Clinical Study Report Synopsis **GE Healthcare**
GE-067-005

Title: A Principal Open-Label Study to Assess the Prognostic Usefulness of Flutemetamol F 18 Injection for Identifying Subjects with Amnestic Mild Cognitive Impairment Who Will Convert to Probable Alzheimer's Disease

This is an exact copy of the synopsis from the final clinical study report for the study GE-067-005. The final clinical study report (document-identifier: GE-067-005 CREP) was authorized for use on 2-May-2014 (Version 2.0).

<table>
<tr><td>Name of Sponsor/Company:
GE Healthcare Ltd. and its Affiliates
Name of Finished Product:
Flutemetamol F 18 Injection
Name of Active Ingredient:
[^{18}F]Flutemetamol</td><td>Individual Study Table Referring to Part of Dossier in Which the Individual Study or Study Table is Presented:

Volume:

Reference:</td><td>(For National Authority Use only)</td></tr>
<tr><td colspan="3">Title of Study: A principal open-label study to assess the prognostic usefulness of Flutemetamol F 18 Injection for identifying subjects with amnestic mild cognitive impairment who will convert to probable Alzheimer's disease</td></tr>
<tr><td colspan="3">Investigators and Study Centers: 28 centers in Europe and the US</td></tr>
<tr><td colspan="3">Investigators and Centers for Independent Evaluation of Images: Image Review Center, GE Healthcare</td></tr>
<tr><td colspan="3">Publication (reference): None</td></tr>
<tr><td colspan="2">Study Period: 11 Nov 2009 (first subject, first visit) through 16 Jan 2014 (last subject, last visit).</td><td>Phase of Development: 3</td></tr>
<tr><td colspan="3">Objectives:
Primary Objective:
• To compare the time to conversion to probable Alzheimer's Disease (pAD) in amnestic Mild Cognitive Impairment (aMCI) subjects with normal (negative for amyloid β) and abnormal (positive for amyloid β) patterns of [^{18}F]flutemetamol uptake based on the blinded visual assessment of Positron Emission Tomography (PET) scans by independent readers.
Secondary Objectives:
• To compare the proportions of normal and abnormal subjects who convert to pAD within the follow-up period.
• To compare the time to conversion to pAD in aMCI subjects with [^{18}F]flutemetamol uptake below and above a pre-defined threshold based on quantitative assessment of a Flutemetamol F 18 Injection PET scan.
• To determine the sensitivity and specificity of the ability of [^{18}F]flutemetamol uptake to predict eventual conversion to pAD based on clinical testing in the time period of the study conduct. Separate determinations were made for blinded visual image assessments and the categorizations of quantitative image assessments.
• To determine the inter-reader (between-reader) agreement of blinded visual image assessment, as measured by Fleiss' kappa (>70% = good; >80% = very good; >90% = excellent).
• To determine the intra-reader (within-reader) reproducibility of blinded visual image assessment, as measured by their percentage of self-consistency.</td></tr>
<tr><td colspan="3">Study Design: This was a multi-center, open-label PET study to evaluate the efficacy and safety of a single intravenous dose of Flutemetamol F 18 Injection for predicting more rapid conversion to pAD in subjects</td></tr>
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diagnosed with aMCI who have normal (negative for amyloid β) and abnormal (positive for amyloid β) patterns of [^{18}F]flutemetamol uptake in the brain, as concluded from the visual inspection of the PET images. Subject allocation to Flutemetamol F 18 Injection was non-randomized, with all subjects being dosed. The order of blinded visual evaluations was randomized. The visual assessment of Flutemetamol F 18 Injection brain PET images was performed by 5 independent readers trained in the evaluation of PET amyloid imaging. These readers were blinded to the subjects' medical history and diagnoses. Subjects were assessed clinically on-site every 6 months until conversion to pAD (as determined by an independent Clinical Adjudication Committee (CAC); see below) or completion of 36 months of follow-up, whichever came first. Clinical assessments were performed by a trained on-site clinician who collected the results of a battery of tests, the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) diagnostic criteria for pAD, and clinical assessment; this clinician was blinded to the subjects' PET images and interpretations until the study was complete. The follow-up data were regularly submitted to the CAC, which determined whether or not the subject had converted to pAD. The time to conversion to pAD for subjects who converted and the time to last known date of non-conversion (censoring time) for subjects who did not convert were included in survival analyses (survival refers to non-conversion to pAD). The primary analysis was a Cox proportional hazards model, which was used to calculate for each blinded reader the hazard ratios (HRs) for subject conversion to pAD.

