CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-290

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

Statistical Review and Evaluation

CLINICAL STUDIES

NDA/Serial Number:	22,290 / S000
Drug Name:	AdreView™ (Iobenguane I ^{123} Injection)
Indication(s):	Imaging agent for the detection of primary or Metastatic pheochromocytomas and neuroblastomas
Applicant:	GE Healthcare
Date(s):	Submission Date: March 20, 2008 PDUFA Date: September 19, 2008
Review Priority:	Priority
Biometrics Division:	Division of Biometrics V
Primary Statistical Reviewer:	Xiaoping (Janet) Jiang, Ph.D.
Secondary Statistical Reviewer:	Anthony Mucci, Ph.D.
Concurring Reviewers:	Team Leader: Jyoti ZalkiKar, Ph.D. Division Director: Aloka Chakravarty, Ph.D.
Medical Division:	Division of Medical Imaging and Hematology
Clinical Team:	Reviewer: Robert J Yaes, M.D. Team Leader: Alex Gorovets, M.D.
Project Manager:	James Moore

Keywords: Sensitivity, Specificity, Meta-Analysis

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1 EXECUTIVE SUMMARY

1.1 CONCLUSIONS AND RECOMMENDATIONS

In this NDA, the sponsor submitted the results of study MBG308 and study MBG304 to seek an approval of ^{123}I-*m*IBG (Iobenguane I ^{123}) to be used as an imaging agent for the detection of primary or metastatic pheochromocytomas and neuroblastomas. This reviewer verified the sponsor's primary efficacy results of sensitivity and specificity from study MBG308. The sponsor claimed that observed sensitivity and specificity of ^{123}I-*m*IBG with corresponding lower bounds of the 95% confidence intervals (CI) as shown in the following table.

Results of Sensitivity and Specificity in Study MBG308

	Reader A	Reader B	Reader C
Estimated Sensitivity (N=159)	0.80	0.77	0.79
95% CI	0.73, 0.86	0.70, 0.84	0.71, 0.85
Estimated Specificity (N=52)	0.77	0.73	0.69
95% CI	0.63, 0.87	0.59, 0.84	0.55, 0.81

As shown in the table, the lower bounds of the 95% CI of sensitivity and specificity are less than 80% for all readers. From this reviewer's point of view, these results from the study MBG308 failed to meet the primary objectives to demonstrate that ^{123}I-*m*IBG planar scintigraphy was sensitive and specific to the pre-specified levels of 80% in confirming or excluding the diagnoses of neuroblastoma and phaeochromocytomas. Whether ^{123}I-*m*IBG scintigraphic imaging can provide clinical value in diagnosis of phaeochromocytoma or neuroblastoma will be deferred to the clinical judgment.

1.2 BRIEF OVERVIEW OF CLINICAL STUDIES

Iobenguane I ^{123} Injection is a radiopharmaceutical intended for intravenous injection. In this NDA submission, efficacy data were collected by the sponsor from study MBG308. Study MBG308 was an open-label, multicenter, Phase 3 scintigraphy study. The objective of study MBG308 was to demonstrate that ^{123}I-*m*IBG planar scintigraphy was sensitive and specific in confirming or excluding the diagnoses of neuroblastoma and phaeochromocytoma. The primary

efficacy endpoint was focal increased uptake (presence or absence) on planar scintigraphy that was used to determine the sensitivity and specificity of ^{123}I -mIBG imaging. A total of 251 subjects being evaluated for known or suspected pheochromocytoma or neuroblastoma were enrolled and received a dose of ^{123}I-*m*IBG. Among them, 179 were in the US, and 72 in the Europe (EU). This study was conducted in 24 centers where 16 were in US and 8 in EU. The primary efficacy population, also known as the intent-to-diagnose (ITD) population, consisted of subjects injected with ^{123}I-*m*IBG, who had a standard of truth diagnosis based upon "current" histopathology or a definitive decision (positive or negative) from an Expert Panel. Sensitivity and specificity of ^{123}I-*m*IBG planar scintigraphy in confirming or excluding the diagnoses of neuroblastoma andpheochromocytoma were estimated for the ITD population for each reader. Among 251 patients who were administered ^{123}I*m*IBG, 250 subjects were evaluable for efficacy (one subject was withdrawn due to a protocol violation).

