Clinical Study Report Synopsis **GE Healthcare**

GE-067-007

Title: **A Principal Open-Label Study to Compare the Brain Uptake of [^{18}F]Flutemetamol with Brain Fibrillar Amyloid β Levels Determined Post-mortem**

This is an exact copy of the synopsis from the final clinical study report for the study GE-067-007. The final clinical study report (document-identifier: GE-067-007 CREP) was authorized for use by the Head of Global Medical on 05-Sep-2012 (Version 1.0).

2 SYNOPSIS

Name of Sponsor/Company: GE Healthcare Ltd. and its Affiliates	**Individual Study Table Referring to Part of Dossier in Which the Individual Study or Study Table is Presented:**	**(For National Authority Use only)**
Name of Finished Product: Flutemetamol F 18 Injection		
Name of Active Ingredient: [^{18}F]Flutemetamol	**Volume:**	
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Title of Study: A Principal Open-Label Study to Compare the Brain Uptake of [^{18}F]Flutemetamol with Brain Fibrillar Amyloid β Levels Determined *Post-mortem*

Investigators and Study Centers: 15 recruiting sites in the United States and 4 in the United Kingdom

Investigators and Centers for Independent Evaluation of Images: The blinded independent visual interpretation of images was coordinated by the Image Review Center, GE Healthcare, Oslo, Norway and the Imaging Technology group, GE Healthcare, Amersham, UK

Publication (reference): None

Study Period: 22 June 2010 to 23 November 2011 (study stopping rule met)

Phase of Development: Phase 3

Objectives:

Primary: To determine the sensitivity of blinded visual interpretations of [^{18}F]flutemetamol Positron Emission Tomography (PET) images *without* anatomic brain images for detecting brain fibrillar amyloid β.

Secondary:

(1) To determine the specificity of the visual interpretations of [^{18}F]flutemetamol PET images *without* anatomic brain images for detecting brain fibrillar amyloid β.

(2) To determine the sensitivity and specificity of blinded visual interpretations of [^{18}F]flutemetamol PET images *with* anatomic brain images using x-ray computed tomography (CT) for detecting brain fibrillar amyloid β.

(3) To determine the level of association between global and regional estimates of brain uptake (standard uptake value ratio [SUVR]) of [^{18}F]flutemetamol and corresponding estimates of brain fibrillar amyloid β levels made *post-mortem*.

Study Design: This was a multicenter, open-label PET study to evaluate the efficacy and safety of a single intravenous (i.v.) dose of Flutemetamol F 18 Injection for the detection of cortical fibrillar amyloid β. Subjects underwent anatomic brain imaging (usually CT), followed by open-label i.v. administration of approximately 185 to 370 megabecquerels (MBq) (5 to 10 millicuries [mCi]) of study drug, followed by PET imaging of the brain. Subjects were followed until death or study termination, whichever occurred first. The brains of subjects who died during the study were analyzed for neuritic (amyloid) plaque density.

Subjects had up to 3 visits: 1) screening within 35 days before the administration of study drug, 2) a second screening visit if the anatomic imaging and clinical assessments could not be performed during a single visit, and 3) the PET imaging visit.

On the day of PET imaging, each subject received a single i.v. dose of Flutemetamol F 18 Injection, given within approximately 40 seconds. PET imaging for 30 minutes was to start approximately 90 minutes after the injection. For subjects who could not tolerate lying still for 30 minutes, a higher activity (up to 370 MBq) could be used to shorten the imaging time. Subjects and their families were blinded to imaging results during the study.

PET images without corresponding anatomic images were interpreted visually by 5 independent readers, trained in the interpretation of such images and blinded to the standard of truth (SoT) and all other information about the subject. Images were classified as normal (negative for fibrillar amyloid β) or abnormal (positive for fibrillar amyloid β). Each interpretation of a PET image set without the anatomic images had to be recorded and the read session concluded before interpretation of another image set could be conducted. After all of the PET-only image sets had been interpreted, the order of PET image presentation was re-randomized and each PET scan was presented together with corresponding anatomic images to the reader. Personnel conducting image preparation and those facilitating the visual image interpretations were blinded to autopsy results as well as all clinical information about the subjects.

