Clinical Study Report Synopsis
MBG308

GE Healthcare

Title: An Open-Label, Multicentre, Phase 3 Scintigraphy Study Assessing 123I-mIBG Uptake in Subjects Being Evaluated for Phaeochromocytoma or neuroblastoma

2 SYNOPSIS

<table>
<tr><td>Name of Sponsor/Company:
GE Healthcare Ltd. and its Affiliates (hereinafter referred to as the “sponsor”)</td><td rowspan="3">Individual Study Table Referring to Part of Dossier in Which the Individual Study or Study Table is Presented:

Volume:

Reference:</td><td rowspan="3">(For National Authority Use only)</td></tr>
<tr><td>Name of Finished Product:
^{123}I-mIBG</td></tr>
<tr><td>Name of Active Ingredient:
meta-iodobenzylguanidine</td></tr>
<tr><td colspan="3">Title of Study: An Open-Label, Multicentre, Phase 3 Scintigraphy Study Assessing ^{123}I-mIBG Uptake in Subjects Being Evaluated for Phaeochromocytoma or Neuroblastoma</td></tr>
<tr><td colspan="3">Investigators and Study Centre: 24 centres enrolled and dosed 251 subjects, 179 in the United States (U.S.) and 72 in Europe.</td></tr>
<tr><td colspan="3">Investigator and Centres for Independent Evaluation of Images: Image evaluation of all subjects was performed by 3 independent blinded readers at the Image Core Laboratory (ICL), Princeton, US. Two Expert Panels (EP) (a neuroblastoma panel and a phaeochromocytoma panel, each comprised of 2 physicians), reviewed subjects’ clinical information without access to ^{123}I-mIBG imaging data.</td></tr>
<tr><td colspan="3">Publication (reference):None</td></tr>
<tr><td colspan="2">Study Period: 02 August 2005 to 28 September 2006</td><td>Phase of Development: Phase 3</td></tr>
<tr><td colspan="3">Objectives:

Primary objective:
To demonstrate that ^{123}I-mIBG planar scintigraphy was sensitive and specific in confirming or excluding the diagnoses of neuroblastoma and phaeochromocytoma.

Secondary objective:
• To determine the incremental value of single photon emission computed tomography (SPECT) for improving the sensitivity and specificity of ^{123}I-mIBG planar scintigraphy for the diagnoses of neuroblastoma and phaeochromocytoma.
• To collect safety data on ^{123}I-mIBG.</td></tr>
</table>

Name of Sponsor/Company: GE Healthcare Ltd. and its Affiliates (hereinafter referred to as the "sponsor")	**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: ^{123}I-*m*IBG	**Volume:**	
Name of Active Ingredient: meta-iodobenzylguanidine	**Reference:**	

Study Design:

Each subject (or parent/legal guardian) signed an informed consent form prior to the conduct of any study procedures. The screening evaluations were to be performed at 1 or more visits within 30 days before the conduct of the baseline visit. In addition, results of physical examinations, vital signs, electrocardiograms (ECGs), and laboratory tests performed as part of routine clinical care during this period were to be recorded in the subject's case report form (CRF). If replicate assessments were performed during the screening interval, the results from those performed closest in time to baseline were to be recorded in the CRF.

At 1 hour (±15 minutes) before administration of ^{123}I-*m*IBG, any pre-administration events (symptoms that occurred before dosing) and the use of concomitant medications were to be recorded. A limited physical examination was also to be performed. A urine pregnancy test was to be performed for all female subjects of childbearing potential.