Sensitivity was defined as number patients with true positives (presence of active tumor) divided by no. of patients diagnosed with active tumor and specificity was defined as number of patients with true negatives divided by no. of subjects without active tumor.

The null hypothesis of study MBG308 was that the sensitivity and specificity were each 80%. In other words, if the lower bound of confidence interval (CI) for the estimate of sensitivity (or specificity) for a reader was >80%, the hypothesis would be rejected. For the trial to achieve statistical success, the null hypothesis for both sensitivity and specificity needed to be rejected by at least two readers.

The standard of truth, presence (or absence) of tumor, was established by current histopathology results of tissue obtained during surgery or biopsy. If no current histopathology was obtained, the appropriate expert panel (EP) (determined by tumor 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 tumor status on the day of ^{123}I-mIBG administration, the SOT was recorded as indeterminate.

The results of meta-analysis study MBG304 are also included in this NDA submission. Study MBG304 was a meta-analysis study to evaluate the performance of ^{123}I-mIBG image for the detection of neuroblastoma and phaeochromocytoma at the subject level. The objective of this study was to combine available published data on the diagnostic performance of 123I-mIBG as an imaging agent for localizing specific tumors of neural crest origin, including neuroblastoma and phaeochromocytoma, in order to obtain best estimates of the sensitivity and specificity of the scintigraphic method. In order to accomplish this objective, the data from all available articles on 123I-mIBG imaging published between 1980 and 2004 on the topics of interest were collected, combined, and systematically analyzed using meta-analysis methodology. A total of 19 eligible articles were included in study MBG304. Most of the studies described in those articles were conducted in Europe, with the remainder from the U.S. and Japan. Thirty-seven percent (37%) of the studies were initiated before the year of 1991.

The meta-analysis results for ^{123}I -mIBG imaging for sensitivity of neuroblastoma and sensitivity and specificity of phaeochromocytoma are all >90% and consistent with the widely held perception of the value of the scintigraphic method. There were insufficient quality published data to permit a similar analysis of ^{123}I -mIBG imaging performance for diagnosis of carcinoid, MTC, and paraganglioma.

1.3 STATISTICAL ISSUES AND FINDINGS

In this NDA, pivotal study MBG308 was conducted to establish efficacy of 123I-mIBG. A total of 251 patients were in the study and 250 patients were included in the primary efficacy population, also known as the intent-to-diagnose (ITD) population. The ITD population was to consist of all subjects who received ^{123}I-mIBG and had a diagnosis according to the standard of truth (SOT), other than indeterminate. The null hypothesis was that the sensitivity and specificity were each 80%. The results of sensitivity and specificity failed to reject the null hypothesis by any readers.

Statistical Issues:

The followings are two statistical issues in this application.

- The estimates of sensitivity and specificity of 123I-*m*IBG imaging that were derived from the results of the meta-analysis in studyMBG304 were used to pre-specify the levels of sensitivity and specificity of 123I-*m*IBG imaging in the null hypotheses of study MBG308. However, the population of patients that was used in the meta-analysis was different from the population in pivotal study MBG304. The primarily patients in the population in meta-analysis based on publications,were described with histologically-proven new diagnoses whereas the majority of patients enrolled in MBG308 had established diagnoses (86% of neuroblastoma and 57% of phaeochromocytoma) and were previously treated.

- Different blinded reading conditions in study MBG308 and study MBG304 was another issue in this application. Reading was conducted under blinded condition in study MBG308 while the blinding was not mentioned in the major selected articles for Meta-analysis in study MBG304.

Findings:

The primary efficacy endpoint was focal increased uptake (presence or absence) on planar scintigraphy, was used to determine the sensitivity and specificity of ^{123}I -mIBG imaging. The SOT for the presence or absence of active phaeochromocytoma or neuroblastoma was established by histological (i.e., biopsy or surgery), radiological (i.e., CT, MRI, 131I-mIBG 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 expert panel.

Sensitivity was defined as Number of True Positives divided by No. of Subjects diagnosed with active tumor and Specificity: (No. of True Negatives) ÷ (No. of Subjects without active tumor), where true positive was defined as a subject with truth standard diagnosis of active neuroblastoma or phaeochromocytoma and abnormal uptake on 123I-mIBG planar scintigraphy identified as active phaeochromocytoma or neuroblastoma. 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 tumor on 123I-mIBG planar scintigraphy.