Selection of Subjects:

Inclusion Criteria:

1. The subject had at least a six grade education or a good work history (sufficient to exclude mental retardation).
2. The subject's general health was adequate to comply with study procedures, as ascertained by review of their screening medical history and physical examination.
3. 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 investigational medicinal product administration) were negative.
4. The subject and/or the subject's legally acceptable representative, if applicable, in accordance with local regulations, had signed and dated an informed consent.
5. The subject was 55 years old or older.
6. The subject met the Petersen criteria for aMCI including:
    a. The subject had a memory complaint or a study partner that could verify a memory complaint
    b. Abnormal memory function using the scoring on the Logical Memory II subscale revised (delayed paragraph recall) from the Wechsler Memory Scale - Revised
        i. Less than or equal to 11 for 16 or more years of education
        ii. Less than or equal to 9 for 8-15 years of education
        iii. Less than or equal to 6 for 0-7 years of education
    c. Clinical Dementia Rating (CDR) global rating of 0.5
    d. General cognition and functional activities of daily living (ADL) performance sufficiently preserved such that the diagnosis of possible or probable AD by NINCDS-ADRDA criteria could not be made at screening
    e. An informant was available who had frequent contact with the subject and could accompany the subject to all clinic visits or be available to talk on the telephone about the subject's memory.
7. The subject had a score of less than or equal to 4 on the Modified Hachinski Ischemic Scale.
8. The subject had a Mini-Mental State Examination (MMSE) score of 24-30 (exceptions could be made for

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subjects with less than 8 years of education at the discretion of the Investigator).

9. The subject had adequate visual and auditory acuity to allow neuropsychological testing.
10. The subject had a non-contrast magnetic resonance imaging (MRI) examination as part of the screening visit or within the previous 6 months, that excluded aMCI arising from structural causes (e.g. vascular disease, hydrocephalus) and was of sufficient diagnostic quality (details provided in Imaging Manual) for Volume of Interest definition.
11. The subject was willing and able to participate for at least 3 years.
12. The subject had a Hamilton Depression Scale (HAM-D) Score of 12 or less on the HAM-D 17.

Exclusion Criteria:

1. The subject had participated in any other clinical study utilizing an investigational agent within 30 days of study entry.
2. The subject was pregnant or lactating.
3. The subject had a history of alcohol and/or drug abuse within the last 2 years based upon a review of medical records.
4. The subject had any significant neurologic disease other than suspected aMCI; such as Parkinson's disease, Huntington's disease, normal pressure hydrocephalus, brain tumor, supranuclear palsy, seizure disorder, subdural hematoma, multiple sclerosis, or history of significant head trauma followed by persistent neurologic deficits, or known structural brain abnormalities.
5. The subject had one or more aneurysm clips, artificial heart valves, metal implants, embedded metal fragments, or pacemakers that would pose a risk during an MRI.
6. The subject had major depression, bipolar disorder, as described in the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) within the past 1 year
7. The subject had history of schizophrenia (DSM-IV criteria).
8. The subject had, within the prior 3 months, psychotic features, agitation, or behavioral problems that could lead to protocol compliance issues.
9. The subject had a known or suspected hypersensitivity/allergy to [^{18}F]flutemetamol or to any of the excipients.
10. The subject had clinically significant abnormalities in serum B12, folate, or thyroid functions that might interfere with the study.
11. The subject regularly took medication with known anticholinergic effects (which could impair memory) within the last 3 months or in the view of the Investigator the subject was taking a drug that could impair cognition.
    a. Patients on psychoactive medications e.g., certain antidepressants, neuroleptics, chronic anxiolytics or sedative hypnotics were excluded. Note: subjects could take stable doses of antidepressants lacking anticholinergic side effects, if they were not depressed and had not had a history of a major depressive episode within the past 2 years.