All subjects were to have ^{123}I-*m*IBG administered on the day of the baseline visit. All eligible subjects were to receive potassium perchlorate (approximately 400 mg for adults, body-weight adjusted for children) or potassium iodide, potassium iodate or Lugol solution (containing an equivalent of 100 mg of iodine for adults, body-weight adjusted for children) to block uptake of free iodine in the thyroid. Each investigator was responsible for obtaining the appropriate thyroid blockade agent and for its administration in accordance with national and local regulations and guidelines. The type of thyroid blockade agent, time of administration, and quantity of iodine compound were to be recorded on the CRF. Each eligible subject was to receive an injection of ^{123}I-*m*IBG. Adverse event (AE) and injection site monitoring were to be performed for 30 minutes following the administration of ^{123}I-*m*IBG, at which time the subject was discharged from the clinic unless the investigator determined that further monitoring was required.

At 24 (±6) hours post-administration of ^{123}I-mIBG, the subject was to return to the investigational site for scintigraphic imaging. Anterior and posterior whole-body imaging were to be performed from the head to below the knees. Alternatively, for studies on children or for sites where whole-body imaging was not performed because of equipment limitations or local practice standards, overlapping spot images extending from the head to below the knees were to be acquired. Additional spot images were to be performed as deemed appropriate by the investigator for optimal subject assessment.

SPECT imaging of the thorax and abdomen was to be obtained unless the investigator judged that either the subject could not tolerate the procedure or the information that might be obtained would be of negligible clinical value.

On-site image assessments were to be performed per standard practice at the investigational site. Data for the on-site interpretation were to be collected and all images were to be sent in digital format to the ICL.

Name of Sponsor/Company: GE Healthcare Ltd. and its Affiliates (hereinafter referred to as the "sponsor")	**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: ^{123}I-*m*IBG	**Volume:**	
Name of Active Ingredient: meta-iodobenzylguanidine	**Reference:**	

Study Design (cont'd):

All subjects who received ^{123}I-*m*IBG were to be evaluated for safety. The intent-to-diagnose (ITD; primary efficacy) population was to consist of all subjects who received ^{123}I-*m*IBG and had a diagnosis according to the standard of truth (SOT), other than indeterminate. Additional efficacy analyses were to be performed on a) subjects with diagnostic (optimal or sub-optimal) ^{123}I-*m*IBG images (as determined by independent blinded readers) and a diagnosis according to the SOT and b) all-dosed subjects regardless of the outcome of the SOT.

Vital signs, oxygen saturation, and 12-lead ECGs were to be obtained at baseline, at 5 (±2) minutes and 30 (±10) minutes post-administration of ^{123}I-*m*IBG, and at the 24-hour imaging visit. If new clinically notable changes in subject status (eg, vital signs, ECG) and/or an AE were observed between dosing and discharge (30±10 minutes) or observed since discharge, specified laboratory tests were to be performed at discharge.

All 12-Lead ECGs were to be analysed by both site personnel and a cardiologist at the ECG Core Laboratory. Injection site monitoring was to be performed at Baseline, at 5 (±2) and 30 (±10) minutes post-administration of ^{123}I-*m*IBG, and at the 24 (±6)-hour imaging visit. A limited physical examination was to be performed prior to discharge (30 [±10] minutes) on the baseline date and at the conclusion of the 24 (±6)-hour imaging visit.

Selection of Subjects:
No subjects were enrolled under the original protocol.

Inclusion Criteria:

<u>For subjects recruited under Amendment 01</u>:

(1) a) The subject has known or suspected neuroblastoma and is undergoing evaluation of disease status (for which a ^{123}I-*m*IBG scintigraphic examination is clinically appropriate)

<u>OR</u>

b) The subject is ≥18 years of age with either:
   i) Known phaeochromocytoma.
   ii) Suspected phaeochromocytoma based on abnormal levels of catecholamines or metabolites in the urine or blood with difficult to control chronic or paroxysmal hypertension and/or abnormalities in the adrenal region on ultrasound, computerised tomography (CT), or magnetic resonance imaging (MRI).
   iii) A diagnosis of a familial or hereditary condition known to be associated with phaeochromocytoma (multiple endocrine neoplasia, von Hippel-Landau disease, neurofibromatosis, etc).

