CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204677Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology Review

NDA	204-677
Package Insert Revision	January 16, 2014, SDN 41
Major Amendment	December 11, 2013, SDN 38
Original NDA	December 21, 2012, SDN 1
Type/Category	Original-1 (Type 1 - New Molecular Entity)
Brand Name	Neuraceq
Generic Name	Florbetaben F 18 Injection
Proposed Indication	Florbetaben F 18 Injection is indicated for the detection of beta-amyloid in the brain, thereby assisting in the differential diagnosis in adult patients who are being evaluated for Alzheimer's disease (AD) or other causes of cognitive decline.
Dose	300 MBq (8.1 mCi); < 30 ug
Route of Administration	Intravenous Injection
Applicant	Piramal Imaging SA
Reviewing Division	Division of Clinical Pharmacology 5 (DCP 5)
Medical Division	Division of Medical Imaging Products (DMIP)
Primary Reviewer	Christy S. John, Ph.D.
Secondary Reviewer	Gene Williams, Ph.D.

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1. EXECUTIVE SUMMARY

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. On December 21, 2012 Piramal Imaging SA submitted an original 505(b)(1) New Drug Application (NDA 204677) for Neuraceq (florbetaben F 18 injection). The clinical pharmacology review was completed date, on August 22, 2013.

At that time, an FDA Complete Response (CR) action was anticipated because of the assessment by the clinical and statistical reviewers that the data in the original submission were not adequate to establish the effectiveness of florbetaben F 18. As a CR was anticipated, the clinical pharmacology review did not include recommendations for edits to the proposed package insert.

On November 22, 2013 the applicant submitted a clinical re-read study (same images as submitted in the original NDA, but read by different readers) to the NDA and requested that the submission be considered a major amendment. The submission was accepted as a major amendment. As a result of the study, an approval action is now anticipated, and the package insert will soon be negotiated. The current review documents clinical pharmacology's proposed edits for the package insert.

1.1. Recommendations

Our previous finding (review of Augst 22, 2013) that the application is acceptable, provided an agreement is reached in labeling, is unchanged.

1.2. Phase 4 Requirements and Commitments

See Clinical Pharmacology review in DARRTS submitted on August 22, 2013.

1.3. Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

See Clinical Pharmacology review in DARRTS submitted on August 22, 2013.

2. QUESTION BASED REVIEW

See clinical pharmacology review in DARRTS submitted on August 22, 2013.

3. DETAILED CLINICAL PHARMACOLOGY LABELING RECOMMENDATIONS

Edits to clinical pharmacology related portions of the proposed package insert appear on the next two pages of this review. To assure consistency and avoid potentially inaccurate distinctions that could be used promotionally, edits were made bearing in mind the package inserts for the two recently approved B-amyloid imaging agents (Amyvid and Vizamyl) that have similar indications. The entirety of the applicant's proposed package insert is appended to this review (Appendix 4.1).

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4. Appendices

4.1. Applicant's Proposed Package Insert (original, annotated)

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/s/

CHRISTY S JOHN
01/31/2014

GENE M WILLIAMS
01/31/2014

Clinical Pharmacology Review

NDA	204-677
Submission Dates	December 21, 2012 SDN 001 May 7, 2013 SDN 13
Type/Category	Original-1 (Type 1 - New Molecular Entity)
Brand Name	Neuraceq
Generic Name	Florbetaben F 18 Injection
Proposed Indication	Florbetaben F 18 Injection is indicated for the detection of beta-amyloid in the brain, thereby assisting in the differential diagnosis in adult patients who are being evaluated for Alzheimer's disease (AD) or other causes of cognitive decline.
Dose	300 MBq (8 mCi)
Route of Administration	Intravenous Injection
Applicant	Piramal Imaging SA
Reviewing Division	Division of Clinical Pharmacology 5 (DCP 5)
Medical Division	Division of Medical Imaging Products (DMIP)
Primary Reviewer	Christy S. John, Ph.D.
Secondary Reviewer	Gene Williams, Ph.D.

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1. Executive Summary

The applicant, Piramal Imaging SA, has submitted NDA (204-677) for Florbetaben F18 Injection as a diagnostic PET (Positron Emission Tomography) imaging agent indicated for [redacted] (b) (4)

The pivotal trial, Study 14595, was performed in end-of-life patients with probable Alzheimers Disease (AD). Post mortem brain biopsy was the Standard of Truth (SoT) to identify beta amyloid. The basis of the NDA is an interim analysis of efficacy conducted after brain autopsy from 32 patients were available. The success criteria for the co-primary endpoints of the study were to show that the sensitivity was higher than the pre-specified threshold of 60% and that the specificity was higher than the pre-specified threshold of 80%. As both thresholds were exceeded by the lower bounds of the respective 95% CI, the co-primary endpoints of the study were met. However, the individual reads (in a pooled read analysis for five readers, Study 16034) by individual nuclear medicine physicians showed that physicians failed to read the images correctly with respect to specificity. The combined null hypothesis that sensitivity is smaller or equal to 0.6 and specificity is smaller or equal to 0.7 could only be rejected for 1 out of the 5 readers. Thus, the study's goal of rejecting this hypothesis for at least 4 out of the 5 readers was not met for specificity.

The primary endpoints for efficacy studies relied on visual read of images. Clinical pharmacology review includes a comparison of visual read results to automated reading (standard uptake value ratio, SUVR). It appears that SUVR offers an improvement to the reading of Florbetaben F 18 images. If future studies are performed, formalizing the use of SUVR in the protocols is recommended.

A dose of 300 MBq was selected for all efficacy and safety studies. This dose was selected based on i) results of dosimetry studies confirming that organ radiation is within accepted limits at the proposed radioactivity dose, ii) adequate diagnostic performance of the allowable radioactivity dose, and iii) theoretical grounds. Dose finding is judged acceptable.

The analysis set for pharmacokinetics included healthy volunteers, Alzheimer's Disease (AD) patients and frontotemporal lobe dementia (FTLD) patients. Dose-adjusted C_{MAX} and AUC in all three groups were comparable. Uptake of radioactivity in the brain is rapid, reaching about 6% of injected 18F-radioactivity at 10 minutes post injection. Florbetaben is eliminated from plasma with a mean half-life of about 1 h. No radioactivity could be measured in blood at about 4 hours post injection. Florbetaben F 18 was metabolized to 4 major radioactive metabolites. Only 6% of the radioactivity in plasma 60 minutes after injection was unchanged parent compound. Based on *in vitro* investigations, florbetaben is metabolized by several CYP enzymes with significant contributions by the CYP2J2, 3A4, and 4F families. By 12 hours post-injection, up to approximately 30% of the injected radioactivity (decay corrected total activity excreted, physical half-life of F 18 is about 2 hours) has been excreted in urine.

Mild and moderate renal impairment did not appear to influence the efficacy of florbetaben and no dose adjustment in patients with renal impairment is recommended. The effect of hepatic impairment was not studied. Pharmacokinetics of florbetaben were similar between healthy Caucasian and Japanese subjects.

1.1. Recommendations

The Office of Clinical Pharmacology, Division of Clinical Pharmacology 5, has reviewed the submission NDA 204-677. The application is acceptable from a clinical pharmacology standpoint, provided an agreement is reached in labeling.

1.2. Phase 4 Requirements and Commitments

We have no recommendations for post-marketing requirements or commitments. If future studies or re-analyses are performed, we recommend formalizing the use of automated reading (SUVR) in the re-analysis plans or protocols.

1.3. Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

The primary endpoints for efficacy studies relied on visual read of images. Clinical pharmacology review include a comparison of visual read results to automated reading (standard uptake value ratio, SUVR). SUV is the ratio of (1) the tissue radioactivity concentration c (e.g. in MBq/kg = kBq/g) at time point t, and (2) the injected activity (e.g. in MBq, extrapolated to the same time t) divided by the body weight (e.g. in kg). SUVR is the ratio of SUV in a region of interest (in the current case, a cortical region) as compared to a reference region (in the current case, cerebellum). It appears that SUVR can improve the reading of Florbetaben F 18 images. If future studies are performed, formalizing the use of SUVR in the protocols is recommended.

A dose of 300 MBq was selected for all efficacy and safety studies. This dose was selected based on i) results of dosimetry studies confirming that organ radiation is within accepted limits at the proposed radioactivity dose, ii) adequate diagnostic performance of the allowable radioactivity dose, and iii) theoretical grounds. Dose finding is judged acceptable.