Number of Subjects (Planned and Analyzed):
Planned evaluable for efficacy: 230
Enrolled: 365
Administered Flutemetamol F 18 Injection: 232
Evaluable for Safety: 232
Evaluable for Efficacy: 232

Treatment of Subjects:
Investigational Medicinal Product: Each subject received one 185-MBq intravenous dose of Flutemetamol F 18 Injection (≤10 μg total flutemetamol) injected within 40 seconds. A 185-MBq dose exposes the subject to an effective dose of 5.92 millisieverts of radiation.

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Imaging: PET imaging started approximately 90 minutes after dosing. Imaging data were collected for 30 minutes in six 5-minute frames. Images were assessed visually by 5 blinded, independent readers and quantitatively by the sponsor. Based on the blinded image evaluation, each of 5 independent readers separately categorized each subject as having either "normal" (negative for amyloid β) or "abnormal" (positive for amyloid β) uptake based on the PET image pattern. The blinded read was performed in accordance with the GE067-005 Image Review Charter and its associated Image Review Training Manual.

Criteria for Conversion to Probable AD: The clinical endpoint for each subject (conversion to pAD or not) was decided by the CAC based on its review of longitudinal clinical data collected every 6 months for up to 3 years after baseline [^{18}F]flutemetamol PET imaging. The CAC consisted of 4 experts in the diagnosis of memory disorders. The CAC reviewed all study data (excluding the investigator's conversion assessment and flutemetamol and any other amyloid imaging data) for each subject to determine whether or not the subject had converted to pAD. The decision rules to be used in defining a conversion to pAD were established by the CAC before reviewing any subject's data.

Duration of Treatment: Each subject had a minimum of 3 and a maximum of 10 study visits. The duration of subject participation depended on whether or not he/she converted to pAD (or dropped out) before the completion of 36 months of follow-up.

Endpoints

Efficacy:

Primary Endpoint:

The primary endpoint was the time to conversion to pAD of aMCI subjects with normal and abnormal patterns of [^{18}F]flutemetamol uptake based on the independent, blinded visual assessment of a PET scan. Time 0 was the date of the PET imaging, the time of pAD diagnosis was the event time for subjects diagnosed with pAD, and the time to last completed follow-up visit was the censoring time for subjects without a diagnosis of pAD by the end of the study and for those who left the study early. The final determination of whether or not a subject converted to pAD was made independently by the CAC, which evaluated the information and rendered a decision (AD or no AD) that served as the primary clinical endpoint.

Secondary Endpoints:

- Numbers of subjects with normal and abnormal patterns of [^{18}F]flutemetamol uptake who converted to pAD.
- Numbers of subjects with [^{18}F]flutemetamol uptake below or above a pre-specified threshold who converted to pAD. Uptake was determined using the standard uptake value ratio (SUVR), which is a quantitative measure of specific tracer uptake from a volume of interest (VOI), normalized for the non-specific mean uptake in a reference region. The SUVR was a composite based on multiple volumes of interest. The composite SUVR was determined from anterior cingulate, frontal cortex, parietal cortex, lateral temporal cortex, and a VOI covering precuneus and posterior cingulate. The reference region used for this study was the cerebellar cortex. SUVR was determined as SUV_{VOI}/SUV_{REF} with SUV being the integrated activity over a given time. The pre-specified SUVR threshold was 1.56.
- Time to conversion to pAD for subjects with SUVR below or above the SUVR threshold.

Safety: The safety of Flutemetamol F 18 Injection was assessed by the incidence of adverse events (AEs), changes in clinical laboratory values (chemistry, hematology and coagulation), vital signs, electrocardiograms (ECGs), and physical/neurological examinations.

