**Clinical Study Report Synopsis** **GE Healthcare**

**GE-067-015**

**Title:** **A Single-Arm Open-Label Multi-Center Study to Determine the Specificity of Flutemetamol F 18 Injection for Excluding the Presence of Brain Amyloid in Healthy Young Adult Subjects Aged 18 to 40**

This is an exact copy of the synopsis from the final clinical study report for the study GE-067-015. The final clinical study report (document-identifier: GE-067-015 CREP) was authorized for use by the Head of Global Medical on 12-Jul-2012 (Version 4.0).

# 2 SYNOPSIS

<table>
<tr><td>Name of Sponsor/Company:<br>GE Healthcare Ltd. and its Affiliates<br>Name of Finished Product:<br>Flutemetamol F 18 Injection<br>Name of Active Ingredient:<br>[$^{18}$F]Flutemetamol</td><td>Individual Study Table Referring to Part of Dossier in Which the Individual Study or Study Table is Presented:<br><br>Volume:<br><br>Reference:</td><td>(For National Authority Use only)</td></tr>
<tr><td colspan="3">Title of Study: A Single-Arm Open-Label Multi-Center Study to Determine the Specificity of Flutemetamol F 18 Injection for Excluding the Presence of Brain Amyloid in Healthy Young Adult Subjects Aged 18 to 40</td></tr>
<tr><td colspan="3">Investigators and Study Centers: 6 recruiting sites in the United States, 2 in the United Kingdom, 1 in Finland and 1 in Belgium</td></tr>
<tr><td colspan="3">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: 2 December 2010 through 18 March 2011</td><td>Phase of Development: 3</td></tr>
<tr><td colspan="3">Objectives:<br>Primary:<br>To determine the overall specificity of Flutemetamol F 18 Injection for excluding the presence of brain amyloid based on the visual assessment of a positron emission tomography (PET) scan by independent blinded readers reviewing images from a population of healthy young adult subjects aged 18 to 40.<br>Secondary:<br>(1) To characterize the safety ascribed to a single dose of Flutemetamol F 18 Injection.<br>(2) To determine the composite standard uptake value ratio (SUVR) (an average of frontal, anterior cingulate, parietal, lateral-temporal and posterior cingulate/precuneus uptake) following Flutemetamol F18 Injection in a population of healthy young adult subjects aged 18 to 40.<br>(3) To determine the composite SUVR following Flutemetamol F 18 Injection by individual demographic parameter (gender, age [18 to ≤30 and >30 to ≤40], ethnicity, race), clinical site and geographic location, and the commonly used scanners used to obtain the images in this study.<br>(4) To determine the specificity of Flutemetamol F 18 Injection for excluding the presence of brain amyloid based on the visual assessment of a PET scan by independent blinded readers for individual demographic parameters (gender, age [18 to ≤30 and >30 to ≤40], ethnicity, race), clinical site and geographic location, and the commonly used scanners used to obtain the images in this study.</td></tr>
<tr><td colspan="3">Study Design: This was a multi-center, open-label PET study to determine the specificity of Flutemetamol F 18 Injection for excluding the presence of brain amyloid in healthy young adult subjects aged 18 to 40 based on visual PET image assessment.<br>Each subject attended a screening visit 45 days before their Flutemetamol F 18 Injection. During the screening visit subjects were required to sign an informed consent form, meet entrance criteria and undergo safety assessments (vital signs, electrocardiograms [ECGs], blood samples for clinical laboratory tests [chemistry, hematology, and coagulation], and physical/neurological examination) and brain magnetic resonance imaging (MRI) scanning. A second screening visit occurred if the MRI and clinical assessments could not be performed in a single visit. On the day of PET scanning, each subject was administered Flutemetamol F 18 Injection and underwent a PET scan of 30 minutes duration. Adverse events (AEs) were monitored during the course of the study and at a 24-hour post-injection follow-up telephone call. Subjects were instructed to report serious adverse events (SAEs) occurring within 30 days of administration of Flutemetamol F 18 Injection for which a causal relationship could not be ruled out. The subject allocation to Flutemetamol F 18 Injection was non-randomized (each subject was dosed) while the order of blinded visual and quantitative PET image evaluations was randomized.<br>The visual assessment of [$^{18}$F]flutemetamol PET images was performed by 5 independent readers trained in the evaluation of PET brain amyloid imaging.</td></tr>
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| **Name of Active Ingredient:** [$^{18}$F]Flutemetamol | **Volume:** | |
| | **Reference:** | |

**Selection of Subjects:**

**Inclusion Criteria:**

(1) The subject was ≥18 and ≤40 years old.
(2) Subject had no evidence of cognitive impairment by medical history.
(3) The subject had a Mini-Mental State Examination score of ≥28, and was considered to be cognitively normal per Investigator's judgment.
(4) The subject had an MRI scan as part of the screening visit of sufficient diagnostic quality and consistent with normal brain function.
(5) The subject had at least 6 years of education or had a good work history (sufficient to exclude mental retardation).
(6) The subject's general health was adequate to comply with study procedures, as ascertained by review of their medical history, and laboratory and physical examinations, which must have been performed within 45 days before administration of Flutemetamol F 18 Injection.
(7) 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 3 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) were negative.
(8) Informed consent was signed and dated by the subject in accordance with local regulations.
(9) The subject was willing and able to participate in all study procedures.

