Region 5a	Region 6
100011014 AD	Yes	Yes	Yes	Yes	Yes (diffuse plaques)	Yes	Yes	No
100013002 AD	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
140010002 AD	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
140010008 AD	Yes	Yes	Yes	Yes	Yes (diffuse plaques)	Yes	Yes (diffuse plaques)	Yes (diffuse plaques and vascular amyloid)
140010009 AD	Yes	Yes	Yes	Yes	Yes (diffuse plaques)	Yes (diffuse plaques)	Yes (diffuse plaques)	Yes (sparse diffuse plaques)
140010011 AD	No	No	No	No	No	No	No	No
140010012 AD	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes (vascular amyloid)
140010015 AD	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes (vascular amyloid)
140010017 AD	No	No	No	No	No	No	No	No
140030006 AD	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes (diffuse plaques and vascular amyloid)
140050001 NDV	No	No	No	No	No	No	No	No
140050003 AD	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes (diffuse plaques and vascular amyloid)
140070001 NDV	Yes	Yes	No	Yes	Yes	Yes (diffuse plaque)	Yes (diffuse plaques)	No
140070003 AD	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes (vascular amyloid)
200010003 AD	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes (diffuse plaques and vascular amyloid)
200010004 NDV	Yes (diffuse plaques)	Yes	No	Yes (diffuse plaques)	Yes (diffuse plaques)	Yes (diffuse plaques)	No	Not assessable
200010006 Other Dem	No	No	No	No	No	Yes (diffuse plaque)	No	No
200020001 NDV	No	No	No	No	No	No	No	No
200020004 AD	No	No	No	No	No	No	No	No

Subject ID	Region 1	Region 2	Region 3	Region 3a	Region 4	Region 5	Region 5a	Region 6
200020006 AD	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not assessable
200020009 AD	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
200040004 AD	Yes (vascular amyloid)	Yes (vascular amyloid)	Yes (diffuse plaques)	No	Yes (vascular amyloid)	No	No	Yes (vascular amyloid)
200040005 AD	Yes (diffuse plaques)	Yes (diffuse plaques and vascular amyloid)	Yes	Yes (diffuse plaques)	Yes (diffuse plaques)	Yes (diffuse plaques)	Yes (diffuse plaques)	No
200040010 AD	No	No	No	No	No	No	No	No
200040012 DLB	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes (vascular amyloid)
200040024 Other Dem	No	No	No	No	No	No	No	No
200040025 AD	Yes	Yes	Yes	Yes	Yes (diffuse plaques)	Yes (diffuse plaques)	Yes (diffuse plaques)	No
200040027 NDV	Yes	Not assessable	Yes	Yes	Yes	Yes	Yes (diffuse plaques)	Yes (vascular amyloid)
200040028 NDV	Yes (diffuse plaques)	Yes (diffuse plaques and vascular amyloid)	Yes	Yes (diffuse plaques)	Yes (diffuse plaques)	Yes (diffuse plaques)	Yes (diffuse plaques)	No
400010011 AD	Not assessable	Not assessable	Not assessable	Not assessable	Not assessable	Not assessable	Not assessable	Not assessable
400010016 AD	Yes (diffuse plaques)	No	No	No	No	No	Yes (diffuse plaques)	No
140060004 AD	Yes	Yes	Yes	Yes	Not assessable	Yes	Yes	No

AD: Alzheimer's Disease; NDV: non-demented volunteer; DLB: dementia with Lewy bodies; Other Dem: other dementia

The sensitivity P_{sens} was defined as the true proportion of brain regions classified as abnormal from all brain regions where an SoT was available and the SoT was ‘ β -amyloid present’.

The specificity P_{spec} was defined as the true proportion of brain regions classified as normal from all brain regions where an SoT was available and the SoT was ‘ β -amyloid not present’.

The following hypotheses were formulated:

$$H_{0,sens}: \text{sensitivity} \leq 0.6 \text{ vs. } H_{1,sens}: \text{sensitivity} > 0.6$$

$$H_{0,spec}: \text{specificity} \leq 0.8 \text{ vs. } H_{1,spec}: \text{specificity} > 0.8$$

$H_{0,sens}$ would be rejected if the lower bound of the two-sided 95% confidence is larger than 0.6.

$H_{0,spec}$ would be rejected if the lower bound of the two-sided 95% confidence is larger than 0.8.

The results of the primary efficacy analysis are shown in Table 9. For the 6 brain regions of interest, the sensitivity for the majority read was 77.36% (95% CI: 65.35% – 89.37%) and the specificity was 94.20% (95% CI: 88.57% – 99.84%). Therefore, the combined hypothesis for this study that sensitivity is $\leq 60\%$ or specificity is $\leq 80\%$ could be rejected.