The number of subjects diagnosed with active tumor was all subjects with 123I-mIBG planar scintigraphy and a diagnosis according to the SOT. The following table is the primary efficacy results in Study MBG308.

Table A: Results of Sensitivity and Specificity in Study MBG308

	Reader A	Reader B	Reader C
Sensitivity			
N	159	159	159
Estimate	0.80	0.77	0.79
95% CI	0.73, 0.86	0.70, 0.84	0.71, 0.85
Specificity			
N	52	52	52
Estimate	0.77	0.73	0.69
95% CI	0.63, 0.87	0.59, 0.84	0.55, 0.81

Table B: Results of Sensitivity and Specificity by Presence of Current Histopathology

	Reader A	Reader B	Reader C
Sensitivity			
N	42	42	42
Estimate	0.86	0.83	0.83
95% CI	0.71, 0.95	0.69, 0.93	0.69, 0.93
Specificity			
N	8	8	8
Estimate	1.00	0.75	1.00
95% CI	0.63, 1.00	0.35, 0.97	0.63, 1.00

Reviewer Comments:

- The estimates of sensitivity and specificity of 123I-*m*IBG imaging that were derived from the results of the meta-analysis in studyMBG304 may not be appropriate to be used as the pre-specified levels of sensitivity and specificity of 123I-*m*IBG imaging in the null hypotheses of MBG308 because of the following two reasons.
    - The meta-analysis was based on publications that described primarily patients with histologically-proven new diagnoses, whereas the majority of subjects enrolled in MBG308 had established diagnoses and were previously treated.
    - Artificiality of the blinded reading conditions in study MBG308 while the blinding was not mentioned in the major selected articles in study MBG304.

2 INTRODUCTION

2.1 OVERVIEW

During the past 25 years, both ^{123}I-mIBG and ^{131}I-mIBG have been extensively used in research and clinical imaging of neural crest and neuroendocrine tumors. Increased uptake of mIBG in tumor compared with surrounding normal or uninvolved tissue on scintigraphic imaging allows differentiation of tumor from non-neoplastic tissue at initial diagnosis, and provides a means for later evaluating for the presence of residual, occult, or recurrent disease. In this NDA submission, pivotal Study MBG308 was conducted to demonstrate the efficacy of ^{123}I-mIBG scintigraphy for confirming or excluding the diagnoses of neuroblastoma or phaeochromocytoma. Study MBG308 was an open-label, multicenter, Phase 3 scintigraphy study; a total of 251 patients were in the study. Among them, 179 were in the US, and 72 in the Europe (EU).

The standard of truth, presence (or absence) of tumor, was established by current histopathology results of tissue obtained during surgery or biopsy. The trial null hypothesis was that the sensitivity and specificity were reach 80%. In other words, if the lower bound of confidence interval (CI) for the estimate of sensitivity (or specificity) for a reader was >80%, the hypothesis would be rejected. For the trial to achieve statistical success, the null hypothesis for both sensitivity and specificity needed to be rejected by at least two readers.

A meta-analysis study MBG304 was also included in this NDA submission. The primary objective of study MBG304 was to obtain best estimates of the sensitivity and specificity of the scintigraphic method by evaluating the performance of 123I-mIBG image for the detection of neuroblastoma and phaeochromocytoma at the subject level based on published data. A total of 19 eligible articles were selected in this study. Of the 19 eligible articles, 7 applied 123I-*m*IBG in the diagnosis of neuroblastoma, 9 in phaeochromocytoma. Thirty-seven percent of the studies were initiated before the year of 1991. Most of the studies were conducted in Europe, with the

remainder from the U.S. and Japan. The number of subjects in the studies ranged from 19 to 284, with percentage male ranging from18% to 70%.

Reviewer Comments:

[1] Per the sponsor, the SPA agreement was obtained on 20 May 2005.

2.2 DATA SOURCES

Data used for review are from the electronic submission received in March 2008. The network path is "\\cdsesub1\evsprod\nda022290\0000" in the EDR.

3 STATISTICAL EVALUATION

Section 3.1 in this review includes efficacy evaluation for the study MBG308 and study MBG304.

3.1 EVALUATION OF EFFICACY

This section provides the efficacy results of study MBG308 and study MBG304 based on the sponsor's study reports. Any difference between the sponsor's study report and the protocol is also discussed in this section.

