Clinical Study Report Synopsis
MBG203

GE Healthcare

Title: MBG203 CLINICAL STUDY REPORT SYNOPSIS

This is an exact copy of the synopsis from the final clinical study report for the study MBG203. The final clinical study report (document-identifier: PC MBG203 CREP) was authorised for use by the Head of Global Medical on 23 April 2007 (Version 1.0, effective date 24 April 2007).

2 SYNOPSIS

<table>
<tr><td>Name of Sponsor/Company:
GE Healthcare Ltd. and its Affiliates</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 2 Study Evaluating the Utility of ^{123}I-mIBG Scintigraphy for Assessing Arrhythmic Risk as Compared to Cardiac Electrophysiology Testing in Subjects with Left Ventricular Dysfunction</td></tr>
<tr><td colspan="3">Investigators and Study Centre(s): Seventeen centres located in Europe and 1 centre in the USA participated in this study.</td></tr>
<tr><td colspan="3">Investigators and Centres for Independent Evaluation of Images: Image evaluation was performed by 3 independent blinded readers at the Image Review Centre (IRC), Oslo, Norway. A Clinical Adjudication Committee (CAC), comprised of 3 cardiologists with training in electrophysiology (EP), cardiac EP testing and the treatment of arrhythmic disorders, reviewed the results of the cardiac EP studies.</td></tr>
<tr><td colspan="3">Publication (reference): None</td></tr>
<tr><td colspan="2">Study Period: 15 December 2004 to 27 September 2006</td><td>Phase of Development: Phase 2</td></tr>
<tr><td colspan="3">Objectives:
Primary:
• To investigate the relationship between cardiac EP test results and myocardial sympathetic innervation as represented by the meta-iodobenzylguanidine (^{123}I) (^{123}I-mIBG) planar heart to mediastinum (H/M) ratio.
• To investigate the relationship between cardiac EP test results and myocardial sympathetic innervation as represented by the total mismatch score between ^{123}I-mIBG myocardial Single Photon Emission Computed Tomography (SPECT) and MYOVIEW Myocardial Perfusion Imaging (MPI) SPECT.</td></tr>
</table>

Name of Sponsor/Company: GE Healthcare Ltd. and its Affiliates **Name of Finished Product:** ^{123}I-*m*IBG **Name of Active Ingredient:** meta-iodobenzylguanidine	**Individual Study Table Referring to Part of Dossier in Which the Individual Study or Study Table is Presented:** **Volume:** **Reference:**	**(For National Authority Use only)**

Secondary:

- To investigate the relationship between cardiac EP test results and parameters of myocardial ^{123}I-mIBG uptake with other clinical parameters (e.g. left ventricular ejection fraction [LVEF], New York Heart Association [NYHA] classification, brain natriuretic peptide [BNP] and norepinephrine [NE] levels, MYOVIEW electrocardiogram (ECG)-gated SPECT MPI, and venous blood pool activity).
- To collect safety data on ^{123}I-*m*IBG.

Study Design:

This was a phase 2, open-label, multicentre exploratory trial that investigated the relationship between cardiac EP test results and myocardial sympathetic innervation as represented by findings on ^{123}I-*m*IBG planar and SPECT scintigraphy. One hundred subjects were planned to be enrolled in the USA and Europe.

To be included in the efficacy analysis, a subject had to have cardiac EP results, and diagnostic images (optimal or sub-optimal) for a given reader. The maximum time for subject involvement in the study was expected to be up to 28 days post ^{123}I-mIBG administration, including a screening period of up to 7 days, a baseline visit, administration of investigational medicinal product (IMP) and MYOVIEW (where given as a study procedure) and a 24 ± 6 hour post-administration period. Cardiac EP testing had to be scheduled no more than 21 days after the administration of ^{123}I-mIBG unless it had already been performed prior to ^{123}I-*m*IBG imaging (Amendment 03).

Selection of Subjects:

Inclusion Criteria:

(1) The subject was ≥18 years of age at study entry.

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

(3) The subject was male, or a female who was surgically sterile (with a documented bilateral oophorectomy and/or documented hysterectomy), postmenopausal (cessation of menses for more than 1 year), non-lactating, or if of childbearing potential had a urine pregnancy test performed before administration of IMP and the result was negative.