Table 9: Primary Analysis Results for Study 14595: Sensitivity and specificity of β -amyloid plaque load detection at the brain regional level, by majority read of 3 blinded readers

Region	Method key item	TP	TP+FN	Sensitivity [%]	95% Sens. LCL [%]	95% Sens. UCL [%]	TN	TN+FP	Specificity [%]	95% Spec. LCL [%]	95% Spec. UCL [%]
Total	Maj. read	82	106	77.36	65.35	89.37	130	138	94.20	88.57	99.84
	Reader 1	85	106	80.19	67.39	92.99	125	138	90.58	83.60	97.55
	Reader 2	86	106	81.13	72.14	90.12	126	138	91.30	84.58	98.03
	Reader 3	63	106	59.43	46.81	72.06	127	138	92.03	85.36	98.70
Region 1	Maj. read	18	21	85.71			19	20	95.00		
	Reader 1	18	21	85.71			17	20	85.00		
	Reader 2	20	21	95.24			18	20	90.00		
	Reader 3	14	21	66.67			18	20	90.00		
Region 2	Maj. read	16	18	88.89			19	22	86.36		
	Reader 1	16	18	88.89			19	22	86.36		
	Reader 2	18	18	100.00			17	22	77.27		
	Reader 3	11	18	61.11			19	22	86.36		
Region 3	Maj. read	12	21	57.14			20	20	100.00		
	Reader 1	16	21	76.19			18	20	90.00		
	Reader 2	11	21	52.38			20	20	100.00		
	Reader 3	7	21	33.33			20	20	100.00		
Region 4	Maj. read	18	20	90.00			18	21	85.71		
	Reader 1	18	20	90.00			18	21	85.71		
	Reader 2	19	20	95.00			18	21	85.71		
	Reader 3	15	20	75.00			18	21	85.71		
Region 5	Maj. read	18	22	81.82			17	18	94.44		
	Reader 1	17	22	77.27			16	18	88.89		
	Reader 2	18	22	81.82			16	18	88.89		
	Reader 3	16	22	72.73			17	18	94.44		
Region 6	Maj. read	0	4	0.00			37	37	100.00		
	Reader 1	0	4	0.00			37	37	100.00		
	Reader 2	0	4	0.00			37	37	100.00		
	Reader 3	0	4	0.00			35	37	94.59		

Reviewer's comments: Although the study won on pre-specified criteria for primary efficacy analysis on sensitivity and specificity on a brain regional level, the primary efficacy analysis artificially included 10 healthy volunteers whose histopathology standard of truth is presumed to be negative (absence of amyloid deposition). Note during the IND phase of the product, the FDA review team repeatedly advised Bayer HealthCare not to include the 10 young healthy

volunteers in the primary efficacy analysis to artificially inflate the number of true negatives. In a sense, one of the study's weaknesses is that the study's patient population is almost entirely in end-of-life patients. True negatives should be patients with mild cognitive decline or suspected of Alzheimer's Disease whose brain autopsy revealed absence of clinically significant levels of amyloid deposition. The study has total of 138 negative brain regions based on standard of truth, of which 60 brain regions are from the 10 young healthy volunteers.

Additional limitations of the study include:

- 1) The study used the majority read of 3 independent readers in its primary efficacy analysis. In clinical practice, each Florbetaben PET is likely to be read by only one reader, and relying on the majority read of 3 readers would not be practical. So if one reader is wrong, and the other two readers are right, the majority read is still right and would not reflect the one wrong.*
- 2) The primary efficacy analysis was conducted at the brain regional level. The clinical significance of brain regional β -amyloid deposition is not clear to the medical community. Furthermore, only special cropped PET image of the brain regions that were evaluated for histopathology were displayed to the blinded readers, i.e. the readers were not presented with the whole brain PET images that would be normally read by imaging physicians in clinical practice.*
- 3) Binary Florbetaben PET reading methodology was used for primary efficacy analysis, however, this binary reading methodology is not being proposed for clinical practice by the applicant.*
- 4) PET-MRI co-registration is used for the images displayed to the blinded readers. Since many centers in the U.S. may not have PET-MR co-registration capability, the co-registration of PET-MR used in the blinded read is not representative of current real world clinical practice.*

Because the majority read is not practice for clinical practice, the brain regional analysis of amyloid deposition is of unclear clinical significance, and the binary PET reading methodology is not being proposed for clinical practice by the applicant, and the study population does not truly reflect the intended patient population of the product, Study 14595 did not assess the product's performance characteristics in settings resembling future clinical practice. The study therefore does not bear as much clinical significance as the 'Pooled Read Study', which assesses the product's performance characteristics in settings resembling future clinical practice.

6.3.2 Sensitivity and Specificity of Florbetaben PET Visual Assessment At Subject Level Compared To Histopathology As Standard of Truth (SOT) Based On 54 Autopsy Cases (Data From Histopathology Study 14595, Analyzed In Pooled Read Study 16034)

Sensitivity and specificity of the florbetaben PET visual assessment *at the subject level* with histopathology as the Standard of Truth (SoT) using all available autopsy cases is an efficacy analysis requested by the FDA review team for the Pooled Read Study (16034), the second pivotal study.

Reviewer's comments: The FDA review team requested this analysis largely due to the fact that the first pivotal study, Histopathology Study (#14595), assessed sensitivity and specificity of florbetaben PET visual assessment at the brain regional level, and brain regional amyloid deposition is of unclear clinical significance to the medical community. Although this analysis is listed as a secondary efficacy endpoint by the company's protocol, the FDA review team considers it as important as the primary efficacy analysis, which assesses inter-reader agreement. Throughout clinical development of florbetaben, the FDA review team repeatedly advised Bayer HealthCare to conduct primary efficacy analysis of phase 3 pivotal studies at the subject level.