Using the specification for minimal specific activity, the 300 MBq dose will result in a mass dose of < 30 ug. (b) (4) . The potential influence of different mass doses on safety and efficacy was investigated in three different Phase I studies, two studies in Caucasians and one in Japanese. The low mass doses ranged from 0.2 – 3.2 µg and the high mass doses from 50 to 55 µg. No differences were observed with respect to efficacy and pharmacokinetics across the ranges.

The applicant conducted a total of four dosimetry studies. The estimates of effective doses using the FDA approved software program OLINDA and an administration of 300 MBq (8.1 mCi) yielded effective doses ranging from 4.4 mSv to 6.2 mSv. This radiation exposure is similar to other approved PET F 18 labeled drugs such as FDG F 18 and Amyvid F 18. The radiation doses

delivered to the critical organs, gall bladder, , upper large intestine wall and liver are, respectively, 41 mSv, 21 mSv, 12 mSv and 12 mSv.

The analysis set for pharmacokinetics included healthy volunteers, Alzheimer's Disease (AD) patients and frontotemporal lobe dementia (FTLD) patients. Dose-adjusted C_{MAX} and AUC in all three groups were comparable. Uptake of radioactivity in the brain is rapid, reaching about 6% of injected 18F-radioactivity at 10 minutes post injection. Florbetaben is eliminated from plasma with a mean half-life of about 1 h. No radioactivity could be measured in blood at about 4 hours post injection. Florbetaben F 18 was metabolized to 4 major radioactive metabolites. Only 6% of the radioactivity in plasma 60 minutes after injection was unchanged parent compound. Based on *in vitro* investigations, florbetaben is metabolized by several CYP enzymes with significant contributions by the CYP2J2, 3A4, and 4F families. By 12 hours post-injection, up to approximately 30% of the injected radioactivity (decay corrected total activity excreted, physical half-life of F 18 is about 2 hours) has been excreted in urine.

Mild and moderate renal impairment did not influence the efficacy of florbetaben and no dose adjustment in patients with renal impairment is recommended. The effect of hepatic impairment was not studied. Pharmacokinetics of florbetaben were similar between healthy Caucasian and Japanese subjects.

Pharmacogenetic analysis was undertaken in a hypothesis-generating genetic sub-study to investigate the association between the apolipoprotein-E (*APOE*) genotype and florbetaben PET scan results in subjects with low probability of cerebral β-amyloid deposition [i.e., non-demented (NDV) healthy volunteers (HV)] and in subjects with high probability of cerebral β-amyloid deposition (e.g., subjects diagnosed with AD or Dementia with Lewy bodies (DLB)]. The sub-study showed a correlation between the *APOE* genotype pattern and β-amyloid deposition as determined by florbetaben cerebral uptake pattern in subjects with β-amyloid plaques detected by postmortem histopathology.

2. Question Based Review

2.1. What *In Vitro* and *In Vivo* Clinical Pharmacology and Biopharmaceutics studies and Clinical Studies contributed PK and/or PD information to the application?

Dosimetry studies reflect the radiation exposure and biodistribution of the radiopharmaceutical to different organs. The reviewer considers dosimetry studies as a part of clinical pharmacology studies and therefore contribute to clinical pharmacology review. Thus dosimetry and pharmacokinetics studies (Study Reports A42404, A35694, A 40922, A42441) and pharmacodynamics cross-over study (A41147) have formed the basis of this review. These studies are copied from the submission and shown in **FDA Table 1.** A total of ten studies were conducted under the Sponsor's florbetaben clinical development program. In three studies investigating healthy Caucasian subjects and healthy Japanese subjects , PK and dosimetry was studied. The efficacy evaluations from studies supporting the use of florbetaben for the detection of β-amyloid in the brain of individuals with dementia are discussed in this section.

- The first-in-human proof-of-mechanism investigator-sponsored Melbourne study (Study Report A42404; no Study number was given)

- The proof-of-mechanism Leipzig study (Study 310863)
- Four additional Phase 1 studies (Studies 91790, 311722, 312161, and 312043)
- Two supportive Phase 2 studies (Studies 14311 and 311741)
- One pivotal Phase 3 study (Study 14595)
- One pivotal Non-Interventional 'Pooled read study' (Study 16034)

FDA Table 1. Table of Clinical Studies

Type of Study Clinical Phase	Study No. Report No.	Objective(s) of the Study	Study Design and Type of Control	Test Product(s) Radioactive Dose Mass Dose Specification	Numbers of Subjects	Healthy Subjects or Diagnosis of Patients	Study Status Type of Report
Proof of Mechanism /Phase 1 ISS study	No study # available A42404	Safety, Dosimetry, Efficacy in HV and dementia patients	Single center, open label pilot study	Drug product florbetaben 300 MBq ≤5 µg	60	19 HV 15 AD 11 FTLD 6 DLB 5 PD 4 VaD	Ongoing Integrated report
Proof of Mechanism / Phase 1	#310863 A35694	Safety, Dosimetry, Efficacy in HV and dementia patients	Single center, open label, non-randomized	Drug product florbetaben 300 MBq ≤5 µg	28	14 HV 10 AD 4 FTLD	Complete Full
Dosimetry study in healthy volunteers/ Phase 1	#311722 A40922	Dosimetry, Safety Pharmacokinetics and cerebral uptake	Single center, placebo-controlled, randomized	Drug product florbetaben 300 MBq ≤ 5 µg and 50-55* µg	24	24 HV	Complete Full

*fixed mass dose (spiked)

Type of Study Clinical Phase	Study No. Report No.	Objective(s) of the Study	Study Design and Type of Control	Test Product(s) Radioactive Dose Mass Dose Specification	Numbers of Subjects	Healthy Subjects or Diagnosis of Patients	Study Status Type of Report
Dosimetry study in healthy volunteers/ Phase 1	#91790 A42441	Dosimetry, Safety Pharmacokinetics and cerebral uptake	Single center, placebo-controlled, randomized	Drug product florbetaben 300 MBq ≤5 µg and 50-55* µg respectively	24	24 HV	Complete Full
Pharmaco-dynamic cross over Phase 1 study	#312161 A41147	To show comparability of visual evaluation of PET images with a low and a high tracer mass dose	Single-blinded, single-centre, cross-over study	Drug product florbetaben 250 MBq ≤5 µg and 50-55* µg respectively	16	8 HV 8 AD	Complete Full
Phase 1	#312043 A50622	Investigate the ability to distinguish patients with MCI progressing to AD from those with MCI not progressing to AD	Open-label, single-center, non-randomized study	Drug product florbetaben 300 MBq ≤5 µg	45	45 MCI	Complete Full

*fixed mass dose (spiked)

Type of Study Clinical Phase	Study No. Report No.	Objective(s) of the Study	Study Design and Type of Control	Test Product(s) Radioactive Dose Mass Dose Specification	Numbers of Subjects	Healthy Subjects or Diagnosis of Patients	Study Status Type of Report	Location of Study Report
Efficacy and safety Phase 2 study	#311741 A45264	To determine the sensitivity and specificity of the independent visual assessment of the florbetaben PET images	Open-label, multi-center, non-randomized single dose study	Drug product florbetaben 300 MBq Part A ≤5 µg Part B ≤50 µg	422	Part A: 69 HV, 81 AD Part B: 125 HV, 147 AD	Complete Full	5.3.5.2
Efficacy and safety study Phase 2	#14311 A51672	To determine the sensitivity and specificity of the independent visual assessment of the florbetaben PET images	Open-label, single-center, non-randomized single dose study	Drug product florbetaben 300 MBq ≤5 µg	109	39 with DS 70 young HV	Complete Full	5.3.5.2

Type of Study Clinical Phase	Study No. Report No.	Objective(s) of the Study	Study Design and Type of Control	Test Product(s) Radioactive Dose Mass Dose Specification	Numbers of Subjects	Healthy Subjects or Diagnosis of Patients	Study Status Type of Report	Location of Study Report
Pivotal Efficacy and safety Phase 3	#14595 A47592 and PH-36927 (Safety addendum)	To determine the sensitivity and specificity of the independent visual assessment of the florbetaben PET images compared to post mortem histopathology	Open-label, multi-center, non-randomized single dose study	Drug product florbetaben 300 MBq ≤50 µg	216	137 AD, 31 other dementia, 5 DLB, 32 NDV, 11 HV	Complete for primary analysis, ongoing for follow-up Full	5.3.5.1
Confirmatory pooled read analysis	#16034 PH-36928	To assess the reproducibility of the visual assessment of florbetaben PET scans in a clinical situation that mimics the "future use" situation in terms of patient population and training methodology.	A non-interventional study Images from clinical studies Phase 1, 2 and 3 will be visually assessed by five blinded readers	Not applicable,	PET images from 462 cases will be pooled and randomly assigned for blinded visual assessment by three independent blinded readers.	12 FTLD, 10 DLB, 5 PD, 4 VascD, 4 other Dementia 51 MCI, 182 AD 188 HV/NDV 6 Other diagnoses	Complete Full	5.3.5.1