(4) The subject had a history of prior myocardial infarct (MI).

(5) <u>For subjects recruited under Amendment 03</u>:
The subject was either (a) scheduled to undergo a clinically indicated cardiac EP study to assess for ventricular tachyarrhythmia inducibility within the next 21 days; or (b) underwent a clinically indicated cardiac EP study which was positive for inducible ventricular tachyarrhythmia within the 12 months preceding study entry and subsequently had placement of an implanted cardioverter defibrillator (ICD).
<u>For subjects recruited prior to Amendment 03:</u>
The subject was scheduled to undergo a clinically indicated cardiac EP study within the next 21 days because of one of the following:
- Non-sustained ventricular tachycardia with coronary heart disease.
- Syncope of undetermined origin.

(6) <u>For subjects recruited under Amendment 03</u>:
The subject had a rest LVEF <50% measured by an appropriate method (i.e. radionuclide ventriculography, contrast ventriculography, ECG-gated SPECT MPI, or echocardiography) within 90 days of study entry.
<u>For subjects recruited prior to Amendment 03</u>:
The subject had a rest LVEF ≤40% measured by an appropriate method (i.e. radionuclide

Name of Sponsor/Company: GE Healthcare Ltd. and its Affiliates	**Individual Study Table Referring to Part of Dossier in Which the Individual Study or Study Table is Presented:**	**(For National Authority Use only)**
Name of Finished Product: ^{123}I-*m*IBG		
Name of Active Ingredient: meta-iodobenzylguanidine	**Volume:**	
	Reference:	

ventriculography, contrast ventriculography, ECG-gated SPECT MPI, or echocardiography) within 30 days of study entry.

(7) The subject was clinically stable for at least 7 days before study entry (e.g. not experiencing continuing chest pain or haemodynamic instability).

Exclusion Criteria:

(1) The subject had a history of non-ischaemic cardiomyopathy.

(2) The subject had experienced an acute MI within 30 days of study entry.

(3) For subjects recruited under Amendment 03:
The subject was scheduled for EP testing and had a functioning pacemaker, ICD, or had received external defibrillation to treat a previous arrhythmic event.
For subjects recruited prior to Amendment 03:
The subject had a functioning pacemaker, ICD, or had received external defibrillation to treat a previous arrhythmic event.

(4) The subject was previously entered into this study or had participated in any other IMP or medical device study within 30 days of study entry.

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

(6) The subject had previously received either ^{123}I-*m*IBG or ^{131}I-*m*IBG.

(7) The subject had poorly controlled hypertension (as determined by a resting measurement of >180 mm Hg systolic or >110 mm Hg diastolic).

(8) The subject used medications for non-cardiac medical conditions that were known to interfere with ^{123}I-*m*IBG uptake and these medications could not be safely withheld 24 hours before study procedures.

(9) The subject had a percutaneous cardiac revascularisation (either a percutaneous transluminal coronary angioplasty [PTCA] or percutaneous coronary intervention [PCI] within 15 days of study entry or a coronary artery bypass graft [CABG] within 45 days of study entry).

(10) The subject presented with any other clinically active, serious, life-threatening disease with a life expectancy of less than 12 months, or participation in this study would compromise the management of the subject, or any other reason that in the judgement of the investigator(s) made the subject unsuitable for participation in the study.

(11) The subject had a serious non-cardiac medical condition associated with significant elevation of plasma catecholamines including pheochromocytoma.

(12) The subject was scheduled to have a revascularisation procedure (e.g. PCI or CABG) or cardiac transplant within 30 days of study entry.

(13) The subject was claustrophobic or had a movement disorder that prevented him/her from lying still in a supine position for up to an hour at a time.

(14) The subject had poorly controlled Type I or Type II diabetes mellitus as defined by a non-fasting serum glucose level >200 mg/dl (11 mmol/l) or a fasting serum glucose level >150 mg/dl (8.3 mmol/l).

(15) The subject had renal insufficiency (serum creatinine >3.0 mg/dl [265 μmol/l]).