The Pooled Read Study (16034) has two hypothesis testing: 1) inter-reader agreement (discussed in the next section of the review; 2) Sensitivity and specificity of the florbetaben PET visual assessment at the subject level with histopathology as the Standard of Truth (SoT) using all available autopsy cases (54 autopsy cases enriched with 10 young healthy volunteers).

Reviewer's comments: The goal of the two hypothesis testing for the Pooled Read Study is to demonstrate that readers agree with each other in reading florbetaben PET from a wide variety of patients, and they agree on the right conclusion (as evaluated by sensitivity and specificity of the florbetaben PET visual assessment in a subset of subjects who have brain histopathology available as the standard of truth).

All the available autopsy cases in the analysis are from the Histopathology Study (14595). The clinical study report of the Histopathology Study (14595) was completed when a total of 32 autopsy cases had accumulated (31 evaluable brains, 1 non-assessable brain). Since then 24 additional autopsy brains from subjects enrolled in the Histopathology Study (14595) became available (23 evaluable brains, 1 non-assessable) for analysis when the Pooled Read Study (16034) was conducted. Therefore there are 54 evaluable brains with available histopathology included in this efficacy analysis. In addition, the sponsor included 10 young healthy volunteers, who do not have histopathology as the standard of truth. Rather their 'standard of truth' is presumed to be negative for amyloid deposition.

Reviewer's comments: The FDA review team repeatedly advised Bayer HealthCare not to include 10 young healthy volunteers in the efficacy analysis.

The following combined hypotheses were tested:

$H_{0, \text{sens}}$: sensitivity ≤ 0.6 vs. $H_{1, \text{sens}}$: sensitivity > 0.6

$H_{0, \text{spec}}$: specificity ≤ 0.7 vs. $H_{1, \text{spec}}$: specificity > 0.7

The combined hypotheses would be rejected if the lower limits of the 95% confidence intervals for sensitivity and specificity are higher than the thresholds of 0.6 and 0.7 respectively for at least 3 out of the 5 blinded readers.

Sensitivity and specificity of the visual assessment at the subject level with histopathology as the Standard of Truth (SoT) using 55 (or 54 evaluable) autopsy cases enriched with 10% healthy volunteers (Table 10): The sensitivity for the Blinded Readers 1 and 2 was 90% (95% CI: 80.70 – 99.30) and that for blinded readers 3 and 4 was 87.5% (95% CI: 77.25 – 97.75). Blinded Reader 5 provided a value of 77.50% (95% CI: 64.56 – 90.44). The lower bound of the 95% confidence intervals for sensitivity was above the 60% threshold level for all 5 readers.

The specificity ranged from 62.5% (95% CI: 43.13 – 81.87) for Blinded Reader 3 to 91.67% (95% CI: 80.61 – 100.00) for Blinded Reader 5. The lower bound of the 95% confidence interval ranged 43.13 – 80.61, with 4 out of 5 readers below the pre-specified 70% threshold, i.e. only 1 out of 5 readers reached the pre-specified specificity threshold of 70%. Therefore the study failed to reject the combined null hypotheses that the lower limits of the 95% confidence intervals for sensitivity is ≤ 0.6 and for specificity is ≤ 0.7 for at least 3 out of the 5 blinded readers. The study failed to provide substantial evidence of effectiveness in terms of specificity.

Table 10: Sensitivity and specificity of the subject level visual assessment of florbetaben PET compared to histopathology as standard of truth – full analysis set (Pooled Read Study 16034)

Reader	No. of TP	No. of TP + FN	Sensitivity [%]	Sensitivity 95% LCL – UCL [%]	No. of TN	No. of TN + FP	Specificity [%]	Specificity 95% LCL – UCL [%]
Blinded Reader 1	36	40	90.00	80.70 - 99.30	20	24	83.33	68.42 - 98.24
Blinded Reader 2	36	40	90.00	80.70 - 99.30	15	24	62.50	43.13 - 81.87
Blinded Reader 3	35	40	87.50	77.25 - 97.75	18	24	75.00	57.68 - 92.32
Blinded Reader 4	35	40	87.50	77.25 - 97.75	19	24	79.17	62.92 - 95.41
Blinded Reader 5	31	40	77.50	64.56 - 90.44	22	24	91.67	80.61 - 100

FN = false negative; FP = false positive; LCL = lower confidence level; TP = true positive, TN = true negative; UCL = upper confidence level. Analysis includes 10 HVs without autopsy for whom β -amyloid pathology in the brain was assumed negative by default.

Sensitivity and specificity of the subject level visual assessment with histopathology as the Standard of Truth (SoT) using 55 (or 54 evaluable) autopsy cases *excluding* the healthy volunteers:

A descriptive sub-analysis was performed excluding the 10 HVs (Table 11). Point estimates for specificity decreased even further. When excluding the healthy volunteers, 14 subjects contributed to the analysis of specificity (for the primary analysis of this secondary endpoint where 14 + 10 = 24 subjects contributed to the analysis of specificity).