AD = Alzheimer's disease; HV = healthy volunteers; MCI = mild cognitive impairment; DLB = Dementive-Levy bodies; FTLD = frontal temporal lobular dementia; PD = Parkinson's disease; NDV=Subjects with a low probability of cerebral β-amyloid deposition (non-demented volunteers) PET = positron emission tomography; ISS = Investigator-Sponsored Study

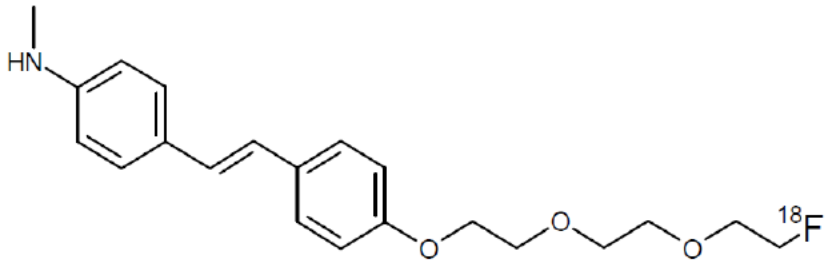
2.2. General Attributes of the Drug

2.2.1. What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product?

Florbetaben F 18 (BAY 94-9172, ZK 6013443), an [^{18}F]-labeled polyethylene glycol stilbene derivative, is 4-(N-methyl-amino)-4'-{2-[2-(2-[18F]-fluoro-ethoxy)-ethoxy]-ethoxy}-stilbene. The structural formula, molecular formula and molecular weight are presented in **FDA Figure 1.**

FDA Figure 1. Florbetaben F 18

Structural formula



Molecular formula $C_{21}H_{26}{}^{18}F\,NO_3$

Relative molecular weight 358.45

2.2.2. What are the proposed mechanism of action and therapeutic indications?

The following (indented) is reproduced from the package insert.

> "Florbetaben (18F) is a (18F)-labeled stilbene derivative, which binds (b) (4) to beta-amyloid (b) (4) in the brain. (b) (4) Florbetaben (18F) does not bind to tau and α-synuclei (b) (4) ."

The proposed indication is "… (b) (4) "

2.2.3. What are the proposed dosages and routes of administration?

(b) (4)

The recommended dose of NEURACEQ is 300 MBq (8.1 mCi) administered as a single slow intravenous bolus in a total volume of up to 10 mL. Inspect the radiopharmaceutical dose solution prior to administration and do not use it if it contains particulate matter. Use aseptic technique and radiation shielding to withdraw NEURACEQ solution. The activity of NEURACEQ has to be measured with calibrator immediately prior to injection.

NEURACEQ should be administered without dilution. The injection must be intravenous in order to avoid irradiation as a result of local extravasation, as well as imaging artifacts. Thus, patency of the indwelling catheter should be verified by a saline test injection prior to administration of drug product.

An injection (1 mL/6 sec) into a large vein in the arm is recommended, followed by a saline flush of approximately 10 mL.

(b) (4)

Using the specification for specific activity of the commercial formulation the mass dose will be below 30 μg.

2.2.4 What is the radiation absorbed dose associated with the proposed dose of Florbetaben F 18 Injection?

The applicant conducted a total of four dosimetry studies. The estimates of effective doses using the FDA approved software program OLINDA and an administration of 300 MBq (8.1 mCi) yielded effective doses ranging from 4.4 mSv to 6.2 mSv. This radiation exposure is similar to other approved PET F 18 labeled drugs such as FDG F 18 and Amyvid F 18. The radiation doses delivered to the critical organs, gall bladder, upper large intestine wall and liver are, respectively, 41 mSv, 21 mSv, 12 mSv and 12 mSv.

2.2.4. What drugs (substances, products) indicated for the same indication are approved in the US?

The first beta amyloid imaging agent, (Amyvid), was approved in 2012. The following indication (indented) is reproduced from the Amyvid package insert.

> Amyvid is indicated for Positron Emission Tomography (PET) imaging of the brain to estimate β-amyloid neuritic plaque density in adult patients with cognitive impairment who are being evaluated for Alzheimer's Disease (AD) and other causes of cognitive decline. A negative Amyvid scan indicates sparse to no neuritic plaques and is inconsistent with a neuropathological diagnosis of AD at the time of image acquisition; a negative scan result reduces the likelihood that a patient's cognitive impairment is due to AD. A positive Amyvid scan indicates moderate to frequent amyloid neuritic plaques; neuropathological examination has shown this amount of amyloid neuritic plaque is present in patients with AD, but may also be present in patients with other types of neurologic conditions as well as older people with normal cognition. Amyvid is an adjunct to other diagnostic evaluations.
>
> Limitations of Use:
>
> • A positive Amyvid scan does not establish a diagnosis of AD or other cognitive disorder.

- Safety and effectiveness of Amyvid have not been established for:
  - Predicting development of dementia or other neurologic condition;
  - Monitoring responses to therapies.

2.3. General Clinical Pharmacology

2.3.1. What are the design features of the clinical pharmacology and biopharmaceutics studies and the clinical studies used to support dosing or claims?

A total of ten studies were conducted under the Sponsor's florbetaben clinical development program (see **FDA Table 1.**).

One pivotal trial and a pooled read analysis using data from multiple studies were used to support efficacy, and thus the dosing claim. The path to arriving at the Phase 3 dose is presented in Section **2.4.1**.

The pivotal clinical trial, Study 14595, was an open-label, non-randomized study to evaluate the efficacy and safety of Florbetaben F 18 positron emission tomography (PET) imaging for detection/exclusion of cerebral β-amyloid when compared to postmortem histopathology. The primary objective of this trial was to determine the sensitivity and specificity of the visual assessment of regional tracer uptake in the florbetaben PET images compared to histological verification of the presence or absence of cerebral β-amyloid in the respective postmortem specimens as the standard of truth (SoT).

In Study 14595, each subject received a single IV injection of the study drug and scanning was performed from 90 to 110 minutes post-injection. A total of 200 patients were planned to be studied. The study has yet to complete, the NDA contains an interim analysis of efficacy which was conducted after brain autopsy from 32 patients were available.

The co-primary efficacy variables were evaluated using majority results of the 3 independent blinded readers. This majority read value was determined based on the match to the SoT. If at least 2 readers matched the SoT, the majority reader response was considered a match. The 95% confidence intervals (CI) were calculated for the majority read and for each blinded reader separately. Readers received of in-person training prior to reading the scans.

The co-primary efficacy variables for this study were the sensitivity and specificity of the visual assessment of regional tracer uptake in the florbetaben PET images in correctly differentiating between brain regions with and without β-amyloid deposition. 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 hypothesis for this study that sensitivity is ≤ 60% or specificity is ≤ 80% was rejected. However, the individual reads (in a pooled read analysis for five readers, Study 16034) by individual nuclear medicine physicians showed that physicians failed to read the images correctly with respect to specificity. The combined null hypothesis that sensitivity is smaller or equal to 0.6 and specificity is smaller or equal to 0.7 could only be rejected for 1 out of the 5 readers. Thus, the study's goal of rejecting this hypothesis for at least 4 out of the 5 readers was not met for specificity

The pooled read analysis (designated Study 16034, but consisting only of patients from already completed studies) assessed the reliability, reproducibility and efficacy of the florbetaben β-amyloid PET scan visual assessments after readers completed a computer-(Web)-based training. The primary objective of this study was to assess the reproducibility of the visual assessment of PET scans from a patient population that closely represents the "future use" population via assessing the inter-reader agreement of the visual assessment results of 461 florbetaben PET scans pooled from various florbetaben clinical studies. The sensitivity and specificity data to detect β-amyloid on a subject level with histopathology as the SoT using PET scan images from 55 autopsy cases were enriched with the images of 10 healthy volunteers from Study 14595.