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Safety variables included adverse events (AEs) and changes in physical and neurological examinations, electrocardiogram (ECG), clinical laboratory parameters (chemistry, hematology, and coagulation), and vital signs (blood pressure, heart rate, body temperature, and respiratory rate). Subjects were monitored during the course of the study, including the scanning procedures, and at a 24-hour telephone follow-up.
Personnel conducting *post-mortem* brain analyses for tissue amyloid were blinded to imaging data and results as well as to all clinical information about the subject.

Selection of Subjects:
Inclusion Criteria:

(1) The subject had a short life expectancy (approximately 1 year or less) as estimated by the investigator.
(2) The subject was 55 years of age or older and had been diagnosed with a terminal illness.
(3) The subject and/or the subject's legally acceptable representative, if applicable, signed and dated the informed consent in accordance with local regulations.
(4) The subject had a caregiver who was reliable and ensured that the subject complied with the protocol, if necessary in the judgment of the Investigator.
(5) The subject's general health was adequate to undergo the study procedures.
(6) For women who were either surgically sterile (had a documented bilateral oophorectomy and/or documented hysterectomy) or were postmenopausal (cessation of menses for more than 2 years), enrollment in the study without a pregnancy test at screening was allowed. For women of childbearing potential, the results of a serum and urine human chorionic gonadotropin pregnancy test (with the result known on the day of and before Flutemetamol F 18 Injection administration) had to be negative.
(7) The subject was able to tolerate undergoing diagnostic quality anatomic brain imaging (usually CT).

Exclusion Criteria:

(1) The subject had known or suspected structural brain abnormalities, such as infarcts or tumors, which might interfere with the interpretation of PET images.
(2) The subject had a contraindication for PET.
(3) The subject was pregnant or lactating.
(4) The subject had a known or suspected hypersensitivity/allergy to Flutemetamol F 18 Injection or to any of the excipients.
(5) The subject was unable to tolerate or cooperate with study procedures.
(6) The subject had participated in any clinical study using an investigational agent within 30 days of signing consent.

Number of Subjects (planned and analyzed): Up to 200 subjects were planned; 203 subjects were enrolled and 23 subjects withdrew prior to receiving study drug. Study drug was administered to 180 subjects.
Subjects evaluable for safety: 180
Subjects evaluable for efficacy (included in blinded visual image interpretation): 176
Subjects undergoing brain autopsy: 69
Subjects evaluable for *post-mortem* analyses: 68
Non-completers: 4

Treatment of Subjects
Investigational Medicinal Product (IMP): Subjects received a single open-label i.v. administration of Flutemetamol F 18 Injection; the administered activity was 185 to 370 MBq (5 to 10 mCi). Higher activity (up to 370 MBq) could be used to shorten the diagnostic imaging time for subjects who could not tolerate lying still for 30 minutes.
Imaging: Subjects underwent anatomic brain imaging (usually CT-often using the CT capability of the PET/CT scanners), followed by Flutemetamol F 18 Injection and PET imaging of the brain. PET imaging for 30 minutes was to start approximately 90 minutes after injection of IMP.
Adjunctive Drugs: If necessary to treat agitation, subjects could be sedated (e.g., up to 2.5 mg of lorazepam)

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for the PET imaging procedure according to local clinical practice.
Duration of Treatment: Subjects received 1 dose of Flutemetamol F 18 Injection; the follow up period for safety was 24 hours, equivalent to approximately 5.3 elimination half-lives of [^{18}F]flutemetamol.

Efficacy Endpoints:
Primary: Blinded visual interpretation of each subject's Flutemetamol F 18 Injection brain PET images as normal or abnormal, *without* anatomic brain images for reference
Secondary:

- Blinded visual interpretation of each subject's Flutemetamol F 18 Injection brain PET images as normal or abnormal, *with* anatomic CT brain images for reference
- Global and region-specific estimates of cortical tracer uptake (SUVR value) determined from quantitative analysis of the [^{18}F]flutemetamol PET image, normalized for the mean uptake in reference regions known to have low or no amyloid (cerebellum and pons)