The applicant argues that the low specificity is due to the small sample size when the 10 healthy volunteers were excluded. However the decrease in sample size would affect the 95% confidence interval, but should not substantially affect the point estimates. Therefore the reviewer disagrees with the applicant’s argument that the low specificity is due to small sample size.

The sensitivity data was identical to that when the HVs were included in the analysis. The specificity values were lower than above for 4 out of the 5 readers, and higher for one reader.

Table 11: Sensitivity and specificity of the subject level visual assessment of florbetaben PET scans compared to histopathology as SoT excluding the HVs (Study 16034) – FAS

Investigator	No. of TP	No. of TP + FN	Sensitivity estimate [%]	Sensitivity 95% LCL [%]	Sensitivity 95% UCL [%]	No. of TN	No. of TN + FP	Specificity estimate [%]	Specificity 95% LCL [%]	Specificity 95% UCL [%]
Blinded Reader 1	36	40	90.00	80.70	99.30	10	14	71.43	47.76	95.09
Blinded Reader 2	36	40	90.00	80.70	99.30	9	14	64.29	39.19	89.39
Blinded Reader 3	35	40	87.50	77.25	97.75	10	14	71.43	47.76	95.09
Blinded Reader 4	35	40	87.50	77.25	97.75	9	14	64.29	39.19	89.39
Blinded Reader 5	31	40	77.50	64.56	90.44	12	14	85.71	67.38	100.00

PET = positron emission tomography; SoT = standard of truth; HVs = healthy volunteers; FAS = full analysis set; FN = false negative; FP = false positive; LCL = lower confidence level; TP = true positive, TN = true negative; UCL = upper confidence level. Analysis excluded the 10 healthy volunteers from Study 14595.

Reviewer's comments: Overall Study 16034 failed because the pre-specified combined null hypotheses for sensitivity and specificity were not rejected, even though the null hypothesis for primary efficacy on reader agreement was rejected. In clinical sense, the 5 readers agreed with each other, but they agreed on the wrong thing – particularly for specificity!

The fact that the 5 readers agreed with each other but they were agreeing on the wrong thing suggests a systematic error in the proposed Florbetaben PET reading methodology (which changed multiple times during the Florbetaben product development) and/or the web-based reader training module.

6.3.3 Inter-Reader Agreement Based on Kappa Statistics (Pooled Image Read Study #16034)

While the first pivotal study (Histopathology Study 14595) evaluated sensitivity and specificity of the florbetaben PET visual assessment using histopathology as the standard of truth, as the reviewer commented above, one of the weaknesses of the study was that the study patient population were mostly end-of-life patients, which do not represent the intended patient population for florbetaben in future clinical practice. The second pivotal study, the Pooled Read Study (16034), therefore attempts to evaluate the product's performance in a population representative of the intended patient population of the product. Since most of these subjects will not have brain histopathology available as the standard of truth, the primary efficacy analysis of the study aims to assess the reproducibility of the product by evaluating inter-reader agreement of the florbetaben PET visual assessment.

The primary efficacy endpoint of the study is:

- Inter-reader agreement of the visual assessment results assessed on the subject level using kappa values across all 5 blinded readers. This assesses the reproducibility of the visual assessment of PET scans from a patient population that closely represents the “future use” population comprised of 461 florbetaben PET scans pooled from various florbetaben clinical studies.

The kappa value κ_{inter} across the 5 blinded readers for the [binary assessment normal / abnormal](#) on the subject level will be calculated over all images read. The confidence interval will be calculated based on an asymptotic variance estimate. The hypothesis to be tested is

$$H_{0, \text{inter}}: \kappa_{\text{inter}} \leq 0.6 \text{ vs. } H_{1, \text{inter}}: \kappa_{\text{inter}} > 0.6$$

The hypothesis will be rejected, when the lower bound of the confidence interval for κ_{inter} is larger than 0.6.

Kappa statistic across 5 readers was 0.787, with 95% confidence interval ranged 0.750 - 0.824 (Table 12). The lower bound of the 95% confidence interval for the 10 reader pairs ranged between 0.609 (between Readers 2 and 5) and 0.819 (between Readers 1 and 3). Therefore the primary endpoint of inter-reader agreement exceeded the pre-specified kappa value threshold of 0.6 (for the lower bound of the two sided 95% CI). The hypothesis that kappa is less than or equal to 0.6 could thus be rejected, since the inter-reader agreement across all 5 readers was greater than 0.6.

Table 12: Agreement across all five blinded readers (inter individual kappa) and for all 10 reader pairs – full analysis set (Study 16034)

Readers	Kappa estimate	Lower 95% confidence limit	Upper 95% confidence limit
Across all 5 readers	0.7870	0.7502	0.8237
Readers 1 and 2	0.7310	0.6687	0.7933
Readers 1 and 3	0.8651	0.8192	0.9110
Readers 1 and 4	0.8079	0.7539	0.8619
Readers 1 and 5	0.7787	0.7208	0.8366
Readers 2 and 3	0.7657	0.7070	0.8245
Readers 2 and 4	0.7352	0.6733	0.7971
Readers 2 and 5	0.6766	0.6092	0.7441
Readers 3 and 4	0.8559	0.8085	0.9032
Readers 3 and 5	0.7916	0.7351	0.8480
Readers 4 and 5	0.8345	0.7834	0.8856

6.4 Analysis of Secondary Endpoints(s) - Composite “Whole Brain” Regional Assessment Using Majority Read, In-Person Training and Binary PET Reading Methodology (Study 14595)

Sensitivity and specificity of the whole brain regional visual assessment compared to the composite whole brain histopathological assessment for individual blinded readers as well as the majority read can be found in Table 13. The sensitivity and specificity of the whole brain regional assessment compared to the SoR were 86.96% (95% CI: 73.19 – 100.00%) and 88.89% (95% CI: 74.37% – 100.00%), respectively, for the majority read.

