Clinical Study Report Synopsis **GE Healthcare**
GE-001-013

Title: A multicentre, randomised, open label, comparative Phase 4 trial to assess changes in dementia diagnostic category and diagnostic confidence after DaTSCAN imaging in subjects with an uncertain diagnosis of dementia with Lewy bodies (possible DLB)

This is an exact copy of the synopsis from the final clinical study report for the study GE-001-013. The final clinical study report (document-identifier: GE-001-013 CREP) was authorized for use on 04-Sep-2013 (Version 1.0).

<table>
<tr><td>Name of Sponsor/Company:
GE Healthcare Ltd. and its Affiliates
Name of Finished Product:
DaTSCAN™
Name of Active Ingredient:
Ioflupane (^{123}I)</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 multicentre, randomised, open label, comparative Phase 4 trial to assess changes in dementia diagnostic category and diagnostic confidence after DaTSCAN imaging in subjects with an uncertain diagnosis of dementia with Lewy bodies (possible DLB)</td></tr>
<tr><td colspan="3">Investigators and Study Centres: Twenty-one centres in Europe recruited subjects in this study.</td></tr>
<tr><td colspan="3">Publication (reference): None</td></tr>
<tr><td colspan="2">Study Period: 14 January 2011 to 08 October 2012</td><td>Phase of Development: Phase 4</td></tr>
<tr><td colspan="3">Objectives:
Primary:
To evaluate the impact of DaTSCAN™ (hereafter referred to as DaTSCAN) imaging on diagnostic category in subjects with an uncertain diagnosis of DLB (possible DLB).
Secondary:
To demonstrate that the use of DaTSCAN improves confidence in diagnosis (COD) in these subjects.</td></tr>
<tr><td colspan="3">Study Design:
This study was a multicentre, randomised, open label, comparative Phase 4 trial to assess changes in a diagnostic category relating to DLB (e.g., a change from possible DLB to probable DLB) and diagnostic confidence after DaTSCAN imaging in subjects with an uncertain diagnosis of DLB (possible DLB). Subjects were randomised with a 2:1 probability to either an active or a control group and underwent baseline clinical diagnostic assessments, including recording of a diagnostic category and COD of dementia. The active group then underwent DaTSCAN imaging, while the control group did not. Diagnostic assessments were repeated at 8 and 24 weeks. Subjects in the control group were allowed to undergo DaTSCAN imaging after the 24-week assessment but the results did not form a part of this study.</td></tr>
<tr><td colspan="3">Selection of Subjects:
Inclusion Criteria
(1) Male or female 55 years of age or older.
(2) Mini-Mental State Examination between 10 and 28.
(3) Subjects with Possible DLB as defined by the International Consensus Criteria (dementia +1 core feature or 1 or more suggestive features), who may or may not have also fulfilled criteria for Alzheimer's disease (AD).
(4) The subject and a reliable informant (e.g., the subject's carer or relative or legally acceptable</td></tr>
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representative) were able and willing to comply with study procedures and signed and dated informed consent was obtained from each. **NOTE:** Two signatures on the informed consents were required for this study irrespective of the patient's competence level.

(5) Women who were surgically sterile (had had documented oophorectomy and/or documented hysterectomy) or were postmenopausal (cessation of menses for more than 1 year) were allowed to enrol in the study without a pregnancy test at Screening.

Exclusion Criteria

(1) Having an established/certain clinical diagnosis of probable DLB or a non-DLB form of dementia.

(2) Parkinsonism >1 year prior to onset of dementia.

(3) Severe extrapyramidal symptoms (Unified Parkinson's Disease Rating Scale, Part 3 [UPDRS-III] >30) or Parkinson's disease dementia.

(4) Known/suspected significant vascular pathology with multiple or strategic infarcts or vascular pathology in the striatum/basal ganglia as shown preferably by previous magnetic resonance imaging (MRI) or computed tomography (CT) examination. If MRI was not available prior to Baseline and there was no contraindication, the subject had to undergo an MRI scan during the course of the study to confirm that no significant vascular pathology was present. If an MRI was not clinically feasible, cerebral CT imaging within 6 months prior to Baseline or during the study was also acceptable.

(5) Symptoms suggestive of multiple system atrophy, corticobasal degeneration, progressive supranuclear palsy, or Huntington's disease.

(6) Persistent severe mental illness including depression, schizophrenia and schizoaffective illness.

(7) Normal pressure hydrocephalus.

(8) Use of any concomitant medication that is known or suspected to interact with striatal uptake through direct competition with binding of DaTSCAN to the DaT that could not be discontinued for at least 5 half-lives if the subject were to be randomised to the DaTSCAN group (these include amphetamine, benztropine, bupropion, cocaine, mazindol, methylphenidate, phentermine and sertraline).