FDA Table 2. presents the results of Study 16034.The sensitivity for each of the five blinded readers ranged from 77-90% (95% CI ranged from 64.56-99.30). The specificity ranged from 62.5-91.67% (95% confidence interval ranged 43.13-100%) for five blinded readers. As the specificity estimates were only based on 24 subjects, the estimates were not very precise, which is reflected in the wide CI. The combined null hypothesis that sensitivity is smaller or equal to 0.6 and specificity is smaller or equal to 0.7 could only be rejected for 1 out of the 5 readers. Thus, the study's goal of rejecting this hypothesis for at least 4 out of the 5 readers was not met for specificity.

FDA Table 2. Sensitivity and specificity of the visual assessment (Sponsor's analysis) of Florbetaben F 18 PET scans compared to histopathology as SoT (Study 16034)

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	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	100.00

PET = positron emission tomography; SoT = Standard of Truth; 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 includes 10 HVs without autopsy for whom β-amyloid pathology in the brain was assumed negative by default.
Source: Module 5.3.5.1, PH-36928, Table 14.1.2/2

This reviewer sent out an information request on April 13, 2013 to ask the applicant to compare the results Study 14595 (visual reads performed after in-person training) and Study 16034 (visual reads performed after electronic media training) to automated reading (standard uptake value ratio, SUVR). SUV is the ratio of (1) the tissue radioactivity concentration c (e.g. in MBq/kg = kBq/g) at time point t, and (2) the injected activity (e.g. in MBq, extrapolated to the same time t) divided by the body weight (e.g. in kg). SUVR is the ratio of SUV in a region of interest (in the current case, a cortical region) as compared to a reference region (in the current case, cerebellum).

Results from the requested analysis are presented in **FDA Table 3.** In interpreting the table, emphasis should be placed upon specificity rather than sensitivity or accuracy, as the package insert indication is for ruling out the presence of B-amyloid, not for detecting it or accurately assessing it. The SUVR results show that automated reading is superior to either of the visual read methods: the

specificity of composite SUVR (90.3%) exceeded that of visual read for 7 of 8 readers, and equaled that of the eighth reader.

FDA Table 3. Individual Results by Scan Interpretation Method

Test Performance (n= 64)[a]	Composite SUVR (Cut-off 1.47)	In-Person Training (Histopathology Study 14595)			Electronic Media Training (Pooled Read Study 16034)				
		Reader			Reader				
		1	2	3	1	2	3	4	5
Sensitivity (%)	**90.9**	**100.0**	**100.0**	**100.0**	**100.0**	**100.0**	**100.0**	**97.0**	**87.9**
95% CI	81.1-100.0	100.0-100.0	100.0-100.0	100.0-100.0	100.0-100.0	100.0-100.0	100.0-100.0	91.1-100.0	76.7-99.0
Specificity (%)	**90.3**	**90.3**	**87.1**	**83.9**	**77.4**	**61.3**	**74.2**	**74.2**	**87.1**
95% CI	79.9-100.0	79.9-100.0	75.3-98.9	70.9-96.8	62.7-92.1	44.1-78.44	58.8-89.6	58.8-89.6	75.3-98.9
Accuracy (%)	**90.6**	**95.3**	**93.8**	**92.2**	**89.1**	**81.3**	**87.5**	**85.9**	**87.5**

[a] 54 autopsied patients and 10 HVs, SoT: subject-level onsite histopathology based on CERAD criteria; CI: normal approximated confidence interval

It appears that SUVR can improve the reading of Florbetaben F 18 images. If future studies are performed, formalizing the use of SUVR in the protocols is recommended.

2.3.2. What is the basis for selecting the response endpoints and how are they measured in clinical pharmacology studies?

There were no stand alone clinical pharmacology studies. The non-imaging clinical pharmacology related endpoints measured were radiation throughout the body (i.e., dosimetry), urinary excretion of radioactivity, and QT-interval.

2.3.3. Are the active moieties in plasma and clinically relevant tissues appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Only parent drug is reported in PK studies. Metabolites are present, but their activity was not assessed directly. The applicant argues, and the reviewer concurs, that the early eluting metabolite peaks were unlikely to represent an active moiety, as they are polar compounds and unlikely to penetrate the blood-brain barrier. The late eluting peak, which represented much lower radioactivity than the parent, was not followed and could be that of an active metabolite.

2.4. Exposure-Response

2.4.1. What are the characteristics of the exposure-response relationship for effectiveness?

2.4.2. What are the characteristics of the exposure-response relationships for safety?

A dose of 300 MBq was selected. This dose was selected based on i) results of dosimetry studies confirming that organ radiation is within accepted limits at the proposed radioactivity dose, ii) adequate diagnostic performance of the allowable radioactivity dose, and iii) theoretical grounds.

Prior to administering doses that were likely to allow brain imaging, two dose cohorts received doses for the purpose of assuring a lack of pharmacologic effect. The anticipated dose based on extrapolation from mouse bio-distribution data and human imaging data for other B-amyloid binding agents was 300 MBq. The first dose examined was 0.01X (3 MBq), no pharmacological effects occurred; brain imaging was not conducted. The subsequent dose examined was 0.1X (30MBq) no pharmacological effects occurred; brain imaging was not conducted. The third dose examined was 300 MBq. The resulting effective dose was 4.2 mSv. Doses higher than 300 MBq were not studied because there was a desire to maintain an effective dose lower than 8 mSv due to international limits on subject radiation exposure. The brain imaging results using 300 MBq were judged satisfactory. Simulation of dose of 150 MBq and 450 MBq were performed. The 150 Mbq dose was judged to be likely inadequate, and the 450 MBq dose appeared to result in limited improvement over the 300 MBq dose. The 300 MBq dose was carried forward for all subsequent studies. Using the specification for minimal specific activity, the 300 MBq dose will result in a mass dose of $\leq$ 30 ug.

The timing of image acquisition was not investigated – images were collected for a 30 minute period, beginning at 90 minutes post-injection, throughout development.

Dose finding is judged acceptable.

2.4.3. Does this drug prolong QT/QTc Interval?

The mean changes observed in QT_C are shown **FDA Table 4**. It appears that florbetaben administration causes a slight (< 7 msec) average increase in QT_C. The number of subjects who had QT_C changes greater than the applicant's pre-specified values of 30 msec and 60 msec are shown in **FDA Table 5**. For this single administration drug, the reviewer judges the observed changes as clinically insignificant.

FDA Table 4. Fridericia Corrected QT intervals from baseline

Table 4-4: Corrected QT interval (via Fridericia's formula) change from baseline by time