Table 13: Sensitivity and specificity of the 'whole brain' visual regional assessment compared to the composite 'whole brain' histopathological assessment, by blinded reader (including majority read) (Study 14595 full analysis set)

Parameter	Method key item	TP or TN ^a	TP+FN or TN+FP ^b	Estimate [%]	95% LCL [%]	95% UCL [%] ^c
Sensitivity	Maj. read	20	23	86.96	73.19	100.00
	Reader 1	20	23	86.96	73.19	100.00
	Reader 2	22	23	95.65	87.32	100.00
	Reader 3	20	23	86.96	73.19	100.00
Specificity	Maj. read	16	18	88.89	74.37	100.00
	Reader 1	13	18	72.22	51.53	92.91
	Reader 2	14	18	77.78	58.57	96.98
	Reader 3	16	18	88.89	74.37	100.00

7 Review of Safety

Safety Summary

Close to 900 subjects received florbetaben administration. There was no death or serious adverse reactions caused by the drug. The most common adverse reactions include injection site reactions (pain, hematoma, erythema, irritation, etc), followed by headache. Overall safety results show that florbetaben at the proposed labeling dosing of 300 ^{(b) (4)} MBq and mass doses of up to ^{(b) (4)} µg per injection, is safe and well tolerated.

7.1 Adequacy of Safety Assessments

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Safety population is comprised of 872 subjects who received 978 florbetaben administrations and 12 subjects who received vehicle. Table 14 lists the clinical studies used for safety evaluation of florbetaben.

Table 14: Number of subjects in the integrated safety pool by study

Protocol number	Assigned to study drug		Received study drug		Administration of study drug	
	Florbetaben N = 878 N (%)	Vehicle N = 13 N (%)	Florbetaben N = 872 N (%)	Vehicle N = 12 N (%)	Florbetaben N = 978 N (%)	Vehicle N = 12 N (%)
310863	29 (3.3)	0	28 (3.2)	0	28 (2.9)	0
311722	18 (2.1)	6 (46.2)	18 (2.1)	6 (50.0)	18 (1.8)	6 (50.0)
91790	18 (2.1)	7 (53.8)	18 (2.1)	6 (50.0)	18 (1.8)	6 (50.0)
312161 ^a	16 (1.8)	0	16 (1.8)	0	32 (3.3)	0
312043 ^a	45 (5.1)	0	45 (5.2)	0	122 (12.5)	0
14311	109 (12.2)	0	109 (12.5)	0	109 (11.1)	0
311741	425 (48.4)	0	422 (48.4)	0	422 (43.1)	0
14595 ^{a, b}	218 (24.5)	0	216 (24.8)	0	229 (23.4)	0

^a Subjects with multiple treatment periods (Studies 14595, 312043, 312161) are analyzed by period (administration of study drug). Thus, the number of analyzed subjects (administrations of study drug) is higher than the number of subjects who received study drug.

N: Number of subjects or the number of administrations

7.1.2 Demographics of Target Populations

Demographics of the safety population are shown in Table 15. The population was almost equally divided between males and females. The mean age of the population was 67.7 ± 15.6 years (range: 21 to 98 years); 70.5% of the subjects (698/990) were ≥ 65 years old.