Standard of Truth (SoT): SoT results were available for those subjects who died during the study and underwent brain autopsy. The SoT used to classify the accuracy of image interpretations was the categorization of each autopsied subject's brain as either normal or abnormal for neuritic (amyloid) plaque density, based on a pre-defined threshold (1.5) of neuritic plaque density score; brain tissue assessments were based on Bielschowsky silver stain. Specimens were taken from 8 cortical regions in the left hemisphere: the precuneus, mid-frontal, superior temporal, middle temporal, inferior parietal, anterior cingulate gyrus, posterior cingulate gyrus, and primary visual cortex regions of the brain. Two tissue blocks, one anterior and one posterior, were taken from each region, and 3 microscope slides were prepared from each block (for a total of 48 slides per subject). For each slide, each of five 100x-magnification grey-matter fields were scored from 0 to 3 for neuritic plaque density using a modified Consortium to Establish a Registry for Alzheimer's Disease (CERAD) scale: 0 = none (0 plaques); 1 = sparse (1 to 5 plaques); 2 = (6 to 19 plaques); 3 = (≥20 plaques). The five scores per slide were averaged to give a mean slide score, and the 6 mean slide scores per region were averaged to give a mean region score. Each region score was classified *normal* if < 1.5, and *abnormal* if > 1.5. A brain was classified abnormal if at least one region was classified as abnormal.
Other Reference Standards: Cortical amyloid β levels quantitatively determined as percentage area for each sampled brain region on immunohistochemically (IHC)-stained sections using a monoclonal antibody raised against amyloid β (4G8).
Other Endpoints: Plaque counts (the number of 4G8-positive plaques/mm^2) were determined for each cortical brain region sampled; a further 11 subcortical regions, in addition to the eight neocortical regions used for the amyloid β analyses, were sampled and samples were assessed to determine the presence or absence of various types of dementia. No formal analyses were performed on these endpoints.
Safety Endpoints: AEs; changes from baseline in physical and neurological examination, electrocardiogram (ECG), clinical laboratory parameters (chemistry, hematology, and coagulation), and vital signs (blood pressure, heart rate, body temperature, and respiratory rate)

Statistical Analyses
The full analysis set (FAS) was defined as all subjects who received a dose of Flutemetamol F 18 Injection and had a PET scan that was usable for either visual interpretation or SUVR assessment. A *post-mortem* analysis set (PAS) was defined as FAS subjects who had an evaluable *post-mortem* amyloid assessment. The Safety Analysis Set (SAS) population was defined as all subjects who received any dose of Flutemetamol F 18 Injection. Study population variables (disposition, demographics, medical history, previous and concurrent medications, physical examinations, neurological examinations, body measurements, and IMP exposure) were summarized. Each blinded visual PET image interpretation was compared with the SoT for classification as true positive, true negative, false positive, or false negative.
Primary Efficacy Evaluation: Sensitivity of the blinded visual interpretation of images *without* the aid of

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anatomic images was determined for each of the 5 independent readers; point estimates and their exact 95% binomial confidence interval limits were calculated. The study was to be deemed successful if the lower bound of the two-sided 95% exact confidence limit for sensitivity was greater than the *a priori* threshold of 70% for at least 3 of the 5 readers.

Secondary Efficacy Evaluations:

(1) The specificity of the blinded visual image interpretations *without* anatomic images was determined as point estimates and their exact 95% binomial confidence interval limits for each of the 5 readers.

(2) Sensitivity and specificity of blinded visual image interpretations *with* the aid of anatomic images were determined as point estimates and their exact 95% binomial confidence interval limits for each of the 5 readers.

(3) The levels of association between quantitative estimates of [^{18}F]flutemetamol brain uptake (SUVR values) and *post-mortem* estimates of amyloid were determined on a regional and global basis, for the first 30 brains to undergo autopsy. In addition, data were displayed in scatterplots. SUVR reference regions were the cerebellar cortex and the pons. Both IHC (4G8 stain) and HC (Bielschowsky silver stain) staining methods were used in the *post-mortem* determinations of amyloid. Statistical models used SUVR measures (regional and global) as the independent variables and amyloid measurements (IHC and HC) as the dependent variables. Parameter estimates, standard errors, 95% confidence intervals, and corresponding p-values were displayed for each of the analyses. In addition, for the regression analyses, the overall model F-statistic, p-value, and coefficient of determination were presented.