			Value at visit (ms)		Change from baseline (ms)		
	Time interval	N	Mean (SD)	Median (min, max)	N	Mean (SD)	Median (min, max)
Total subject population							
Total florbetaben experience	Baseline	617	399.8 (22.55)	397.0 (337, 498)			
	> 0 - 15 minutes	538	401.3 (23.14)	399.0 (348, 492)	538	0.5 (13.03)	1.0 (-48, 98)
	> 15 - 30 minutes	360	405.0 (22.41)	402.0 (340, 482)	360	4.6 (12.00)	4.0 (-35, 102)
	> 30 - 60 minutes	139	403.7 (21.78)	406.0 (352, 463)	138	3.5 (11.71)	4.0 (-29, 31)
	> 1 - 3 hr	612	404.6 (22.09)	404.0 (347, 489)	610	4.8 (13.02)	5.0 (-46, 57)
	> 3 - 20 hr	36	404.2 (15.08)	401.8 (362, 441)	36	7.0 (10.62)	7.0 (-22, 28)
	> 20 hr - 2 days	589	397.8 (21.81)	396.0 (332, 478)	588	-2.5 (15.43)	-2.0 (-72, 78)
	2 - 3 days	36	397.2 (16.08)	396.5 (360, 434)	36	-0.1 (17.91)	0 (-73, 46)
	> 3 - ≤ 9 days	80	394.8 (15.93)	391.0 (367, 453)	79	0.7 (10.93)	1.0 (-22, 32)
Tracer mass dose > 10 µg/inj	Baseline	42	394.0 (14.56)	391.0 (365, 431)			
	> 0 - 15 minutes	24	393.2 (17.39)	390.0 (354, 428)	24	-0.1 (11.61)	-0.5 (-33, 25)
	> 15 - 30 minutes	18	399.7 (14.78)	398.5 (378, 427)	18	4.1 (8.52)	2.0 (-9, 24)
	> 30 - 60 minutes	-	-	-	-	-	-
	> 1 - 3 hr	42	399.5 (20.61)	395.0 (367, 445)	42	5.5 (13.98)	5.5 (-30, 43)
	> 3 - 20 hr	18	402.0 (16.47)	401.3 (362, 439)	18	7.1 (12.31)	7.8 (-22, 27)
	> 20 hr - 2 days	42	394.3 (17.00)	390.5 (369, 434)	42	0.3 (11.78)	-0.5 (-37, 30)
	2 - 3 days	18	395.8 (17.58)	395.5 (372, 434)	18	0.9 (14.00)	-1.0 (-18, 46)
	> 3 - ≤ 9 days	26	390.8 (16.07)	389.0 (367, 426)	26	-3.0 (11.54)	-4.5 (-22, 22)
Tracer mass dose ≤ 10 µg/inj	Baseline	575	400.3 (22.97)	397.0 (337, 498)			
	> 0 - 15 minutes	514	401.6 (23.32)	400.0 (348, 492)	514	0.6 (13.10)	1.0 (-48, 98)
	> 15 - 30 minutes	342	405.3 (22.72)	403.0 (340, 482)	342	4.6 (12.17)	4.0 (-35, 102)
	> 30 - 60 minutes	139	403.7 (21.78)	406.0 (352, 463)	138	3.5 (11.71)	4.0 (-29, 31)
	> 1 - 3 hr	570	405.0 (22.16)	405.0 (347, 489)	568	4.8 (12.96)	4.5 (-46, 57)
	> 3 - 20 hr	18	406.4 (13.66)	403.3 (388, 441)	18	6.9 (8.98)	7.0 (-9, 28)
	> 20 hr - 2 days	547	398.0 (22.13)	396.0 (332,478)	546	-2.7 (15.67)	-2.0 (-72, 78)
	2 - 3 days	18	398.5 (14.81)	398.5 (360, 424)	18	-1.1 (21.50)	0 (-73, 24)
	> 3 - ≤ 9 days	54	396.7 (15.65)	392.5 (371, 453)	53	2.5 (10.25)	2.0 (-16, 32)

(Continued)

Table 4-4 (Continued): Corrected QT interval (via Fridericia's formula) change from baseline by time

			Value at visit (ms)		Change from baseline (ms)		
	Time interval	N	Mean (SD)	Median (min, max)	N	Mean (SD)	Median (min, max)
Vehicle	Baseline	12	395.8 (20.85)	394.5 (360, 436)			
	> 0 - 15 minutes	-	-	-	-	-	-
	> 15 - 30 minutes	-	-	-	-	-	-
	> 30 - 60 minutes	-	-	-	-	-	-
	> 1 - 3 hr	12	401.1 (17.70)	399.0 (366, 426)	12	5.3 (13.31)	8.0 (-12, 24)
	> 3 - 20 hr	12	398.4 (18.60)	399.3 (358, 420)	12	2.7 (10.47)	4.0 (-17, 14)
	> 20 hr - 2 days	11	400.4 (18.83)	402.0 (376, 437)	11	1.4 (12.77)	1.0 (-20, 28)
	2 - 3 days	11	397.5 (17.51)	401.0 (375, 427)	11	-1.5 (10.60)	-4.0 (-20, 21)
	> 3 - ≤ 9 days	12	397.1 (20.05)	396.5 (360, 429)	12	1.3 (12.40)	1.5 (-22, 26)

hr = hour(s); inj = injection; N = number of subjects; min, max = minimum, maximum; ms = milliseconds; SD = Standard deviation
Values presented as n (%). If a subject had several values within a time window, the mean value was used. Calculation of changes from baseline was based on those subjects who had a baseline value and a value for the respective time point
Source: Module 5.3.5.3, Integrated Safety Analysis Part 3, Table 3.5.5.

FDA Table 5. Subjects with pre-specified increases in absolute QTcF from basline

Table 4-6:Subjects with pre-specified increases in absolute QT_cF interval from baseline

Time interval	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 (%)	Total N = 990 n (%)
Total -					
> 0 to 15 min., N	539	24	515	0	539
> 30 - 60 ms	8 (1.5)	0	8 (1.6)	0	8 (1.5)
> 60 ms	1 (0.2)	0	1 (0.2)	0	1 (0.2)
> 15 to 30 min., N	365	18	347	0	365
> 30 - 60 ms	5 (1.4)	0	5 (1.4)	0	5 (1.4)
> 60 ms	1 (0.3)	0	1 (0.3)	0	1 (0.3)
> 30 to 60 min., N	141	0	141	0	141
> 30 - 60 ms	1 (0.7)	0	1 (0.7)	0	1 (0.7)
> 60 ms	0	0	0	0	0
> 1 to 3 hrs., N	616	42	574	12	628
> 30 - 60 ms	11 (1.8)	2 (4.8)	9 (1.6)	0	11 (1.8)
> 60 ms	0	0	0	0	0
> 3 to 20 hrs., N	36	18	18	12	48
> 30 - 60 ms	0	0	0	0	0
> 60 ms	0	0	0	0	0
> 20 hr to <2 days,N	596	42	554	12	608
> 30 - 60 ms	10 (1.7)	0	10 (1.8)	0	10 (1.6)
> 60 ms	1 (0.2)	0	1 (0.2)	0	1 (0.2)
2 to 3 days, N	36	18	18	12	48
30 - 60 ms	1 (2.8)	1 (5.6)	0	0	1 (2.1)
> 60 ms	0	0	0	0	0
> 3 to ≤ 9 days, N	80	26	54	12	92
> 30 - 60 ms	1 (1.3)	0	1 (1.9)	0	1 (1.1)
> 60 ms	0	0	0	0	0

inj = injection; ms = milliseconds; N = number of subjects; n -= number of subjects with event/N. Calculation of changes from baseline was based on those subjects who had a baseline value and a value for the respective time point. In case a subject had several values within a time window, the mean value was used. No QT_cF increase was calculated for unscheduled visits, as it was unknown whether they were taken post-baseline.

Source: Module 5.3.5.3, Integrated Safety Analysis Part 3, Table 3.5.13.

2.4.4. Is the dose and dosing regimen selected consistent with the known E-R relationship?

Based upon the route to dose selection, the selected dose is likely As Low As Reasonably Achievable (ALARA). No additional exposure-response relationship was determined for this single administration drug given as microdose.

2.5. Pharmacokinetics

2.5.1. What are the single and multiple dose PK parameters of parent drug and relevant metabolites in healthy adults?

2.5.2. How does the PK of the drug and its relevant metabolites in healthy adults compare to that in patients with the target disease?

2.5.3. What are the inter- and intra-subject variability of the PK parameters in volunteers and patients with the target disease?

PK parameters were determined following single dose administration, only. This is not problematic, as Florbetaben F 18 will be administered only once per patient. The PK results are shown in **FDA Table 6**. A separation method (HPLC) was used prior to measurement, and radioactivity, not mass, was measured. The peak with the retention time of the parent was quantitated. The values in the table are derived by assuming that the administered specific activity (i.e., the ratio of radioactive to cold drug) was maintained in the body.

FDA Table 6. Mean pharmacokinetic parameters of Florbetaben F 18 after single intravenous injection of 300 MBq to patients and healthy volunteers.