Table 15: Demographics and baseline characteristics

Category	Total florbetaben experience N = 978	Tracer mass dose > 10 µg/injection N = 46	Tracer mass dose ≤ 10 µg/injection N = 932	Vehicle N = 12	Total N = 990
Age (year)					
n	978	46	932	12	990
Mean (SD)	67.8 (15.7)	64.0 (15.5)	68.0 (15.7)	60.3 (5.2)	67.7 (15.6)
Median	71.0	67.0	71.0	58.0	71.0
Min, Max	21, 98	23, 887	21, 98	55, 71	21, 98
Age group, n (%)					
< 40 yrs	80 (8.2)	6 (13.0)	74 (7.9)	0	80 (8.1)
40 to < 65 yrs	202 (20.7)	12 (26.1)	190 (20.4)	10 (83.3)	212 (21.4)
65 to < 80 yrs	508 (51.9)	24 (52.2)	484 (51.9)	2 (16.7)	510 (51.5)
≥ 80 yrs	188 (19.2)	4 (8.7)	184 (19.7)	0	188 (19.0)
Sex, n (%)					
Male	527 (53.9)	21 (45.7)	506 (54.3)	10 (83.3)	537 (54.2)
Female	451 (46.1)	25 (54.3)	426 (45.7)	2 (16.7)	453 (45.8)
Race, n (%)					
Caucasian	820 (83.8)	36 (78.3)	784 (84.1)	6 (50.0)	826 (83.4)
Black	17 (1.7)	1 (2.2)	16 (1.7)	0	17 (1.7)
Asian	137 (14.0)	9 (19.6)	128 (13.7)	6 (50.0)	143 (14.4)
Other	4 (0.4)	0	4 (0.4)	0	4 (0.4)
Geographic region, n (%)					
Europe	402 (41.1)	11 (23.9)	391 (42.0)	6 (50.0)	408 (41.2)
Japan	130 (13.3)	9 (19.6)	121 (13.1)	6 (50.0)	136 (13.7)
United States	245 (25.1)	8 (17.4)	237 (25.4)	0	245 (24.7)
Australia	201 (20.6)	18 (39.1)	183 (19.6)	0	201 (20.3)
Weight (kg)					
n	976	46	930	12	988
Mean (SD)	71.3 (15.0)	74.2 (16.7)	71.2 (16.0)	74.4 (9.6)	71.4 (16.0)
Median	71.2	71.5	71.2	75.2	71.2
Min, Max	27.0, 128.8	52.0, 128.8	27.0, 125.2	57.1, 91.6	27.0, 128.8

7.2 Major Safety Results

7.2.1 Deaths and Nonfatal Serious Adverse Events

Due to the nature of the autopsy study and the patients included, deaths occurring more than 7 days post-injection were considered non treatment emergent. Deaths were considered treatment emergent if they occurred after administration of study drug and before the end of the 7-day post-injection period.

A single death occurred within 7 days of study treatment; a subject in the DEM population of Study 14595 (Subject 14595/200040024; tracer mass dose ≤ 10 µg/injection) died 153 hours after the injection. The cause of death was respiratory failure, the investigator noted that the death was not related to either study drug or study procedures.

Thirty-four (34) deaths were reported outside the 7-day p.i. window, one occurred in Study 312043 (cerebrovascular accident); the other 33 deaths were reported for Study 14595 (1 occurred before injection, 32 occurred after the 7-day p.i. window). The design of Study 14595 included a main study population of subjects with short life expectancy (<3 years was preferred, per protocol design) because the study was aiming at histopathological verification after brain

donation; therefore, it was anticipated that deaths would occur in the affected group of individuals.

Table 16: Deaths and serious adverse events occurring within seven days post-injection

Subject group	Gender / age (yrs)	Race	Tracer mass dose	Adverse event (preferred term/ literal wording)	System organ class
DEM	Male / 84	Asian	≤ 10 µg/inj	Respiratory failure / respiratory failure	Respiratory, thoracic and mediastinal disorders
NDV	Female / 67 ≥ 55 yrs	Caucasian	> 10 µg/inj	Neoplasm malignant / malignant tumor of unknown origin	Neoplasms benign, malignant and unspecified (incl cysts and polyps)
MCI	Male / 82	Caucasian	≤ 10 µg/inj	Hemiparesis / transient right-sided weakness	Nervous system disorders

NDV = non-demented volunteer, DEM = other dementia, MCI = mild cognitive impairment; yrs = years.

There are two non-fatal serious adverse events. One occurred in a 67 year old female non-demented volunteer (NDV), who had malignant tumor which was not related to the study drug. The other non-fatal serious adverse event occurred in an 82 year old male MCI subject who had hemiparesis and transient right-sided weakness. This was not considered related to the study drug, either.

7.2.2 Dropouts and/or Discontinuations

None.

7.3 Common Adverse Events

Common treatment-emergent adverse events (TEAEs) are generally those occurring at a rate of ≥ 1% of the total study population.

The most common treatment-emergent adverse events (Table 17) were injection site reactions – pain (3.8%), hematoma (3.2%), erythema (1.2%), and irritation (1.2%). Apart from injection site reactions, 23 subjects (2.4% of the population) experienced headaches, with most occurring in subjects within the first 24 hours after the injection (60.9%, 14/23). Headache was classified as mild in intensity in 20 subjects who received florbetaben and of moderate intensity in 3 subjects.

Table 17: Number of subjects with common ($\geq 1.0\%$) treatment-emergent adverse events by primary system organ class and preferred term

System Organ Class/ Preferred Term	Total florbetaben experience N = 978 n (%)	Tracer mass dose > 10 µg N = 46 n (%)	Tracer mass dose ≤ 10 µg N = 932 n (%)	Vehicle N = 12 n (%)	Overall total N = 990 n (%)
Number of subjects with any TEAE	249 (25.5)	16 (34.8)	233 (25.0)	10 (83.3)	259 (26.2)
General disorders and administration site conditions					
Injection site erythema	12 (1.2)	0	12 (1.3)	0	12 (1.2)
Injection site hematoma	31 (3.2)	0	31 (3.3)	0	31 (3.1)
Injection site irritation	12 (1.2)	2 (4.3)	10 (1.1)	2 (16.7)	14 (1.4)
Injection site pain	37 (3.8)	8 (17.4)	29 (3.1)	4 (33.3)	41 (4.1)
Nervous system disorders					
Headache	23 (2.4)	1 (2.2)	22 (2.4)	1 (8.3)	24 (2.4)
Vascular disorders					
Hematoma	19 (1.9)	0	19 (2.0)	1 (8.3)	20 (2.0)

TEAE = treatment-emergent adverse event(s); N = number of subjects; n = number of subjects with TEAE/N
 For this integrated analysis, MedDRA version 14.1 was used.