Statistical Analyses

Tabulations of summary statistics, graphical presentations, and statistical analyses were performed using SAS® software. The last pre-administration observation was used as the baseline value for calculating post-administration changes from baseline. The planning and reporting of statistical analyses were carried out as described in the Sponsor's standard operating procedures governing clinical studies.

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Primary Analysis:

Times to conversion and censoring times were analyzed in a Cox proportional hazards model to estimate the HR of the abnormal-image and normal-image subjects' rates of conversions to pAD. Risk factors were included to adjust for potential differences in the two groups. The risk factors included in the primary Cox model were age and cognitive level at baseline based on CDR global score (sum of boxes).

The analysis was performed for the efficacy population for each blinded reader, with the criterion for study success requiring that statistical significance be attained for at least 3 of the 5 blinded readers.

Secondary Analyses:

A secondary analysis was performed to compare the proportions of subjects with normal and abnormal image patterns who converted to pAD within the follow-up period. The analysis used a 2-tailed Fisher's exact test to determine if the proportions converting to pAD were different in the two groups. P-values and 95% confidence intervals (CI) were calculated for the majority read and each of 5 independent readers separately. The majority read is the image assessment made independently by the majority of the readers (i.e., at least 3 of the 5 readers).

A secondary analysis was also a time-to-event analysis based on a quantitative image assessment (SUVR); each subject's images were categorized as either below or above a pre-specified SUVR threshold (1.56), and the two groups were compared using a Cox proportional hazards model similar to the primary analysis.

A known risk factor for AD, apolipoprotein E (ApoE) genotype, was added to the Cox proportional hazards model in a subgroup analysis. ApoE genotype was available on the subgroup of subjects consenting to ApoE testing. Analyses of the time to conversion to pAD were performed using the results of visual image assessment (normal/abnormal) and the results of quantitative (SUVR) image assessment (below/above threshold). A similar subgroup analysis was performed for early aMCI subjects vs. late aMCI subjects.

Sensitivity and specificity of the blinded visual assessment of [^{18}F]flutemetamol images were determined for each blinded reader. The standard of truth was each subject's final assessment (pAD or no pAD) made by the CAC. Sensitivity and specificity were also determined based on the SUVR classification (below or above the 1.56 threshold).

Inter-reader (between-reader) agreement was also determined and is reported as Cohen's kappa coefficient with 95% confidence interval for each reader pair as well as Fleiss' kappa for comparison across all readers.

Intra-reader (within-reader) reproducibility was determined by re-reading a random sample of images and is reported as Cohen's kappa.

Interim and Ad-hoc Analyses:

No interim analyses of the data were planned or conducted. However, in response to questions from the European Medicines Agency, an ad-hoc analysis was performed prior to the scheduled end of the study to determine the frequency of conversion from aMCI to clinical AD as a function of [18F]flutemetamol scan status (positive/negative) for a random sample of 70 (30%) of the 232 subjects. Only group level results were reported and the Sponsor remained blinded to subject-level imaging data. The primary analysis was not performed in this ad-hoc analysis and so no adjustment to statistical power or sample size was necessary

In addition, the safety data and the data on inter-reader agreement and intra-reader reproducibility were reported previously in a separate report and were submitted to US and European regulatory authorities as part of the NDA and MAA applications. These data are re-reported here without change, with the exception of corrections to medical history data, correction of dose administration for 1 subject, updates to concurrent medication data to include the follow-up period, update to the number of deaths, and minor typographical corrections.

Safety Variables

Vital signs, ECGs, blood samples for clinical laboratory tests (chemistry, hematology, and coagulation), physical/neurological examination, and AE monitoring.

Summary of Results

Efficacy:

The primary analysis was the time to conversion to pAD based on image evaluation by individual blinded

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readers, assessed by a Cox proportional hazards model. The protocol stated that the primary efficacy objective would be achieved if statistical significance ($p < 0.05$) was attained in at least 3 of the 5 analyses based on individual blinded reader interpretations. The visual interpretations were highly significant ($p \leq 0.0086$) for all 5 blinded readers; thus, the primary efficacy objective was achieved.