Parameter	Patient cohort AD (N=10)	FTLD (N=3)	HV (N=11)
C_{max} (pmol/L)	322 (41.6%)	171 (24.4%)	514 (76.8%)
t_{max} (h)	0.0289 (0.0161 – 0.05)	0.0225 (0.0203 – 0.0342)	0.0331 (0.0150 – 0.0400)
AUC (pmol·h/L)	21.6 (62.7%, N=4)	9.19 (2.77%, N=2)	34.7 (92.7%, N=4)
AUC(0-t_{last}) (pmol·h/L)	19.4 (49.3%)	9.56 (13.2%)	30.2 (72.3%)
$t_{1/2}$ (h)	1.06 (54.1%, N=4)	0.898 (92.6%, N=2)	1.01 (41.7%, N=4)
MRT (h)	0.528 (37.4%, N=4)	0.449 (42.7%, N=2)	0.526 (48.4%, N=4)
CL (L/h)	97.6 (13.1%, N=4)	115 (10.2%, N=2)	86.3 (23.1%, N=4)
V_z (L)	149 (53.9%, N=4)	149 (77.3%, N=2)	126 (44.6, N=4)
V_{ss} (L)	51.6 (31.9%, N=4)	51.8 (31.5%, N=2)	45.4 (39.1%, N=4)
C_{max} / Dose (1/L)	0.145 (15.8%)	0.179 (31.2%)	0.160 (25.9%)
AUC(0-t_{last}/Dose (h/L)	0.00872 (24.7%)	0.00999 (32.1%)	0.00942 (27.6%)

Source: Section 15.3 Table –119 - 121

AUC(0-t_{last}) = area under the concentration – time curve from zero up to the last data point >LLOQ
AUC(0-t_{last} /Dose) = area under the concentration – time curve from zero up to the last data point >LLOQ normalized by the mass dose of ZK 6013443
C_{max} = maximum observed concentration
C_{max}/Dose = maximum observed concentration normalized by the mass dose of ZK 6013443
t_{max} = time to reach maximum concentration
AUC = area under the concentration – time curve from zero up to infinity
AD = Alzheimer´s disease
FTLD = Frontotemporal lobe degeneration
HV = Healthy volunteers
n.d. = not determined
CL = total body clearance
V_{ss} = volume of distribution at steady state
V_z = volume of distribution during terminal phase
MRT = mean residence time
$t_{1/2}$ = terminal half-life
N= number of volunteers

Although for the majority of parameters only 2-4 subjects were studied, it appears that there are no meaningful differences in the pharmacokinetics of Florbetaben F 18 across the three populations. Comparison of the C_{MAX} and AUC values (rows 1 and 3) to the C_{MAX}/Dose and AUC/Dose values (last two rows) shows that the observed differences in C_{MAX} and AUC were caused by the different specific activities of the formulations that were used for the individual treatments resulting in the administration of pronouncedly different mass doses.

2.5.4. What are the characteristics of drug absorption?

Drug absorption was not studied, Florbetaben F 18 injection is administered exclusively as an intravenous injection.

2.5.5. What are the characteristics of drug distribution?

Overall distribution exceeded total body water, the distribution of the terminal phase (V_Z) was greater than 120 L, Florbetaben F 18 is highly bound to plasma proteins (>98.5%). Uptake of radioactivity in the brain is rapid, reaching about 6% of injected 18F-radioactivity at 10 minutes post injection.

On average, 6% of the administered radioactivity dose distributed into the brain 10-13 min after injection. The amount of radioactivity in brain steadily declined to about 3.4% at 40 min and to about 2% at 2 h p.i. The liver was the organ with highest uptake of total radioactivity. Maximum concentrations of about 17% of the radioactivity dose in the mean were measured 10 min after injection. Thereafter, radioactivity declined slowly amounting to about 5.5% of administered radioactivity dose at 6 hr post injection.

2.5.6. Does the mass balance study suggest renal or hepatic as the major route of elimination?

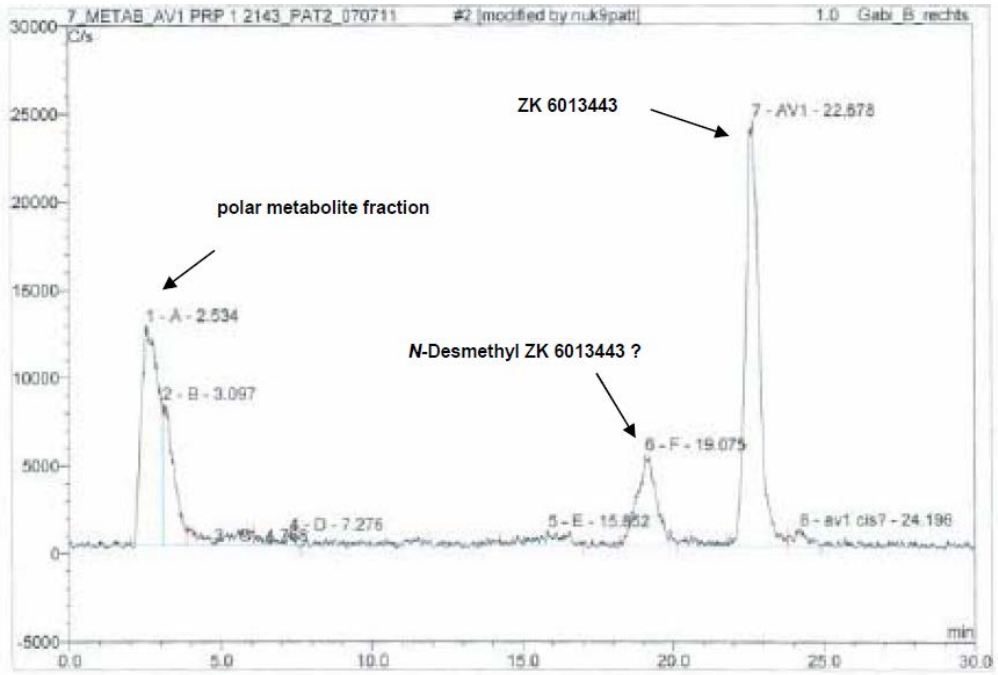
A mass balance study was not performed.

2.5.7. What is the percentage of total radioactivity in plasma identified as parent drug and metabolites?

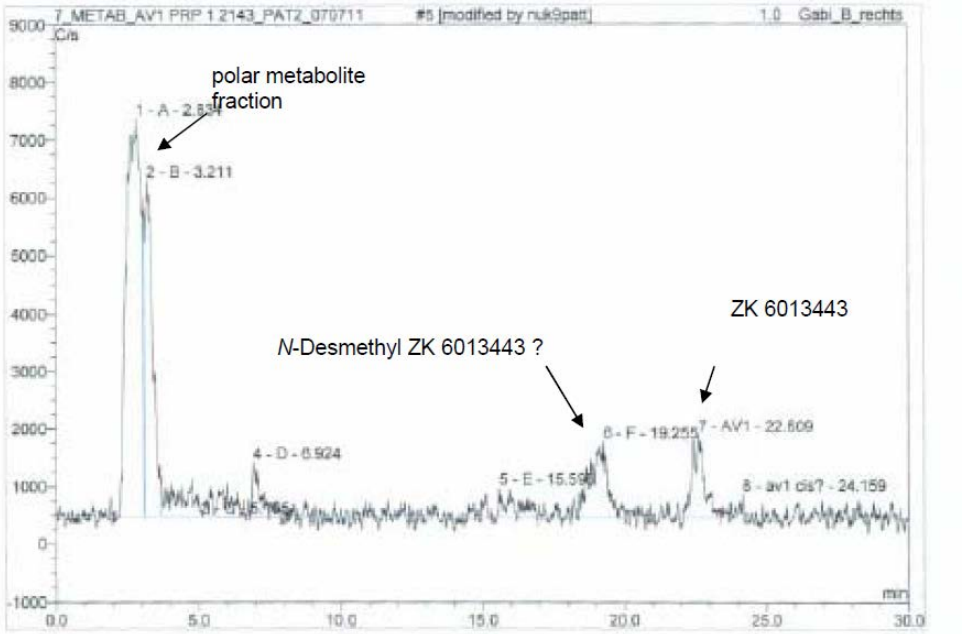
Florbetaben undergoes rapid metabolism into 3-4 metabolites as determined by radio-HPLC/LC-MS/MS of plasma samples. Three representative radiochromatograms of plasma samples are shown for the time points 3 min, 10 min, and 50 min post injection (**FDA Figure 2.**). Florbetaben F 18 (parent compound) is eluting from the column with a retention time of approx. 22.6 min. After 10 and 50 min post injection a polar metabolite fraction can be seen eluting approximately with the solvent front. In addition, a minor metabolite peak was detected with a retention time of approx. 19 min that is suggested to be the *N*-desmethyl derivative of Florbetaben F 18 based on analysis of *in vitro* and preclinical *in vivo* metabolism studies analyzed by HPLC together with LC-MS/MS.

FDA Figure 2. HPLC traces of plasma samples after A) 3 min B) 10 min and C) 50 minutes after Florbetaben F 18 intravenous injection.

B



C



2.5.8. What are the characteristics of drug metabolism?

After administration to humans, Florbetaben F 18 was rapidly metabolized to 3 or 4 major radioactive metabolites. Only 6% of the radioactivity in plasma 60 minutes after injection was unchanged parent compound.

Based on *in vitro* investigations, florbetaben is metabolized by several CYP enzymes with significant contributions by CYP2J2, 3A4, 4F families (see Section **2.7.2.**).