(9) Presence of moderate to severe renal or hepatic impairment.

(10) Occupational exposure to radiation equal to or above 15 mSv per year.

(11) History of abuse or current abuse of drugs.

(12) History of alcohol abuse where period of abstinence is less than 3 years.

(13) Hypersensitivity to DaTSCAN or any of its ingredients.

(14) Female subjects who were pregnant or breast-feeding or planning a pregnancy during the course of this study or within 3 cycles of completing the study. Women of childbearing potential had to provide a negative beta human chorionic gonadotropin (b-HCG) pregnancy test (by urine dipstick method) at Screening and also prior to investigational medicinal product (IMP) administration.

(15) Participation in a clinical study involving an unlicensed pharmaceutical product within 30 days prior to Screening, and/or an unlicensed/licensed radiopharmaceutical within 5 radioactive half-lives prior to Screening.

(16) The subject had a life threatening disease state with a life expectancy of less than 1 year or history of significant medical disease, trauma, or surgical intervention that in the judgement of the investigators made the subject unsuitable for the study.

(17) The subject had already had DaTSCAN single photon emission computed tomography (SPECT) imaging or any other similar functional imaging test of the pre-synaptic and/or post-synaptic dopaminergic system (e.g. ^{18}FDOPA PET, ^{123}I iodobenzamide).

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Number of Subjects (planned and analysed):
A total of 174 subjects at up to 25 centres were planned to be enrolled.
A total of 187 subjects were enrolled in this study; of these, 116 subjects received DaTSCAN and were included in the safety population. A total of 170 subjects were included in the full analysis set (114 received DaTSCAN and 56 were in the control group).

Treatment of Subjects
Investigational Medicinal Product: A single intravenous (i.v.) injection of DaTSCAN (Ioflupane[^{123}I]) (slow injection, not less than 15-20 s), followed by a saline flush, within the dose range of 111-185 MBq.
Duration of Treatment: One administration of DaTSCAN on one day for the active group only. SPECT scanning was performed 3 to 6 hours after DaTSCAN injection. Thyroid blocking was performed according to the hospital routine.

Endpoints
Primary:
- The proportion of subjects in each group who had a change in a diagnostic category between the Baseline visit (V1) and the 8-week visit (V2).

Secondary:
- Confidence of diagnosis of dementia. This was assessed at Baseline (V1), 8 weeks (V2), and 24 weeks (V3) using a visual analogue scale ranging 0 to 100 with predefined qualitative levels of confidence.
- Changes in clinical diagnostic category between the Baseline (v1) and 24-week (V3) visits.

Statistical Analyses:
To ensure adequate numbers of evaluable subjects in each group, 116 subjects in the DaTSCAN group and 58 subjects in the control group (for a total of 174 subjects) were planned to be enrolled. A total of 187 subjects were enrolled. The Safety Analysis Set consisted of 116 subjects who received DaTSCAN. A total of 170 subjects were included in the full analysis set (114 received DaTSCAN and 56 were in the control group).
Three analysis populations were defined and analysed: randomised population, full analysis set (efficacy population) and safety analysis set. The Randomised Population consisted of all subjects who were randomised into 1 of the 2 randomisation groups. The Full Analysis Set (Efficacy Population) included all control subjects who completed V1 and V2, and all DaTSCAN subjects who completed V1 and V2 and for whom a DaTSCAN image interpretation was available. The Safety Analysis Set consisted of all subjects who were randomised to the active group and received any amount of DaTSCAN intravenously.
Tabulations of summary statistics, graphical presentations, and statistical analyses were performed using SAS® software version 9.2. Summary tables and data listings were separated by study group (control and DaTSCAN), if applicable. In addition, when applicable, summarization was also performed for the overall subject group.
All data obtained on the case report form (CRF) and entered into the database were provided in separate data listings showing individual subject values.
Categorical data were summarised using frequencies and percentages. The number of subjects with missing information was also summarised; however, the study group (control and DaTSCAN) comparison was made based on non-missing information. Continuous data were summarised with the number of non-missing observations by mean, standard deviation, median, minimum and maximum values.
The study group comparison for the primary efficacy endpoint was assessed using the Fisher's Exact test to compare the proportion of subjects with a change in clinical diagnostic category at 8 weeks (V2) compared to Baseline (V1) between the 2 study groups (control and DaTSCAN).
For the secondary endpoints, the study group comparison for COD was assessed by comparing the mean change in COD between Baseline and 8 weeks for the 2 study groups using an analysis of covariance model (ANCOVA) with study group as the main effect and baseline COD value as the covariate. This comparison was also performed between Baseline and 24 weeks, and between 8 weeks and 24 weeks. The proportion of

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subjects with a change in clinical diagnostic category at 24 weeks compared to Baseline was compared between the 2 study groups using the Fisher's Exact test.
Additional exploratory efficacy analyses were also performed.
Safety was analysed by assessment of adverse events (AEs) and injection site monitoring.