Controlling for age and CDR score, the HR for visual interpretation ranged from 1.962 (reader 2) to 3.418 (reader 1), with a median of 2.580 (reader 5). Using the median as an example, this means that that the odds were 2.6 to 1 that subjects with abnormal (positive) [^{18}F]flutemetamol scans would convert to pAD earlier than subjects with normal (negative) [^{18}F]flutemetamol scans.

The probability of subjects with an abnormal [^{18}F]flutemetamol scan converting to pAD before subjects with a normal scan ranged from 66% (reader 2) to 77% (reader 1), with a median of 72% (reader 5). Conversely, the probability of subjects with a normal [^{18}F]flutemetamol scan converting to pAD before subjects with an abnormal scan ranges from 23% (reader 1) to 34% (reader 2), with a median of 28% (reader 5). Similar results were also obtained for the majority image interpretation.

The survival estimate (non-conversion to pAD) decreased more rapidly over time for subjects with abnormal images compared with subjects with normal images for all 5 readers. A steady decrease in survival (non-progression) is evident from the data at 12, 24, and 36 months of follow-up, indicating increasing probability of conversion over time in the abnormal-scan group. This is paralleled by an increase in the probability of conversion (1 – survival estimate) over time (more rapid in the abnormal-scan group). After 36 months of follow-up, the probability of not converting was only 14% to 42% across the 5 readers for those subjects with abnormal scans compared with 71% to 75% for those with normal scans. Again, similar results were achieved for the majority interpretation.

For each reader and for the majority interpretation, the proportion of subjects who converted to pAD within the 36-month follow-up period was higher in the abnormal-scan group than in the normal-scan group, and the difference was highly statistically significant (2-tailed Fisher's exact test). This analysis was also performed for 12 months and 24 months of follow-up, with similar results.

The above analyses were repeated using SUVR categorization (as above or below the 1.56 threshold) in place of blinded image evaluation and similar results were obtained. The HR for SUVR was highly significant (HR=2.495, p=0.0001), with subjects who had scans above the SUVR threshold (>1.56) having a 71% probability of converting before those who had scans below the SUVR threshold (≤1.56). Survival estimates decreased more rapidly for subjects with scans above the SUVR threshold. By 36 months follow-up, the probability of not converting was only 29% for those subjects above the threshold compared with 74% for those below. The proportion of subjects who converted to pAD within the follow-up period was also significantly higher for subjects with scans above the SUVR threshold than below the threshold (63% vs. 37 % respectively, p<0.0001, 2-tailed Fisher's exact test).

Although sensitivity and specificity are not stable when the incidence and prevalence of the diagnosis of interest are changing over time, they were assessed and reported at the request of regulatory authorities. Sensitivity and specificity for each independent blinded reader and for the majority read were determined for visual interpretation of the PET scan. The "standard of truth" used for each subject was the final diagnosis (pAD or not pAD) as determined by the CAC. Sensitivity, specificity, positive predictive value, negative predictive value, and likelihood ratios were calculated for 12, 24, and 36 months of follow up. A comparison of the results by time point showed that, as expected, these metrics were changing over time; therefore, caution should be exercised in interpreting these results. Because of this instability, the results of the primary analysis (Cox proportional hazards analysis) should be viewed as the only valid indicator of efficacy.

Additional secondary analyses were conducted to examine the effect of ApoE genotype and aMCI stage (early/late) on time to diagnosis with pAD. ApoE genotype was not a significant factor in the time to diagnosis with pAD. aMCI stage was a significant factor in the time to diagnosis with pAD for all 5 readers and for the majority interpretation ($p = 0.0010$). By reader, the HR ranged from 1.928 (Reader 1) to 2.558 (Reader 2), with