(16) The subject was anaemic (haemoglobin <8.5 g/dl [85 g/l]) or thrombocytopenic (platelet count <100,000/mm^3 [100,000 x 10^9/l]).

(17) The subject had participated in a research study using ionising radiation within 12 months of study entry.

Number of Subjects (Planned and Analysed):
One hundred subjects were planned to be enrolled. A total of 73 subjects were enrolled in this study.

Name of Sponsor/Company: GE Healthcare Ltd. and its Affiliates **Name of Finished Product:** ^{123}I-*m*IBG **Name of Active Ingredient:** meta-iodobenzylguanidine	**Individual Study Table Referring to Part of Dossier in Which the Individual Study or Study Table is Presented:** **Volume:** **Reference:**	**(For National Authority Use only)**

Ten subjects withdrew from the study prior to administration of ^{123}I-*m*IBG. A total of 63 subjects were administered with ^{123}I-*m*IBG. Six subjects did not complete the study and 1 subject was withdrawn from the efficacy analysis due to protocol violation. Therefore 56 subjects were analysed for efficacy. The CAC assessed 30 subjects as EP positive, 20 subjects as EP negative and 6 subjects as indeterminate. All 63 subjects administered with ^{123}I-*m*IBG were analysed for safety.

Treatment of Subjects

Sympathetic innervation of the myocardium was measured by ^{123}I-*m*IBG scintigraphy and was evaluated as a method for assessing arrhythmic risk in subjects with left ventricular dysfunction in comparison to cardiac EP testing, the standard procedure for this assessment. Subjects were also administered Myoview for comparison with ^{123}I-*m*IBG in the Total Mismatch Score.

Investigational Medicinal Product:

^{123}I-*m*IBG was administered as a single intravenous injection of 10 mCi ± 5% (352-388 MBq), at rest. ^{123}I-*m*IBG injection was diluted to a total volume of 5 ml using 0.9% sodium chloride, if required, and injected over 30 to 60 seconds.

Standard of Truth:

The decisions rendered by the CAC were the standard of truth. The CAC reviewed the results of the cardiac EP tests in the absence of ^{123}I-*m*IBG image results and provided a determination of whether the EP study was positive or negative for inducible ventricular tachyarrhythmia.

Adjunctive Drugs:

There were 2 adjunctive treatments:

(1) One hour before the administration of ^{123}I-*m*IBG, subjects received either potassium perchlorate (approximately 400 mg) or potassium iodate, potassium iodide, or Lugol solution (equivalent of 100 mg of iodine) to block uptake of free iodine in the thyroid.

(2) MYOVIEW 20 mCi (740 MBq) (range: 18.9 to 20.3 mCi [700 to 750 MBq]) injection was administered within ± 7 days of ^{123}I-*m*IBG imaging.

Duration of Study/Treatment:

The study duration was up to 28 days. Subjects were screened up to 7 days prior to administration of ^{123}I-*m*IBG and then followed for approximately 24 hours post-administration. Cardiac EP testing was performed between 24 hours and 21 days after ^{123}I-*m*IBG administration unless it had already been performed prior to ^{123}I-*m*IBG imaging (as per Amendment 03).

Endpoints

Efficacy:

Primary endpoints:

Variables employed for primary efficacy endpoint analyses were:

- ^{123}I-*m*IBG uptake (H/M ratio) at 3 hours 50 minutes post-administration on planar scintigraphy in relation to EP results.
- Total Mismatch Score between ^{123}I-*m*IBG SPECT and MYOVIEW MPI SPECT in relation to EP results (using the 4-hour *m*IBG SPECT).

Secondary efficacy endpoints:

The secondary efficacy analyses were:

- H/M ratio (15 to 25 minute summation image)
- *m*IBG Total SPECT Defect Score (25-minute SPECT)
- *m*IBG Total SPECT Defect Score (4-hour SPECT)
- LVEF (clinical history; MPI ECG-gated SPECT)
- NYHA Class (clinical history)

Name of Sponsor/Company: GE Healthcare Ltd. and its Affiliates	**Individual Study Table Referring to Part of Dossier in Which the Individual Study or Study Table is Presented:**	**(For National Authority Use only)**
Name of Finished Product: ^{123}I-*m*IBG		
Name of Active Ingredient: meta-iodobenzylguanidine	**Volume:**	
	Reference:	

- NE and BNP levels

The result of the EP test (positive or negative) was used as the standard of truth.