3.1.1 STUDY OBJECTIVES

3.1.1.1 Study MBG308

The primary objective of study MBG308 was to demonstrate that ^{123}I-mIBG planar scintigraphy was sensitive and specific in confirming or excluding the diagnoses of neuroblastoma and phaeochromocytoma.

The secondary objectives of study MBG308 were:

- To determine the incremental value of SPECT for improving the sensitivity and specificity of ^{123}I -mIBG planar scintigraphy for the diagnoses of neuroblastoma and phaeochromocytoma; and
- To collect safety data on ^{123}I -mIBG.

3.1.1.2 Study MBG304

The primary objective of study MBG304 was to combine available published data on the diagnostic performance of 123I-mIBG as an imaging agent for localising specific tumors of neural crest origin, including neuroblastoma and phaeochromocytoma, in order to obtain best estimates of the sensitivity and specificity of the scintigraphic method.

The secondary objectives of the study MBG304 were:

- To evaluate the performance of ^{123}I -mIBG imaging for the detection of paraganglioma, MCT, and carcinoid tumours at the subject level;
- To compare the performance of ^{123}I -mIBG versus ^{131}I -mIBG imaging against a reference standard in the detection of neuroblastoma and phaeochromocytoma at the subject level.

3.1.2 STUDY DESIGN

3.1.2.1 Study MBG308

Study MBG308 was an open-label, multicenter, Phase 3 scintigraphy study. Effectiveness was judged in terms of the identification of abnormal uptake of the radioactive compound in one or more anatomic locations where tumor was identified at surgery, biopsy, or radiological imaging (computed tomography [CT], magnetic resonance imaging [MRI], 131I-mIBG scintigraphy), and the detection of no abnormal uptake of 123I-mIBG in subjects whose clinical evaluation demonstrated no objective evidence of tumor. Presence of tumor was established by histopathology results of tissue obtained at the time of surgery or biopsy. If no tissue was obtained, the appropriate EP (determined by tumour category) established the SOT.

Subjects were included if they met inclusion criteria and would be excluded if they met exclusion criteria. 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 123I-mIBG, 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. All subjects were to have 123I-mIBG 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 123I-mIBG.

At 24 (±6) hours post-administration of 123I-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.

3.1.2.2 Study MBG304

Study MBG304 was designed to evaluate the performance of ^{123}I-mIBG imaging for the detection of tumors of neural crest origin, including neuroblastoma and phaeochromocytoma. Data from articles were collected, combined, and systematically analyzed using the method of meta-analysis. Study procedures were developed using the FDA guidelines for "Literature-based submissions", and procedures proposed in several published articles on the methodology of meta-analysis.

Literature was identified first using computerized databases such as the National Library of Medicine Medline Index. The criteria/key terms used for identifying related articles were:

- Articles/studies published between the years of 1980 to 2004. Key words were used to search the title, abstract and descriptor fields of the computerized database records;
- Studies dealing with human experiences;
- Topics of the articles devoted to the diagnostic usage of mIBG imaging in phaeochromocytoma, neuroblastoma, MCT, carcinoid tumours, or paragangliomas. The key term mIBG could be spelled out, or cited as iobenguane, or (3-, m-, meta-) iodobenzylguanidine during the search.

To minimize "publication bias", efforts were made to obtain published, as well as unpublished data, such as government reports, on-going studies, conference papers, and unpublished results (i.e., all publicly available data that could be accessed for audit purposes). All potential sources of data were referred to as "articles" in the protocol. Additional literatures were identified through mining the reference lists of retrieved articles.

Key words, medical subject headings (MeSH), and abstracts/summaries of the searched results were manually reviewed against the following checklist of screening criteria:

- The articles had diagnostic information of 123I-mIBG imaging in phaeochromocytoma, neuroblastoma, MCT, carcinoid tumours, or paragangliomas. Articles devoted to areas other than the diagnostic usage of mIBG, such as compound synthesis, imaging techniques, therapeutic results, and dosimetry calculations were excluded. Articles

concerned with other attributes of mIBG imaging such as autonomic nervous system function (especially cardiac) were also excluded;

- The article was not accepted if it was in the form of a letter, comment, or editorial;

- For publications in languages other than English, a minimum requirement was an abstract or article summary in English.