**Exclusion Criteria:**

(1) The subject had received any medical ionizing radiation exposure in the last 12 months (except planar x-ray or head computed tomography) or participated in any other clinical study within 30 days of study entry.
(2) The subject had known allergies to Flutemetamol F 18 Injection or to any of the constituents.
(3) The subject was pregnant or breast-feeding.
(4) The subject had a history of alcohol and/or drug abuse within the last 2 years based upon a review of medical records.
(5) The subject had a contraindication for MRI (including, but not limited to, claustrophobia, pacemaker, and presence of metallic fragments near the eyes or spinal cord, or cochlear implant).
(6) The subject had a history of head injury with loss of consciousness.
(7) The subject had any clinically significant medical, psychiatric or neurological condition or any clinically significant abnormality on physical, neurological or laboratory examination that might be associated with brain pathology, as determined by the Investigator.
(8) The subject had a family history of Alzheimer's disease (AD; more than 1 first degree relative [i.e. birth parents and siblings] with diagnosis of AD).
(9) The subject was undergoing monitoring of occupational ionizing radiation exposure.
(10) The subject had a history of HIV infection or hepatitis.

**Number of Subjects (planned and analyzed):**

Up to 300 subjects were planned to be included. The study was stopped early based on reconsideration of sample size. When the study was halted, 218 subjects had signed informed consent, and 181 were dosed with Flutemetamol F 18 Injection, underwent PET scanning, and completed the study.

**Treatment of Subjects**

**Investigational Medicinal Product:** All subjects received an i.v. dose of approximately 185 MBq (5 mCi) of Flutemetamol F 18 Injection completed within 40 seconds. This corresponded to an effective dose of approximately 6 mSv.

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**Imaging:** PET imaging was conducted for 30 minutes and started approximately 90 minutes after the administration of Flutemetamol F 18 Injection.
**Duration of Treatment:** The study involved a minimum of 2 visits for each subject. Each subject attended a screening visit during which the subjects signed a consent form. Once all of the entrance criteria were met, an MRI scan was performed at the screening visit or at a subsequent screening visit. The baseline (day of PET) visit consisted of the Flutemetamol F 18 Injection administration followed by PET scanning. Safety assessments were conducted on the day of the PET scan and subjects were telephoned approximately 24 hours later to collect data on AEs.

**Endpoints**
**Primary Efficacy Endpoint:** The primary endpoint was visual assessment of the individual [$^{18}$F]flutemetamol PET images (prepared using only the first 10 minutes of the scanning data) classified as normal or abnormal for the presence of brain amyloid based on independent blinded reads conducted by 5 blinded independent readers. All scans from this study were blindly and randomly mixed with approximately equal numbers of [$^{18}$F]flutemetamol scans from the GE-067-005 mild cognitive impairment study (which was expected to contain some abnormal images) to avoid potential bias if readers saw only (or predominantly) normal scans. The blinded read was performed in accordance with the Food and Drug Administration's guidance to Industry and the GE-067-015 Independent Review Charter and its associated Image Review Training Manual.
**Secondary Efficacy Endpoint:** The secondary efficacy endpoint was the composite SUVR defined as an average of frontal, anterior cingulate, parietal, lateral-temporal and posterior cingulate/precuneous uptake following administration of Flutemetamol F 18 Injection.
**Standard of Truth**: The subjects evaluated in this study, healthy young adults aged 18 to 40, are presumed to be amyloid negative and this assumption constituted the standard of truth in this study.
**Primary Safety Endpoints:** Vital signs, clinical laboratory assessments, ECGs, physical/neurological examinations, and AEs were monitored and evaluated.

**Statistical Analyses**
**Primary efficacy analysis:** After blinded visual assessment of [$^{18}$F]flutemetamol PET images, each of 5 independent readers separately categorized subjects as "normal" or "abnormal" for the presence of amyloid based on the pattern of tracer uptake in PET images. The analysis results were tabulated and specificity with 95% confidence intervals presented. The lower bound of the confidence interval for specificity was compared to a threshold of 80%. The analysis was provided for the efficacy population for each of 5 blinded readers. The primary efficacy objective was achieved if at least 3 of 5 blinded readers demonstrated specificity with a lower bound of the 95% confidence interval that exceeded 80%.
**Secondary efficacy analyses:** The exact 95% binomial confidence interval for specificity was calculated and presented for individual sub-populations based on demographic factors, clinical site, and the commonly used PET scanners used in the study:

- Gender
- Age [18 to ≤ 30 and > 30 to ≤ 40]
- Ethnicity
- Race
- Clinical site
- Geographic location
- Scanners type

The SUVR was presented as univariate analyses for the entire population and for the following subgroups:

- Gender
- Age [18 to ≤30 and >30 to ≤40]
- Ethnicity

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- Race
- Clinical site
- Geographic location
- Scanners type

The agreements between readers are presented by reader pairs and all readers together with N and percent in agreement. Subject rereads are presented with N and percent in agreement for subject with rereads of visual PET images.