Summary of Results

Of the 180 dosed subjects, 4 were excluded from the blinded visual image interpretations. PET images could not be obtained for one subject (114-0005) who became agitated after dosing. Two subjects (124-0007 and 124-0017) had large brain lesions showing in the CT scan and were therefore protocol violators (exclusion criterion 1). PET images were reported to be unusable for the 4th subject (125-0002). During follow-up, 69 (38%) of the 180 subjects died and underwent brain autopsy. Of these 69 subjects, 1 subject's brain was considered unevaluable because it had been subjected to standard autopsy by the Medical Examiner (the subject had sustained a fall prior to death).

Efficacy: *Sensitivity*: The point estimates (95% confidence interval limits) for the sensitivity of blinded visual interpretations of [^{18}F]flutemetamol PET images for detecting brain fibrillar amyloid β *without* anatomic brain images were 81% (67%, 92%), 88% (74%, 96%), 93% (81%, 99%), 93% (81%, 99%), and 88% (75%, 96%) for Readers 1 through 5 respectively. Because the lower bound of the 95% confidence limit for sensitivity exceeded 70% for at least 3 of the 5 readers, the primary efficacy objective was achieved. The point estimates (95% confidence interval limits) for sensitivity *with* anatomic images were 91% (78%, 97%), 95% (84%, 99%), 98% (88%, 100%), 91% (78%, 97%), and 91% (77%, 97%) for the same 5 readers, respectively. The 95% confidence intervals for sensitivity with anatomic images overlapped with the 95% confidence intervals of the corresponding estimates obtained without anatomic images, so the results were not significantly different.

Specificity: The point estimates (95% confidence interval limits) for specificity of blinded visual interpretations for detecting brain fibrillar amyloid β *without* anatomic images were 88% (69%, 98%), 92% (74%, 99%), 44% (24%, 65%), 80% (59%, 93%), and 92% (74%, 99%) for Readers 1 through 5, respectively. The point estimates (95% confidence interval limits) for specificity *with* anatomic images was 92% (74%, 99%), 88% (69%, 98%), 56% (35%, 76%), 88% (69%, 98%), and 92% (74%, 99%) for the same 5 readers, respectively. The 95% confidence intervals for specificity with anatomic images overlapped with the 95% confidence intervals of the corresponding estimates obtained without anatomic images, so the results were not significantly different.

Analyses of Association: A direct relationship between regional and global SUVRs and corresponding measurements of amyloid levels made *post-mortem* was evident from analysis of the first 30 brains. Brain region was a significant factor in statistical models of regional amyloid levels. Time from PET scan to death

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was not a significant factor in most models.
Inter-Reader Agreement: Pairwise reader agreement (kappa) scores for the visual interpretation of PET images without anatomic images ranged from 0.44 to 0.91; across all 5 readers, the overall agreement score was 0.72. With anatomic images, the pairwise agreement (kappa) scores ranged from 0.56 to 0.97; across all 5 readers, the overall agreement score was 0.79. Agreement scores for image interpretations performed with and without anatomic images were not significantly different.
Intra-Reader Reproducibility: Without anatomic images, the intra-reader reproducibility for the visual interpretation of PET images ranged from 88% to 100% (kappa 0.60 to 1.00). With anatomic images, the intra-reader reproducibility ranged from 82% to 100% (kappa 0.3 to 1.00). Intra-reader reproducibility scores obtained with and without anatomic images were not significantly different.
Safety: AEs were reported for 9 subjects (5%); 2 subjects had mild flushing deemed at least possibly related to study drug. A total of 69 deaths occurred during the study; all were expected based on the study main inclusion criterion (a life expectancy of ≤1 year). Two (2.5%) of the deaths were reported as the outcomes of serious adverse events (SAEs): one due to prostate cancer and one due to senile dementia; neither was considered related to study drug. Two non-fatal SAEs were reported: anemia and change in mental status (1 subject each); neither was considered related to study drug and both subjects continued in the study. AEs considered severe were prostate cancer, senile dementia, and anemia. All other AEs were mild or moderate in intensity. No clinically important trends or safety signals were noted in any other safety parameter, including clinical laboratory variables, vital signs, and ECG.

Conclusions
Efficacy: In this population of terminally ill patients aged ≥55, blinded visual interpretation of [^{18}F]flutemetamol PET brain images had clinically useful sensitivity and specificity without the need for anatomic brain images. The availability of anatomic brain images did not significantly affect the results.
Safety: Single doses of Flutemetamol F 18 were well tolerated in this population of terminally ill subjects ≥55 years of age.