<u>For subjects recruited under Amendment 02</u> :

(1) a) The subject has known or suspected neuroblastoma and is undergoing evaluation of disease status (for which a ^{123}I-*m*IBG scintigraphic examination is clinically appropriate)

<u>OR</u>

Name of Sponsor/Company: GE Healthcare Ltd. and its Affiliates (hereinafter referred to as the "sponsor")	**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: ^{123}I-*m*IBG	**Volume:**	
Name of Active Ingredient: meta-iodobenzylguanidine	**Reference:**	

Selection of Subjects (cont'd):

b) The subject has either:

i) Known phaeochromocytoma, or,

ii) Suspected phaeochromocytoma based on abnormal levels of catecholamines or metabolites in the urine or blood in conjunction with difficult to control chronic or paroxysmal hypertension and/or abnormalities in the adrenal region on ultrasound, CT, or MRI, or

iii) A diagnosis of a familial or hereditary condition known to be associated with phaeochromocytoma (multiple endocrine neoplasia, von Hippel-Landau disease, neurofibromatosis, etc).

All subjects: (enrolled under Amendments 01 and 02)

(2) The subject is able and willing to comply with study procedures and a signed and dated informed consent is obtained.

(3) The subject was male; or a female who was either pre-menarchal, surgically sterile (had a documented bilateral oophorectomy and/or documented hysterectomy), postmenopausal (cessation of menses for more than 1 year), non-lactating, or of childbearing potential for whom a urine pregnancy test (with the results known prior to investigational medicinal product (IMP) administration) was negative

Exclusion Criteria

(1) The subject was previously entered into this study or had participated in any other investigational medicinal product or medical device study within 30 days of enrolment.

(2) The subject had a history or suspicion of significant allergic reaction or anaphylaxis to iodide or iodinated imaging agents.

(3) The subject presented with any clinically active, serious, life-threatening disease other than neuroblastoma or phaeochromocytoma, with a life expectancy of less than 30 days or where participation in the study would compromise the management of the subject or other reason that in the judgement of the investigator(s) made the subject unsuitable for participation in the study.

(4) The subject had a history of renal insufficiency (serum creatinine >3.0 mg/dL [265 μmol/L]).

(5) The subject used medications that are known to interfere with ^{123}I-*m*IBG uptake and these medications could not be safely withheld for at least 24 hours before study procedures.

Number of Subjects (planned and analysed):

The original estimated sample size was 230, based upon the need to have a minimum of 140 subjects with active tumour and 45 without active tumour in a recruited population expected to have a disease prevalence of 62%. Two hundred fifty five subjects (or parent/guardian) signed informed consent, had CRFs completed, and were entered into the study. A total of 251 subjects were administered ^{123}I-*m*IBG and evaluated for safety and 250 subjects were evaluated for efficacy.

Name of Sponsor/Company: GE Healthcare Ltd. and its Affiliates (hereinafter referred to as the "sponsor")	**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: ^{123}I-*m*IBG	**Volume:**	
Name of Active Ingredient: meta-iodobenzylguanidine	**Reference:**	