Treatment-emergent adverse events (TEAEs) were further divided into drug-related adverse reactions and study conduct/procedure related adverse events by the applicant, as some of the treatment-emergent injection site reactions were considered study procedure related rather than study-drug related. Table 18 lists study drug-related TEAEs. Most of the study drug-related adverse events were injection site pain (37 florbetaben-administered and 4 vehicle-administered subjects), injection site irritation (12 florbetaben-administered and two vehicle-administered subjects), and headache (7 florbetaben-administered subjects).

Table 18: Number of subjects with study drug-related TEAEs by primary SOC and PT

System Organ Class Preferred Term	Total florbetaben experience N = 978 n (%)	Tracer mass dose > 10 µg/inj N = 46 n (%)	Tracer mass dose ≤ 10 µg/inj N = 932 n (%)	Vehicle N = 12 n (%)	Overall total N = 990 n (%)
Number of subjects with any drug-related TEAE	82 (8.4)	11 (23.9)	71 (7.6)	8 (66.7)	90 (9.1)
Gastrointestinal disorders					
Diarrhea	1 (0.1)	0	1 (0.1)	0	1 (0.1)
Nausea	1 (0.1)	0	1 (0.1)	0	1 (0.1)
General disorders and administration site conditions					
Application site erythema	2 (0.2)	0	2 (0.2)	0	2 (0.2)
Catheter site pain	1 (0.1)	0	1 (0.1)	0	1 (0.1)
Fatigue	1 (0.1)	0	1 (0.1)	0	1 (0.1)
Feeling hot	1 (0.1)	0	1 (0.1)	1 (8.3)	2 (0.2)
Injection site discomfort	2 (0.2)	1 (2.2)	1 (0.1)	1 (8.3)	3 (0.3)
Injection site erythema	1 (0.1)	0	1 (0.1)	0	1 (0.1)
Injection site hematoma	1 (0.1)	0	1 (0.1)	0	1 (0.1)
Injection site irritation	12 (1.2)	2 (4.3)	10 (1.1)	2 (16.7)	14 (1.4)
Injection site pain	37 (3.8)	8 (17.4)	29 (3.1)	4 (33.3)	41 (4.1)
Injection site warmth	1 (0.1)	0	1 (0.1)	0	1 (0.1)
Puncture site reaction	3 (0.3)	0	3 (0.3)	0	3 (0.3)
Pyrexia	1 (0.1)	0	1 (0.1)	0	1 (0.1)
Vessel puncture site pain	1 (0.1)	0	1 (0.1)	0	1 (0.1)
Hepatobiliary disorders					
Hepatic function abnormal	1 (0.1)	0	1 (0.1)	0	1 (0.1)
Investigations					
Blood creatinine increased	1 (0.1)	0	1 (0.1)	0	1 (0.1)
Musculoskeletal and connective tissue disorders					
Limb discomfort	1 (0.1)	0	1 (0.1)	0	1 (0.1)
Pain in extremity	1 (0.1)	0	1 (0.1)	0	1 (0.1)
Nervous system disorders					
Burning sensation	3 (0.3)	0	3 (0.3)	0	3 (0.3)
Headache	7 (0.7)	0	7 (0.8)	0	7 (0.7)
Neuralgia	1 (0.1)	0	1 (0.1)	0	1 (0.1)
Tremor	1 (0.1)	0	1 (0.1)	0	1 (0.1)
Skin and subcutaneous disorders					
Hyperhidrosis	1 (0.1)	0	1 (0.1)	0	1 (0.1)
Rash	1 (0.1)	0	1 (0.1)	0	1 (0.1)
Toxic skin eruption	1 (0.1)	0	1 (0.1)	0	1 (0.1)
Vascular disorders					
Flushing	1 (0.1)	0	1 (0.1)	0	1 (0.1)
Hematoma	1 (0.1)	0	1 (0.1)	0	1 (0.1)
Hypotension	1 (0.1)	0	1 (0.1)	0	1 (0.1)

N = number of subjects; n = number of subjects with TEAE/N; PT = preferred term; SOC = system organ class; TEAE = treatment-emergent adverse event(s)

8 Labeling Recommendations

1) The applicant proposes placing the following table in the package insert to state that PET imaging results (negative/positive) were pre-specified to correspond with a specific plaque score, based on modified CERAD criteria using plaque counts as a necessary pathological feature of AD (Table 19).

Table 19: Beta-Amyloid Plaque Counts^{a,b} Correlation to (b) (4) Image Results

(b) (4) Plaque Counts	CERAD Score	(b) (4) PET Image Result
<1	none	Negative
1 - 5	sparse	
6 - 19	moderate	Positive
20+	frequent	

Reviewer's comments: The reviewer recommends removing the above table from Package Insert.