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a median of 2.199 (Reader 5); by the majority interpretation, the HR was 2.257. Using the median as an example, these results indicate that the odds were 2.2 to 1 that subjects with late aMCI would convert to pAD earlier than subjects with early aMCI.
Agreement between pairs of readers ranged from 77% ($\kappa = 0.56$) to 98% ($\kappa = 0.96$). Agreement between Readers 1, 3, 4 and 5 taken in pairs ranged from 90 to 98%, while agreement between Reader 2 and each of the other 4 readers ranged from 77 to 85%. Intra-reader reproducibility was good, ranging from 86% to 100%.
Safety:
One or more AEs were reported by 20 (9%) of the 232 subjects who received Flutemetamol F 18 Injection, and 11/232 (5%) had one or more AEs considered to be at least possibly related to Flutemetamol F 18 Injection. One subject (013-0021) had a serious AE (SAE), an anaphylactoid reaction that was severe and considered related to Flutemetamol F 18 Injection; assessment by the investigator suggested that it was related to Polysorbate 80 in the formulation. One other subject (035-0030) had severe AEs of headache and low back pain that were not considered serious, but were considered possibly related to Flutemetamol F 18 Injection. The most frequent AEs were dizziness in 5 subjects (2%) and headache in 5 subjects (2%). Four of the 5 episodes of dizziness were mild and 1 was moderate; 3 of the 5 were considered possibly related to Flutemetamol F 18 Injection. Three of the 5 headaches were mild, 1 was moderate, and 1 was severe; 3 of the 5, including the severe headache, were considered possibly related to Flutemetamol F 18 Injection. The observed rate of headache was much lower than the background rates reported in healthy people and in clinical trial subjects taking placebo.
Changes from baseline in laboratory parameters, vital signs, ECG, and physical examination parameters were not considered to be clinically significant.
All AEs resolved during the follow-up period, with the exception of one case of elevated lactate dehydrogenase (Subject 033-0008), which was considered possibly related to Flutemetamol F 18 Injection. No AE resulted in withdrawal. Seven deaths occurred more than 30 days after administration of Flutemetamol F 18 Injection; none was reported in association with an SAE.

Conclusions:
Efficacy

- Subjects with abnormal scans were more likely to convert to pAD during the 36-month follow-up period than subjects with normal scans (HRs ranged from 1.962 to 3.418 across the 5 readers, with a median of 2.580). The HR exceeded 2.5 for all but one reader. The probability of subjects with abnormal scans converting to pAD before those with normal scans ranged from 66% to 77% across the 5 readers, and was 71% for the majority read. The HR was highly statistically significant for all readers, and the primary objective of the study was therefore met.
- Age and late aMCI were significant factors in predicting conversion, but ApoE genotype was not. Baseline CDR score was not assessable as a risk factor because all subjects had the same score.
- Consistent with the HRs, the survival estimate (i.e., probability of not converting to pAD) decreased more rapidly over time for subjects with abnormal images compared with subjects with normal images for all 5 readers and for the majority read. After 3 years of follow-up, the probability of not converting was only 14% to 42% across the 5 readers for those subjects with abnormal scans compared with 71% to 75% for those with normal scans. Since conversion rate = 1 – survival estimate, these data indicate an increased probability of conversion for subjects with abnormal scans.
- The proportion of subjects who converted to pAD within the 36-month follow-up period was significantly higher in the abnormal-scan group than in the normal-scan group across all 5 readers (64% were in the abnormal-scan group and 36% were in the normal-scan group, $p<0.0001$, for the majority read).
- Visual image interpretation showed good inter-reader agreement and intra-reader reproducibility.
- SUVR-based results were completely consistent with the results based on visual image interpretation.

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Safety

- Single doses of Flutemetamol F 18 Injection were generally well tolerated.
- Twenty subjects (9%) experienced AEs; 11 subjects (5%) had AEs considered at least possibly related to Flutemetamol F 18 Injection. One subject experienced an SAE (anaphylactoid reaction). The most frequent AEs were dizziness (2%) and headache (2%). There were no deaths or other significant AEs reported during this study.
- No clinically significant abnormalities were noted in clinical laboratory results, ECG results, or results from the physical and neurological examinations.
- The safety profile of Flutemetamol F 18 Injection is favorable in light of the proposed use for predicting the risk of conversion to pAD.