Treatment of Subjects

- **Investigational Medicinal Product:** All subjects ≥18 years of age and children with a weight of ≥70 kg were to receive an intravenous injection of 370 ±10% MBq (333 to 407 MBq [9.0 to 11 mCi] of ^{123}I-*m*IBG). Doses of ^{123}I-*m*IBG for children <18 years of age (with a weight of 8-70 kg) were to be calculated on the basis of a reference activity for an adult scaled to body weight according to the schedule proposed by the European Association of Nuclear Medicine (EANM) Paediatric Task Group; for children <8 kg, a scaled activity or a fixed minimum activity of 80 ±10% MBq (72 to 88 MBq [1.9 to 2.2 mCi]) was permissible.
- **Control:** Not applicable
- **Comparator:** Not applicable
- **Standard of Truth:** Presence (or absence) of tumour was established by current histopathology results of tissue obtained during surgery or biopsy. If no current histopathology was obtained, the appropriate EP (determined by tumour category) established the SOT following review of available clinical, imaging, and histopathology results. If the EP judged that the available information was insufficient to provide a reliable conclusion regarding subject tumour status on the day of ^{123}I-*m*IBG administration, the SOT was recorded as indeterminate.
- **Adjunctive Drugs:** Subjects were to receive either potassium perchlorate (approximately 400 mg for adults, body-weight adjusted for children) or potassium iodate, potassium iodide, or Lugol solution (equivalent of 100 mg of iodine for adults, body-weight adjusted for children) to block uptake of free iodine in the thyroid at approximately 1 hour prior to administration of ^{123}I-*m*IBG.
- **Duration of Treatment:** All subjects were to be followed for at least 24 (±6) hours post-^{123}I-*m*IBG administration. Safety assessments concluded upon completion of ^{123}I-*m*IBG imaging. Efficacy assessments concluded upon completion of the final diagnostic evaluation by the clinical investigator.

Primary Efficacy Endpoint:

Modality	Method of Measurement	Output (relative to injection time)
Planar scintigraphy	Whole-body imaging at 24 (±6) hours post ^{123}I-*m*IBG administration	Focal increased uptake (presence or absence)

The primary efficacy endpoint was used for analyses of sensitivity and specificity of planar scintigraphy.

Secondary Efficacy Endpoint:

Modality	Method of Measurement	Output (relative to injection time)
SPECT scintigraphy	Imaging at 24 (±6) hours post-^{123}I-*m*IBG administration	Focal increased uptake (presence or absence)

Name of Sponsor/Company: GE Healthcare Ltd. and its Affiliates (hereinafter referred to as the "sponsor")	**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: ^{123}I-*m*IBG	**Volume:**	
Name of Active Ingredient: meta-iodobenzylguanidine	**Reference:**	

Endpoints

Focal increased uptake from a combined reading of planar and SPECT scintigraphy was used to estimate the sensitivity and specificity of the diagnosis when both modalities are used.

Safety:

The occurrence of 1 or more treatment-emergent AEs and serious AEs (SAEs), reported through the completion of the 24 (±6) hours imaging visit were summarised using counts and percents. Adverse events were summarised by severity, seriousness, relationship to the investigational medicinal product, and time of occurrence. Vital signs (heart rate [HR], systolic and diastolic blood pressure [SBP and DBP, respectively], and respiration rate), oxygen saturation, 12-lead ECG, injection site monitoring and limited physical examination data were collected and evaluated.

Statistical Methods:

Tabulations of summary statistics, graphical presentations, and statistical analysis were performed using SAS® software.

Relevant summaries for individual centres, or combinations of centres, was presented for primary data. All subject data was presented in separate data listings. The ITD population, consisted of all subjects injected with ^{123}I-*m*IBG who had a diagnosis according to the SOT other than indeterminate. Additional efficacy populations included: a) an Evaluable Diagnostic Image population, including subjects with diagnostic (optimal or sub-optimal) ^{123}I-*m*IBG images and a diagnosis according to the SOT and b) an All-Dosed population. All subjects enrolled in the study and administered ^{123}I-*m*IBG were included in the safety analysis population.

The primary endpoint, focal increased uptake (presence or absence) on planar scintigraphy, was used to determine the sensitivity and specificity of ^{123}I-*m*IBG imaging. The SOT for the presence or absence of active phaeochromocytoma or neuroblastoma was established by histological (ie, biopsy or surgery), radiological (ie, CT, MRI, ^{131}I-*m*IBG scintigraphy) and biochemical (plasma/urine catecholamines and/or metabolites) methods, with the final determinations for subjects without current histopathology results being provided by the independent review of the EPs.