Summary of Results

Efficacy:

Primary endpoint

At the 8-week visit, 70 (61.4%) subjects in the DaTSCAN group and only 2 (3.6%) subjects in the control group recorded a change in diagnostic category as compared to Baseline ($p<0.0001$, Fisher's Exact test).

Secondary endpoint

There was a statistically significant difference between study groups in change in COD versus Baseline at 8 weeks ($p<0.0001$) and at 24 weeks ($p<0.0001$). The change in COD between 8 weeks and 24 weeks did not show any statistically significant difference between the two study groups ($p=0.654$).
At the 24-week visit, 77 (70.6%) subjects in the DaTSCAN group and 9 (16.4%) subjects in the control group recorded a change in diagnostic category as compared to Baseline ($p<0.0001$ Fisher's Exact test).

DLB features

At Baseline, core and suggestive features were present in a small percentage of cases (21.1% to 32.5% subjects) except severe neuroleptic sensitivity that was not reported by any subject. Changes over time were minimal and showed no significant relation to the study group.
Among the supportive features, only 2 of them (Depression and Relative Preservation of Medial Temporal Lobe [MTL] Structures on CT/MRI Scan) showed a clinically significant prevalence but MTL preservation was the only feature that showed some increase in prevalence over follow-up. Only a few patients reported findings related to perfusion scans and none showed abnormal uptake of MIBG by myocardial scintigraphy.

Diagnostic category

At Baseline, all subjects had a dementia diagnosis category of possible DLB. At Week 8, 38 (33.3%) subjects in the DaTSCAN group were re-categorised as probable DLB compared with 0 (0.0%) subjects in the control group and 32 (28.1%) subjects were re-categorised as non-DLB form of dementia compared with 2 (3.6%) subjects in the control group. Similar results were seen at Week 24.

DaTSCAN imaging

Physician review of DaTSCAN images in the full analysis set resulted in images for 65 (57.0%) subjects being classed as normal, images for 9 (8%) subjects being classed as abnormal type 1, images for 24 (21%) subjects being classed as abnormal type 2, images for 5 (4%) subjects being classed as abnormal type 3, and images for 11 (10%) subjects being classed as other abnormal patterns. Two additional subjects, who were not included in the full analysis set as they did not attend the Week 8 visit, had images classed as normal and other abnormal.

Primary endpoint and changes of diagnostic category and COD by results of DaTSCAN imaging

At Week 8, 30 (46%) subjects with normal DaTSCAN images and 40 (82%) subjects with abnormal DaTSCAN images had a change in diagnostic category compared to Baseline. At Week 24, 36 (58%) subjects with normal DaTSCAN images and 41 (87%) subjects with abnormal DaTSCAN images had a change in diagnostic category compared to Baseline.
At Week 8, 46% (30/65) subjects with a normal DaTSCAN image result had a change in diagnostic category to non-DLB and 78% (38/49) subjects with any abnormal image DaTSCAN result had a change in diagnostic category to probable DLB. At Week 24, 58% (36/62) of subjects with a normal DaTSCAN image result had a change in diagnostic category to non-DLB and 81% (38/47) subjects with any abnormal image DaTSCAN result had a change in diagnostic category to probable DLB.
None of the subjects with a normal DaTSCAN image result had a change of diagnosis to probable DLB whereas 4% (2/49) subjects at Week 8 and 6% (3/47) subjects at Week 24 with an abnormal DaTSCAN had a change to