2.5.9. Is there evidence for excretion of parent drug and/or metabolites into bile?

The extent of biliary/fecal excretion was not investigated because quantitation of mass is difficult due to the small amount (< 5 ug) of drug administered, and the rapid decay of the 18F-isotope limits quantification to a maximum of 12 hours post injection, which is too short to monitor the fecal excretion pathway.

2.5.10. Is there evidence for enterohepatic recirculation for parent and/or metabolites?

There is no evidence for enterohepatic recirculation for parent and/or metabolites, but only limited concentration-time data are reported, and data following non-IV administration are not reported.

2.5.11. What are the characteristics of drug excretion in urine?

In three studies investigating healthy Caucasian subjects (Study 310863 and Study 311722) and healthy Japanese subjects (Study 91790), urine was collected for 6 to 12 hours. Similar results were obtained across the studies; about 30% of the administered radioactivity was recovered in urine, primarily during the first 6 hours post-injection.

2.5.12. Based on PK parameters, what is the degree of the proportionality of the dose-concentration relationship?

Dose proportionality results are not reported.

2.5.13. How do the PK parameters change with time following chronic dosing?

Florbetaben F 18 Injection is administered only one time for diagnostic imaging. Repeat dosing results are not reported.

2.5.14. Is there evidence for a circadian rhythm of the PK?

There is not evidence for a circadian rhythm of the PK, but only limited concentration-time data are reported, and data are not reported by time-of-day.

2.6. Intrinsic Factors

2.6.1. What are the major intrinsic factors responsible for the inter-subject variability in exposure (AUC, C_{MAX}, C_{MIN}) in patients with the target disease and how much of the variability is explained by the identified covariates?

PK data collection was limited and occurred only in early studies. There is insufficient data to analyze the effect of intrinsic factors on PK.

2.6.2. Based upon what is known about E-R relationships in the target population and their variability, what dosage regimen adjustments are recommended for each group?

There is not a known E-R relationship, and pharmacokinetic data was not collected in efficacy and safety studies. Only the 300 MBq dose was studied for efficacy. There is no basis for recommending dose adjustments based on E-R relationships.

2.6.2.1. Severity of Disease State

Severity of disease state was not studied.

2.6.2.2. Body Weight

The effect of body weight on imaging was not studied.

2.6.2.3. Elderly

SUVR arithmetic means increased as a function of age in the cortical brain regions used for image interpretation . This is consistent with literature supporting that β-amyloid increases with age and the increase in AD seen with age.

2.6.2.4. Pediatric Patients

Data from pediatric patients are not reported. A pediatric waiver has been granted to the applicant.

2.6.2.5. Race/Ethnicity

There was no observed difference in SUVR means between Caucasian and Black NDVs < 55 years in any of the key cortical gray matter regions, however there were few Black NDVs < 55 (n = 11). There were only two Black NDVs ≥ 55years, so this older age group could not be compared to older age groups of other races. There were no Black AD subjects. The 'other' category of race contained only one subject.

Asian NDVs ≥ 55 years had slightly lower SUVR means than Caucasian NDVs ≥ 55 years. There were only two Asian subjects who were < 55 years so this group could not be compared to younger NDVs of other races. There was no difference observed in the AD populations between Caucasians

and Asians (e.g., in the temporal cortex, the arithmetic means for Caucasian AD subjects and Asian AD subjects were 1.560 and 1.512, respectively), therefore, the differentiation in SUVR means between Asian NDVs and AD subjects was similar to that observed in other races

2.6.2.6. Renal Impairment

Pharmacokinetics of florbetaben have not been investigated in patients with renal impairment. However, the influence of renal impairment on safety and efficacy was evaluated as part of the analysis of a Phase II clinical data (study 91708). In this study, 62% of AD patients (41% of HV) had mild renal impairment (CG-Cl_{CR} 60-89 mL/min) and 6% of AD patients (6% of HV) had moderate renal impairment (CG-Cl_{CR} 30-59 mL/min). Subjects with severe renal impairment were not included in that study. The ANCOVA model for detection of differences in imaging could not detect differences due to renal impairment in patients or in controls.

2.6.2.7. Hepatic Impairment

Pharmacokinetics of florbetaben in patients with renal or hepatic impairment have not been investigated.

2.6.2.8. What pregnancy and lactation use information is available?

No pregnancy or lactation use information is available.

2.6.3. Does genetic variation impact exposure and/or response?

Pharmacogenetic analysis was undertaken in a hypothesis-generating genetic sub-study to investigate the association between the apolipoprotein-E (*APOE*) genotype and florbetaben PET scan results in subjects with low probability of cerebral β-amyloid deposition (eg, NDVs, HVs) and in subjects with high probability of cerebral β-amyloid deposition (eg, subjects diagnosed with AD or DLB). The investigation of the association between *APOE* genotype and PET-scan result revealed a larger proportion of *APOE* ε4 carriers in the group of subjects with a positive PET scan (**FDA Table 7.**).

FDA Table 7. Cross-table of *APOE* genotype and Florbetaben F-18 scan results

***APOE* genotype**	**PET -**	**PET +**	total
ε4/ε3	2	7	9
ε3/ε3	6	5	11
ε2/ε3	3	0	3
	11	12	

Comparison of *APOE* genotype distribution between PET+ and PET- subjects yields a p-value of 0.0503 (Fisher's Exact Test). PET+: positive PET-scan as judged by blinded reading PET-: negative PET scan as judged by blinded reading.

A larger proportion of *APOE* ε4 carriers was observed in subjects clinically diagnosed with AD as compared to healthy controls. In line with published data, the *APOE* ε4 allele was found to be over represented in subjects clinically diagnosed with AD. The allele distribution between healthy volunteers and AD patients in the study cohort is comparable to published data of large scale studies involving thousands of patients and controls. The observed allele distribution supports the clinical diagnosis. Thus, *APOE* ε4 was also associated with positive PET scans.

2.7. Extrinsic Factors

2.7.1. Is there an *in vitro* basis to suspect *in vivo* drug-drug interactions?

Florbetaben is both a substrate and inhibitor of CYP enzymes. However, the margin of safety is sufficient that co-administration of inhibitors would not be a safety issue. Co-administration with an inducer would likely not be an efficacy issue, as drug distribution to the brain occurs more rapidly than metabolism. The CYP inhibitory activity is unlikely to perpetrate drug interactions, as the mass dose is slight compared to the IC50 values. In summary, there is an *in vitro* basis to suspect *in vivo* drug-drug interactions, but the safety margin and low mass dose make it unlikely that the interactions would be significant.

2.7.2. Is the drug a substrate of CYP enzymes?

Florbetaben is subject to two oxidative pathways in human liver microsomes resulting in *N*-demethylation and formation of polar metabolites. *In vitro* CYP reaction phenotyping study was conducted to evaluate the CYP isoforms contributing to the oxidative metabolism. Two different approaches were applied: 1) incubations with recombinant human CYP isoforms, and 2) incubation of 14C-florbetaben with human liver microsomes in the absence and presence of CYP isoform-selective inhibitors, and incubation with a panel of 19 human recombinant CYP isoforms. Several CYP isoforms, mainly CYP1A1, 2J2, 4F2, 4F3b, and 4F12 mediated the *N*-demethylation, whereas CYP2J2 as well as 3A4 contributed to the formation of polar metabolites. Incubation of 14C-florbetaben (0.5 μM) with human liver microsomes in the presence of CYP isoform-selective inhibitors confirmed the contribution of several CYP isoforms to the oxidative metabolism. No significant involvement of polymorphic enzymes CYP2C19 and 2D6 was observed.

In summary, florbetaben is a substrate of several CYP isoforms. Clinically, florbetaben plasma levels are not expected to be highly variable due to involvement of polymorphic CYPs (2D6, 2C19) or to be significantly altered when inhibitors of single CYPs are co-administered to patients.

2.7.3. Is the drug an inhibitor and/or an inducer of enzymes?

The potential of 19F-florbetaben to act as a direct inhibitor of major human cytochrome P450 isoforms (CYP1A2, 2C8, 2C9, 2D6, and 3A4) was evaluated *in vitro* using pooled human liver microsomes. The potential of 19F-florbetaben to act as a time-dependent inhibitor of CYP3A4 was evaluated by comparing the inhibitory potential of 19F-florbetaben after co-incubation and after 30 min preincubation with NADPH-supplemented liver microsomes.