Sensitivity: (No. of True Positives) ÷ (No. of Subjects diagnosed with active tumour) and

Specificity: (No. of True Negatives) ÷ (No. of Subjects without active tumour) , where:

True Positive was defined as a subject with truth standard diagnosis of active neuroblastoma or phaeochromocytoma and abnormal uptake on ^{123}I-*m*IBG planar scintigraphy identified as active phaeochromocytoma or neuroblastoma

Name of Sponsor/Company: GE Healthcare Ltd. and its Affiliates (hereinafter referred to as the "sponsor")	**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: ^{123}I-*m*IBG	**Volume:**	
Name of Active Ingredient: meta-iodobenzylguanidine	**Reference:**	

Statistical Methods (cont'd):

True Negative was defined as a subject in whom active neuroblastoma or phaeochromocytoma has been ruled out according to the truth standard, and there is no abnormal uptake consistent with active tumour on ^{123}I-*m*IBG planar scintigraphy.

The number of subjects diagnosed with active tumour was all subjects with ^{123}I-*m*IBG planar scintigraphy and a diagnosis according to the SOT.

Subjects for which no diagnosis was made by an independent reader were excluded from both True Positive and True Negative categories but were accounted for in the denominator of both sensitivity and specificity.

For each reader, the primary analyses tested the hypothesis: H_0: $p_a = 0.80$ vs. H_1: $p_a > 0.80$, where, for sensitivity, p_a is the proportion of sensitive diagnoses for each reader's ^{123}I-*m*IBG uptake assessment (as defined above) and, for specificity, is the proportion of specific diagnoses.

^{123}I-*m*IBG imaging was deemed diagnostically efficacious if lower bounds for 95% confidence intervals (CIs) about both sensitivity and specificity are 80% or greater for 2 out of 3 readers. The exact 95% CIs were presented based upon the results for all subjects injected with ^{123}I-*m*IBG (ie, ITD population: all subjects injected, including any not imaged or with non-diagnostic images, with these included in the sample as incorrect diagnoses and added to the denominator of the estimates).

Analyses of the primary endpoint was performed for the following sub-populations:

(1) All-Dosed population: To determine if there was a bias created by subjects having indeterminate gold standard diagnoses, sensitivity and specificity (and their 95% CIs) will be calculated twice for the all-dosed population. The first analysis assessed these statistics with indeterminate gold standard results being set to positive for tumour. The second analysis assessed these statistics with indeterminate gold standard results being set to negative for tumour.

(2) Evaluable Diagnostic Image population: To determine how well ^{123}I-*m*IBG imaging performed under at least sub-optimal but diagnostic conditions, sensitivity and specificity (and their 95% confidence intervals) were calculated for the Evaluable Diagnostic Image population.

AEs were summarised as previously indicated. Exact 95% CIs will be created for overall AE rates and within each tumour population.

Name of Sponsor/Company: GE Healthcare Ltd. and its Affiliates (hereinafter referred to as the "sponsor")	**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: ^{123}I-*m*IBG	**Volume:**	
Name of Active Ingredient: meta-iodobenzylguanidine	**Reference:**	

Summary of Results

<u>Efficacy:</u>

Primary Analysis:

The lower bounds of the 95% confidence intervals (CI) for sensitivity for Readers A, B, and C were 73%, 70% and 71%, respectively, were not statistically different from 80%. The lower bounds of the 95% CI for specificity for Readers A, B, and C were 63%, 59% and 55%, respectively.

The point estimated and 95% CIs were computed for accuracy, PPV, and NPV based on the ITD population. None of the reader's estimates for accuracy reached 80%, while respective PPV estimates were higher than 80% and ranged between 89% and 91%. Negative Predictive Values ranged between 51% and 56% for all 3 readers.