Alternatively, the reviewer recommends adding separate columns of "neuritic plaques" and "diffuse amyloid plaques" in the table and deleting the cited reference (b) (4). Furthermore florbetaben has two pivotal studies, and the first pivotal study (14595) counted neuritic plaques, diffuse amyloid plaques, and vascular amyloid equally in determining the standard of truth. So the above table would need a third column for vascular amyloid, which does not have supported reference.

2) A Request for Waiver from conducting reproductive and toxicity studies was submitted by Bayer to IND 78,868 on 02 October 2012 [SN0095]. The FDA issued an Advice/Information Request letter on 29 October 2012 stating that the Waiver request was acceptable.

In the Request for Waiver, it was stated that (b) (4). However, Piramal Imaging has provided a draft version of the Prescribing Information which does not include this (b) (4). The rationale for this change is that, although it is unlikely that this product will be used in pregnant women, there may be situations in which the benefit outweighs the risk of use in pregnant women. Also, the previous proposal was based on theoretical risk, and not known hazards. Omission of such a contraindication is consistent with the product labeling of other PET imaging tracers in this class. Section 8.1 of the proposed Prescribing Information provides information for physicians regarding the use of this product during pregnancy (Pregnancy Category C).

Reviewer's comments: The reviewer finds Piramal's proposal acceptable.

9 Pediatric Research Equity Act (PREA) Requirements

The applicant requests full pediatric waiver (0-17 years of age). Florbetaben is indicated for detecting β -amyloid deposition in the brain, which is a condition that occurs almost exclusively in adults. Pediatric studies would be impossible or highly impractical. The reviewer recommends granting the applicant's request for full pediatric waiver.

Clinical Review
Brenda Ye
NDA 204677
Florbetaben

On July 10, 2013, the FDA Pediatric Research Committee (PeRC) discussed the application and agreed with granting a full pediatric waiver.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

BRENDA Q YE
08/23/2013

ALEXANDER GOROVETS
08/23/2013

The primary clinical review is complete. The conclusions of the secondary review will be reflected in the CDTL memo.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number:

Applicant: Piramal Life Sciences

Stamp Date: 12/21/2012

Drug Name: Florbetaben

NDA/BLA Type: NDA

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.				eCTD
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	x			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	x			Some of the clinical study reports lack Table of Tables and Table of Figures, which would hinder our review process.
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (e.g., are the bookmarks adequate)?	x			
5.	Are all documents submitted in English or are English translations provided when necessary?	x			
6.	Is the clinical section legible so that substantive review can begin?	x			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	x			Only a PDF version of the labeling is submitted. Will need to request MS Word version of the label
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (i.e., Module 2 summaries)?	x			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	x			It was agreed with FDA to split the ISE across Module 2 and Module 5 with the narrative portion located in Module 2.7.3 (Summary of Clinical Efficacy) and the appendices of tables, figures and datasets located in Module 5.3.5.3
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	x			It was agreed with FDA to split the ISS across Module 2 and Module 5 with the narrative portion located in Module 2.7.4 (Summary of

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	current worldwide knowledge regarding this product?				
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure ¹) been exposed at the dose (or dose range) believed to be efficacious?			x	Not chronically administered drug
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			x	Not chronically administered drug
23.	Has the applicant submitted the coding dictionary ² used for mapping investigator verbatim terms to preferred terms?				
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?			x	
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	x			
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			x	
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (e.g., label comprehension, self selection and/or actual use)?			x	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	x			Full pediatric waiver request submitted
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			x	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			x	Pivotal study is a multi-center, multi-national study and includes patients from the U.S. as well as patients from Europe, Australia, and Japan
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	x			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	x			

¹ For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

² The “coding dictionary” consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	x			
34.	Are all datasets to support the critical safety analyses available and complete?	x			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	x			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	x			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			x	No additional requests from the Division
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	x			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	x			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? ___ Yes ___

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

- 1) The Pivotal Phase 3 study 14595 appears to only have an interim clinical study report and an addendum of additional safety analysis only. Please provide the final clinical study report of the study and submit to the NDA as one complete report.
- 2) More than half of subjects included in the pivotal ‘pooled read’ study came from study 311741, yet the clinical study report of #311741 (A45264) lacks “Table of Tables” and “Table of Figures”. This significantly hinders our review process. Please revise the clinical study report A45264 to include “Table of Tables” and “Table of Figures” with electronic links to individual tables and figures and resubmit to the NDA.
- 3) Since more than half of subjects included in the pivotal ‘pooled read’ study came from study 311741, please submit clinical site information for study #311741 as you did for study 14595. Include pertinent information such as the number of subjects enrolled, completed, analyzed, and discontinued at each clinical site and the number of protocol violations at each clinical site.
- 4) Only a PDF version of the proposed labeling (package insert) is submitted with the NDA. Please submit both PDF and Word versions of the package insert, incorporating the FDA review team’s labeling comments on 1/18/2013 and at the Applicant Orientation Meeting on 2/4/2013.

Brenda Ye, M.D

2/18/2013

Reviewing Medical Officer

Date

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

Alex Gorovets, M.D.
Clinical Team Leader

2/18/2013
Date

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

BRENDA Q YE
02/18/2013

ALEXANDER GOROVETS
02/18/2013