No direct-acting inhibitory potency of 19F-florbetaben on reactions catalyzed by CYP1A2, 2C8, 2C9, and 2D6 were observed (IC_{50} >2 μM). CYP3A4 activity was inhibited with IC_{50} values of 1.6

μM and 1.4 μM, respectively when midazolam and testosterone were applied as substrates. Preincubation of 19F-florbetaben with NADPH-supplemented human liver microsomes slightly decreased CYP3A4 activities compared to the co-incubation experiment as indicated by IC_{50} values of 1.0 μM on midazolam 1'-hydroxylation and 0.7 μM on testosterone 6β-hydroxylation, respectively. C_{MAX} for florbetaben is approximately 0.005 uM. In view of this estimated maximum plasma concentration, there is not risk that florbetaben will perpetrate clinically relevant drug-drug interactions through inhibition of CYPs.

The ability of florbetaben to induce CYP enzymes was not studied. Florbetaben is for single dose administration at a dose < 30 ug – the potential to perpetrate drug interactions due to action as an inducer is minimal.

2.7.4. Is the drug a substrate, an inhibitor and/or an inducer of transporter processes?

The ability of florbetaben to act as a substrate, an inhibitor and/or an inducer of transporter processes is not reported.

2.7.5. Are there other metabolic/transporter pathways that may be important?

No; there are no other known transporter/metabolic pathways.

2.7.6. What extrinsic factors influence exposure and/or response, and what is the impact of any differences in exposure on effectiveness or safety responses?

The effect of extrinsic factors influence on exposure is not reported and cannot be assessed (see Section **2.6.2.**).

2.7.7. What are the drug-drug interactions?

No drug-drug interaction studies have been performed in humans.

2.7.8. Does the label specify co-administration of another drug?

The label does not specify co-administration of another drug.

2.7.9. What other co-medications are likely to be administered to the target population?

The patients likely to receive Florbetaben F 18 administration are AD patients or patients with cognitive disorder. There will likely be taking their regular AD treatments. Although not formally studied, there is no pharmacologic basis for expectation that agents use to treat AD would interfere with binding of florbetaben to β-amyloid.

2.7.10. Is there a known mechanistic basis for pharmacodynamic drug-drug interactions?

There is no pharmacological basis for pharmacodynamics drug-drug interaction. Florbetaben F 18 did not bind to a panel of CNS receptors, and the dose (30 ug or less) is unlikely to have a pharmacological effect.

2.8 General Biopharmaceutics

2.8.1. Based on the biopharmaceutic classification system principles, in what class is this drug and formulation? What solubility, permeability and dissolution data support this classification?

2.8.2. How is the proposed to-be-marketed formulation linked to the clinical service formulation?

2.8.2.1. What are the safety or effectiveness issues, if any, for BE studies that fail to meet the 90% CI using equivalence limits of 80-125%?

2.8.2.2. If the formulation does not meet the standard criteria for bioequivalence, what clinical pharmacology and/or safety and efficacy data support the approval of the to-be-marketed product?

2.8.3. What is the effect of food on the bioavailability of the drug when administered as solution or as drug product?

2.8.4. Was the bioequivalence of the different strengths of the to be marketed formulation tested? If so were they bioequivalent or not?

2.8.5. If unapproved products or altered approved products were used as active controls, how is BE to the to be marketed product demonstrated? What is the link between the unapproved/altered and to be marketed products?

Florbetaben F 18 Injection is an intravenously administered simple saline solution; the above biopharmaceutics questions are not applicable.

2.9. Analytical Section

2.9.1. How are parent drug and relevant metabolites identified and what are the analytical methods used to measure them in plasma and other matrices?

2.9.2. Which metabolites have been selected for analysis and why?

2.9.3. For all moieties measured, is free, bound, or total measured?

2.9.4. What bioanalytical methods are used to assess concentrations of the measured moieties?

2.9.5. What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting *techniques* were used?

2.9.5.1. What are the lower and upper limits of quantitation?

2.9.5.2. What are the accuracy, precision, and selectivity at these limits?

2.9.5.3. What is the sample stability under conditions used in the study?

2.9.5.4. What is the plan for the QC samples and for the reanalysis of the incurred samples?

Samples were analyzed with HPLC followed by radio-detection. Method validation included mass spectrometry verification that the identity of the peak that eluted with the same retention time as florbetaben contained florbetaben alone (i.e., metabolites did not co-elute). All radioactivity measurements in biological samples were decay-corrected. The measured radioactive concentrations were transformed into mass concentrations of total florbetaben (b) (4) knowing

the specific activity of the formulation and assuming that, except for the effect of decay, specific activity was unchanged *in vivo*.

The in-process performance of the analytical methods was not submitted in the NDA. The PK data that will appear in the package insert is non-critical, in that 1) no changes in PK due to intrinsic or extrinsic factors are reported, 2) no dose adjustments are recommended, and 3) no raw concentration data are presented. The reviewer finds the lack of in-process data acceptable, but not ideal.

3. Detailed Labeling Recommendations

As per discussion with the review team, this NDA will not be approved due to the low specificity of reading relative to the Standard of Truth (SoT). The reviewing medical division has decided to not review the package insert. We have therefore decided to not review the package insert, as any language derived might require subsequent change based upon the content of any re-submission, should such occur.

4. Appendices

4.1. Applicant's Proposed Package Insert (original, annotated)

4.2. Cover sheet and OCPB Filing/Review Form

4.1. Applicant's Proposed Package Insert (original, annotated)

20 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

4.2. Cover sheet and OCPB Filing/Review Form

Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	204-677	**Brand Name**	To be determined
OCP Division (I, II, III, IV, V)	V	**Generic Name**	Florbetaben
Medical Division	Division of Medical Imaging Products	**Drug Class**	Imaging
OCP Reviewer	Christy S. John, Ph.D.	**Indication(s)**	Florbetaben is indicated for the detection of beta-amyloid in the brain, thereby assisting in the differential diagnosis in adult patients who are being evaluated for Alzheimer's disease (AD) or other causes of cognitive decline.
OCP Team Leader	Gene Williams, Ph.D.	**Dosage Form**	Clear Solution
		Dosing Regimen	Administer 300 MBq (8.1 mCi) as a slow single intravenous bolus (6 sec/mL) in a total volume of up to 10 mL. (Mass dose <30 microgram)
Date of Submission	December 21, 2012	**Route of Administration**	Intravenous Injection
Estimated Due Date of OCP Review	August 23, 2013	**Sponsor**	Piramal Imaging SA
PDUFA Due Date	December 21, 2013	**Priority Classification**	S
Division Due Date	August 23, 2013		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	**Number of studies submitted**	**Number of studies reviewed**	**Critical Comments If any**
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.				
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			

Reference Bioanalytical and Analytical Methods				
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:	X	4		
Blood/plasma ratio:				
Plasma protein binding:	X	1		
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X	2		
multiple dose:				
Patients-				
single dose:	X	2		
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vitro effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:	X	1		
gender:	X	1		
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				

alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		11		

Filability and QBR comments		
	"X" if yes	**Comments**
Application fileable ?	**X**	
Comments sent to firm ?	**X**	Please provide evidence that the parent compound eluting at 17 min is florbetaben and not something else. Is there LC/MS data supporting in-vivo parent/metabolite data? Please provide a single dataset containing all of the raw data from the analytical runs for all samples contributing to PK analysis. The file should include (each item is a column): 1) Clinical study number 2) Calendar date of analysis of the sample ("sample" includes blanks, standards, QCs -- all determinations included in the analytical run) 3) Clock time of analysis of the sample 4) Categorical variable describing sample type -- blank, standard, QC, subject data, re-analysis, dilution 5) For subject data only (column is empty for non-subject samples) -- subject ID, nominal post-dose sample time, actual post-dose sample time (these could be split into separate columns if desired) 6) For subject data only (column is empty for non-subject samples and for samples that are not dilutions) -- the degree (x-fold) of dilution 7 (and subsequent) Other information as you desire to include Please provide in vitro amyloid binding data in human brain.
QBR questions (key issues to be considered)	Is there potential that formulation changes could alter PK? If yes, is there PK w/the to-be-marketed formulation? Does the semiquantitative method (SUVR) provide better measurement of beta amyloid than visual read method?	
Other comments or information not included above		
Primary reviewer signature	**Christy S. John, Ph.D.**	
Secondary reviewer Signature and date	**Gene Williams, Ph.D.**	

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/s/

CHRISTY S JOHN
02/18/2013

GENE M WILLIAMS
02/18/2013

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

/s/

CHRISTY S JOHN
08/22/2013

GENE M WILLIAMS
08/22/2013