Secondary Analyses:

- The lower bounds of the 95% confidence intervals (CI) for sensitivity for Readers A, B, and C were 73%, 70% and 71%, respectively, not statistically different from 80%. The lower bounds of the 95% CI for specificity for Readers A, B, and C were 63%, 59% and 55%, respectively, not statistically different from 80%. The Null hypothesis was not rejected for any reader for either sensitivity or specificity.
- None of the reader's estimates for accuracy reached 80%, while respective PPV estimates were higher than 80% and ranged between 89% and 91%. NPV estimates ranged between 51% and 56% for all 3 readers.
- For the All-Dosed population with the SOT for Indeterminate subjects set to active tumour (positive), the range for sensitivity was 67% to 70% for all three readers, while the range for specificity was 69% to 77%.
- For the All-Dosed population with the SOT set to non-active tumour (negative), the range for sensitivity was 77% and 80% for all 3 readers, while the range for specificity was 30% to 74%.
- Accuracy values for the All-Dosed population with the SOT for Indeterminate subjects set to negative (range: 76% to 78%) were greater than the values for the same population with the SOT set to positive (range: 68% to 72%).
- The PPV values were higher for the All-Dosed population with the SOT for Indeterminate subjects set to positive (range: 89% to 92%) than PPV values for the same population with the SOT set to negative (range: 74% to 82%).
- NPV values were lower for the same population with the SOT set to positive (range: 37% to 41%) than NPV values with the SOT set to negative (range: 65% to 68%).
- The estimates for evaluable diagnostic image population were similar to those computed for the ITD population.
- Sensitivity for all readers for the Planar + SPECT population was comparable to the corresponding sensitivity for the primary analysis (range 77% to 80%), while the specificity was lower (range 52% to 57%).

Name of Sponsor/Company: GE Healthcare Ltd. and its Affiliates (hereinafter referred to as the "sponsor")	**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: ^{123}I-*m*IBG	**Volume:**	
Name of Active Ingredient: meta-iodobenzylguanidine	**Reference:**	

Safety:

- Among the 251 subjects administered with ^{123}I-*m*IBG, 13 subjects experienced 17 AEs that were mild or moderate in intensity and the majority of AEs (15/17) were not related to ^{123}I-*m*IBG. No AEs resulted in subject withdrawal. There was 1 SAE (hospitalization for treatment of supraventricular tachycardia due to Wolff-Parkinson-White syndrome) assessed as unrelated to ^{123}I-mIBG and due to a pre-existing medical condition; the subject completed the study. There were no deaths reported in the study.
- AE, vital signs, and ECG data from this trial revealed no significant cardiovascular concerns associated with administration of ^{123}I-*m*IBG. Administration of ^{123}I-*m*IBG produced no systematic changes in QTc intervals (maximum mean change from baseline of 2.1 msec and 3.3 msec using Bazett and Fridericia formulae), with similar frequencies of increased and decreased QTc values. Nine subjects (3.6%) had normal baseline and abnormal 5-minute post-administration QTc values; all had normal QTc intervals on subsequent ECGs during the 24-hour safety monitoring period. No episodes of new heart block were identified during the trial.
- ^{123}I-*m*IBG was generally well tolerated and no significant trends requiring further study were identified.

Conclusion:

While the primary efficacy results for this trial did not achieve the pre-defined statistical target, the data still suggest that ^{123}I-*m*IBG scintigraphic imaging is a valuable technique for the orphan populations of phaeochromocytoma and neuroblastoma subjects. Several secondary analyses of the trial data provide evidence supporting the conclusion that the sensitivity and specificity of the method are both on the order of 85% in patients for whom an adequate SOT is available. In select subpopulations, the maximum achievable performance of this imaging examination is probably between 85% and 90%, particularly if the images are interpreted in combination with correlative anatomic data. While 5 to 10% of appropriately selected patients with tumour may not show active uptake of this agent because of limited tumour expression of the norepinephrine transporter or limited spatial resolution of scintigraphic gamma cameras, even in these patients, a negative imaging study may have important therapeutic implications. Used in the appropriate patient populations and interpreted with modern clinical techniques, the trial data support the conclusion that ^{123}I-*m*IBG imaging is safe and provides reproducible results that are of value to clinicians.