Safety:
Safety data were collected and evaluated at multiple time points from baseline to the end of the imaging portion of the study. Only symptoms/signs that began or worsened in severity after administration of IMP were recorded as adverse events (AEs). Injection site monitoring occurred throughout the post-administration period. All serious and non-serious AEs were followed until the 24-hour follow-up visit or until a final outcome was known, unless a subject withdrew from the study, in which case the AE was followed until the outcome was known or until the time of database lock. Clinical laboratory parameters (haematology, serum chemistry and urinalysis), oxygen saturation and vital signs (heart rate, systolic and diastolic blood pressure, and respiratory rate) were measured at various time points. 12-lead standard ECGs obtained during the study were read at the investigational site by an appropriately trained physician and also independently evaluated by a certified cardiologist at the ECG core laboratory. Physical examinations included assessment for the presence of abnormalities in general appearance, lungs, cardiovascular system, skin, and extremities, with the intent of identifying signs and symptoms of cardiac insufficiency indicative of heart failure.
The investigator assessed each safety parameter for 'normal' or 'abnormal', and 'clinically notable' findings. Clinical laboratory, vital sign, and ECG results were reviewed to determine if they reflected a new abnormality, a significant worsening from pre-administration, or an outlying result or extreme value.

Statistical Analyses:
Tabulations of summary statistics, graphical presentations, and statistical analyses were performed using SAS® software. All efficacy tables and data listings were separated by the 2 evaluable subject groups, namely the cardiac EP test positive and cardiac EP test negative subjects. The safety tables and data listings were not separated by subject groups. The last pre-administration observation was used as the baseline value for calculating post-administration changes from baseline.
Statistical tests used a 0.05 significance level and were 2-sided unless otherwise noted. Confidence intervals, both individual and simultaneous, were at >95% confidence level unless stated otherwise. Missing values were not substituted by estimated values, but treated as missing in the statistical evaluation.

Summary of Results
Efficacy:
The primary objectives of this study were to explore the relationship between EP results and H/M ratio and the relationship between EP results and ^{123}I-*m*IBG SPECT/MPI mismatch scores. The late H/M ratio (3 hour 50 minutes) was not statistically significant as a predictor of EP results; p values for readers A, B and C were 0.4071, 0.5650, and 0.7019 respectively. The mismatch score was not a statistically significant predictor of EP results; p values for readers A, B and C were 0.5626, 0.1116, and 0.4599 respectively. The late *m*IBG SPECT total defect score (sum of defect scores across the 17 individual myocardial segments) was statistically significant as a predictor of EP results; p values for readers A, B and C were 0.0334, 0.0050 and 0.0117 respectively. Inter-reader agreement was very high for H/M ratios (correlation of 0.99). The correlations between *m*IBG SPECT defect scores were low to medium (0.2-0.6); in particular the correlation between readers A and B was very low. Correlations for the MPI defect scores were high.
Safety:
Among the 63 subjects administered with ^{123}I-*m*IBG, 3 subjects experienced 3 AEs that were mild or

Name of Sponsor/Company: GE Healthcare Ltd. and its Affiliates	**Individual Study Table Referring to Part of Dossier in Which the Individual Study or Study Table is Presented:**	**(For National Authority Use only)**
Name of Finished Product: ^{123}I-*m*IBG		
Name of Active Ingredient: meta-iodobenzylguanidine	**Volume:**	
	Reference:	

moderate in intensity and were not related to IMP. No AEs resulted in subject withdrawal. There were no serious AEs or deaths reported in the study. Clinical laboratory values, vital signs and ECGs did not reveal clinically significant trends or safety signals. All changes seen in individual subjects were satisfactorily explained by the underlying cardiac disease and associated medical history.

Conclusions:
The H/M ratio was not statistically significant as a predictor of EP results. The mismatch score was not a statistically significant predictor of EP results. The *m*IBG SPECT total defect score was a statistically significant predictor of EP results. Clinical laboratory values, vital signs and ECGs did not reveal clinically significant trends or safety signals.