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non-DLB type of dementia.
There was an increase in mean COD from Baseline following physician review of DaTSCAN images at Week 8 and Week 24. COD particularly improved when images were assessed as abnormal.
Change in diagnostic category by study group remained statistically significant when this was analysed by the 2-level breakdown of the baseline neurological examination or the neuropsychiatric test.
Primary endpoint and changes of diagnostic category and COD by results of neuropsychiatric battery
There were no statistically significant differences for change in diagnostic category at the 2-level breakdown of the neurological examination or the neuropsychiatric tests except in one case; change in diagnostic category was statistically significant for neuropsychiatric inventory total score in the control group at 24 weeks.
Statistically significant differences in mean change in COD from Baseline for the DaTSCAN group compared to the control group were demonstrated in the neurological examination and neuropsychiatric tests subgroups at the 2-level breakdown of normal/abnormal (for neurological examination) and above and below the median (for neuropsychiatric tests). However, there were no statistically significant differences between the 2-level breakdown of the neurological examination or the neuropsychiatric tests themselves.
Primary endpoint and changes of diagnostic category and COD by centre
There was significant variability among the centres, with rates of change in diagnostic category ranging from 0 to 100% in the DaTSCAN group and 0 to 66.7% in the control group with a majority of centres reporting fairly high rates in the DaTSCAN group but low rates in the control group. From the data, it was apparent that this variability had no relationship with the number of subjects recruited (although no statistical analysis was performed).
In the assessment of COD, there was variability among the centres with mean change in COD for centres with >1 subject ranging from -44.7 to 61.0 in the DaTSCAN group and -30.0 to 35.5 in the control group.
Predictive variables for abnormal DaTSCAN images
After several logistic regression analyses that took into account core and suggestive DLB features by groups, the only feature that was statistically significant was ‘spontaneous features of Parkinsonism’ and this feature was, therefore, the main predictor of an abnormal DaTSCAN image.
Additionally, a stepwise logistic regression analysis that was used to identify the best combination of the predictive core and/or suggestive baseline DLB features for predicting abnormal vs. normal DaTSCAN showed that only “spontaneous features of Parkinsonism” was a highly statistically significant predictor of an abnormal DaTSCAN image.
No other baseline variable analysed (neurological examination and neuropsychiatric battery) was able to predict the results of DaTSCAN image, being the percentages of abnormal DaTSCAN very similar between the 2-level breakdown of the neurological examination or the neuropsychiatric tests
Additional exploratory analyses
The evolution of DLB features over time was slightly different when the data were analysed by DaTSCAN image result, with the biggest difference in the evolution of spontaneous features of Parkinsonism (13.8% to 14.5% in the normal image group vs. 40.8% to 53.2% in the abnormal image group at Baseline and 24 weeks respectively).
Overall, no significant differences were noted in the evolution of the neuropsychiatric tests by the result of the DaTSCAN image. The only small difference was in the UPDRS Part III that increased in the abnormal image group.
For subjects with a final diagnosis of non-DLB, the percentages of subjects with fluctuating cognition, visual hallucination, features of Parkinsonism, and REM sleep behaviour disorders generally decreased at the Week 8 and Week 24 visits compared to Baseline. For subjects with a final diagnosis of possible DLB or probable DLB, the percentages were maintained or increased.
The neuropsychiatric test showed a similar pattern, with very small and non-significant differences between the three diagnoses for the fluctuation scale, ACE-R and its domains and neuropsychiatric inventory (NPI) and

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caregiver distress. The only trend according to the different diagnoses was shown by the UPDRS Part III that showed at Week 24 a bigger mean increase with Baseline as a reference in probable DLB (+4.2) as compared to possible DLB (+1.2) or non-DLB form of dementia (-0.3).
Medication changes were recorded in in a small subset of subjects in both groups. The data did not show any specific relationship with the study group or with the results of the DaTSCAN image.
Safety:
Twenty-four (20.7%) subjects reported a total of 39 treatment-emergent adverse events (TEAEs). There were 8 subjects with serious adverse events (SAEs) and no deaths in this study. No SAEs were suspected to be related to IMP. Two TEAEs led to withdrawal from the study by the physician and 1 additional subject was withdrawn by the reliable informant. Two TEAEs (anxiety attack and bruising at injection site) were considered at least possibly related to administration of DaTSCAN. There were no other significant TEAEs in this study.
Seven (6.0%) subjects experienced TEAEs with a highest intensity of severe, 6 (5.2%) subjects experienced TEAEs with a highest intensity of moderate, and 11 (9.5%) subjects experienced TEAEs with a highest intensity of mild.
Five (4.3%) subjects had abnormal injection site findings at 3 hours post-injection (3 subjects with haematoma, 1 subject with bleeding and haematoma, and 1 subject with bruising).

Conclusions:

- DaTSCAN SPECT imaging significantly contributed to a change in diagnostic category and improved physician's diagnostic confidence in patients with possible DLB.
- Changes in diagnostic category and COD were more frequent when the result of the DaTSCAN imaging was abnormal.
- DaTSCAN imaging showed abnormal uptake in 43% of subjects with possible DLB at Baseline.
- The only core or suggestive feature that predicted abnormality was the presence of features of Parkinsonism at Baseline.
- In this study DaTSCAN was shown to be safe and well tolerated. There were no treatment related SAEs and no deaths reported.