**Safety Analyses**: Changes from baseline in clinical laboratory assessments, vital signs, ECGs, and physical/neurological examinations, were summarized. The numbers and percentages of subjects experiencing treatment-emergent AEs were summarized. The incidence of treatment-emergent AEs and SAEs by maximum reported severity and relationship to study treatment was also summarized.

**Summary of Results**

Efficacy:

*Blinded Visual Assessments*

All subjects who received Flutemetamol F 18 Injection were available for blinded reads. The images were read by 4 out of 5 independent readers as normal in 99-100% of the cases (Reader 1 100%, Readers 3, 4 and 5 99%). Reader 2, however, read 32% of all PET scans as abnormal. The results of blinded reads by 5 independent readers showed specificity of 100%, 68%, 99%, 99% and 99%. The lower bounds of the 95% confidence intervals for specificity for the 5 readers were 98%, 61%, 97%, 97% and 96%, exceeding 95% for 4 of the 5 readers. Since the primary efficacy objective was for the lower bound of the confidence interval to exceed 80% for at least 3 of 5 readers, the primary objective was achieved. There were no notable differences in specificity observed across any of the demographic categories (gender, age category, ethnicity, and race), clinical site, geographic location, and scanner type.

The between-reader agreement was $\geq$99% for all comparisons except those including Reader 2. Within-reader reproducibility was based on each reader re-reading a 10% random sample of images from the full dataset. Readers 1, 3, 4 and 5 re-read the PET images 100% consistently with the first read. Reader 2 re-read 12 of 16 (75%) PET images consistently with the first read. The within-reader reproducibility was 100% for Readers 1, 3, 4 and 5 and 75% for Reader 2.

*SUVR Results*

The composite $SUVR_{CER}$ was 1.12 (SD = 0.097) with cerebellar cortex as the reference region and $SUVR_{PONS}$ was 0.49 (SD = 0.036) with pons as the reference region. The $SUVR_{CER}$ composite values were all well below the upper limit of normal (1.56).

Safety: Twenty-seven (15%) subjects reported AEs. The most frequent AEs were flushing (6%), chest discomfort (4%) and nausea (3%). Four subjects experienced AEs (all moderate in intensity) that were considered to be related to study medication: 1 experienced anxiety and hypertension; 1 experienced vomiting, dysgeusia, dizziness and oral discomfort; 1 experienced chest discomfort, abdominal discomfort, arrhythmia, and hypotonia; and 1 experienced dyspepsia, dyspnea and hypotonia. The majority of AEs were transient lasting a few minutes and were considered mild. There were no deaths, SAEs or other significant AEs reported during this study. There were no changes in clinical laboratory results, vital signs or ECG results that were considered clinically significant and related to the investigational medicinal product. Physical and neurological examinations showed no changes from the screening to the end of scanning.

**Conclusions:**

**Efficacy:**

- The results of blinded reads of [$^{18}$F]flutemetamol images by 5 independent readers showed point estimates

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for specificity of 100%, 68%, 99%, 99% and 99%, and the lower bound of the 95% confidence interval for specificity exceeded 95% for 4 of the 5 readers. Since the primary objective was for the lower bound of the confidence interval to exceed 80% for at least 3 of the 5 readers, the primary efficacy objective was achieved.

- There was high inter-reader agreement for 4 readers, with agreement rates of 99-100%. However, one reader was a clear outlier, with agreement rates of 68-69%.
- Intra-reader agreement was 100% for 4 of 5 independent blinded readers (Readers 1, 3, 4 and 5) and 75% (12 of 16 re-read PET images) for Reader 2.
- There were no effects on specificity across any of the demographic categories (gender, age category, ethnicity, and race), clinical site, geographic location, and scanner type.
- The mean SUVR for the composite cortical region with cerebellar cortex as the reference for non-specific tracer binding was 1.12 (SD 0.097) and with pons as the reference range 0.49 (SD 0.036). All scans had composite SUVRs which were below the upper limit of normal (1.56) established during Phase 2.

**Safety:**

- Twenty-seven (15%) subjects reported AEs. The most frequent AEs were flushing (6%), chest discomfort (4%) and nausea (3%). The majority of AEs were transient and mild. There were no deaths, SAEs, or other significant AEs reported during this study.
- There were no changes in clinical laboratory results, vital signs or ECG results that were considered clinically significant and related to the IMP.
- Physical and neurological examinations showed no changes from the screening to the end of scanning.
- Single doses of [$^{18}$F]flutemetamol were generally well tolerated in healthy subjects of 18 to 40 years of age.