A Literature Search Report was created which contained the following:

- The name of sponsor personnel who requested search;
- The date search was requested;
- The date search was performed;
- Independent external provider(s) performing search;
- Independent external provider(s) performing screening;
- The databases used for the search, with contact information for each;
- The time period for which each database was searched (i.e., start year/month and end year/month);
- The search criteria used, listing exact phrases and key words used for search;
- The number of items/citations retrieved;
- The number of items that met and did not meet the screening criteria;
- An appendix listing all citations that met the screening criteria; and
- An appendix listing all citations that did not meet the screening criteria.

Prior to and during the review of articles by independent reviewers, an additional screening for the identification of redundant data (i.e., multiple publications from the same institution, previously obtained articles, etc.) was performed. If a review of multiple publications from the same institution or author suggested that the same subjects might have been included in more than one publication, then only the data from the most recent review of clinical experience was summarized and all the earlier studies from the same institution were removed from the analysis. Studies that represented part of a multi-centre trial were not used if study report of the multi-centre trial also qualified for inclusion in the meta-analysis. Previously obtained articles were also removed.

Two reviewers independently evaluated each article against the inclusion/exclusion criteria and determined if the article was eligible for the meta-analysis. Each reviewer independently extracted the data from the articles. Data collected on the SRFs were entered into an electronic database and key variables were analyzed using the meta-analysis approach. At the end of an article review, discrepancies between the reviewers regarding the eligibility of an article and the data extracted were resolved by consensus. An additional reviewer resolved any disagreement not settled by the discussion between the 2 primary reviewers.

As a result of his/her examination of a retrieved article or report, a reviewer may have identified additional articles, which were not found through the literature search process but met the screening criteria. Based upon available information (e.g., a quoted ^{123}I-mIBG-sensitivity estimate), a reviewer was permitted to request that the newly identified article be ordered for review. If the article met the screening criteria, the reviewers added it to the collection of articles for examination.

3.1.3 EFFICACY ENDPOINTS

3.1.3.1 Efficacy Endpoints

3.1.3.1.1 Study MBG308

The primary objective of the study was to demonstrate that ^{123}I-mIBG planar scintigraphy is sensitive and specific for confirming or excluding the diagnoses of neuroblastoma and phaeochromocytoma. The primary efficacy endpoint was focal increased uptake (presence or absence) on planar scintigraphy consistent with active tumor. The secondary efficacy endpoint was the focal increased uptake from a combined read of planar and SPECT scintigraphy and was used to estimate the accuracy of the diagnosis when both modalities were used. The primary and secondary efficacy endpoints were matched to the SOT for the calculation of primary and secondary statistical measures, specifically analyses of sensitivity, specificity, accuracy, positive predictive value (PPV), and negative predictive value (NPV).

The definitions of the primary outcomes sensitivity and specificity are as follows.

- Sensitivity was defined as the proportion of number of patients with true positives ^{123}I-mIBG assessment in the number of subjects with positive standard of truth assessment (diagnosed with active tumor).
- Specificity was defined as the proportion of number of patients with true negatives ^{123}I-mIBG assessment in the number of subjects with negatives standard of truth assessment.

The primary efficacy population or the intent-to-diagnosis population consisted of subjects injected with 123I-mIBG who had a diagnosis according to the SOT other than indeterminate.

3.1.3.1.2 Study MBG304

The primary efficacy endpoints and related statistical measures were:

- Performance of ^{123}I-mIBG imaging, measured as sensitivity at the subject level, in correctly identifying neuroblastoma;
- Performance of ^{123}I-mIBG imaging, measured as specificity for identifying subjects without neuroblastoma;
- Performance of ^{123}I-mIBG imaging, measured as sensitivity for identifying subjects with phaeochromocytoma;
- Performance of ^{123}I-mIBG imaging measured as specificity for identifying subjects without phaeochromocytoma.

The secondary efficacy endpoints of the study MBG304 were:

- The sensitivity of ^{123}I-mIBG imaging in the diagnosis of paraganglioma, MCT, and carcinoid tumors at subject level;

- The comparison of sensitivity between ^{123}I-mIBG and ^{131}I-mIBG imaging in the diagnosis of neuroblastoma and phaeochromocytoma at the subject level.

3.1.4 SAMPLE SIZE CONSIDERATIONS

Study MBG308 was designed to have a minimum of 140 subjects with a positive (active tumor) diagnosis of either phaeochromocytoma or neuroblastoma and 45 subjects with a negative diagnosis, (no active tumor) to test the following 1-sided hypotheses at the ≤0.025 level:

H0: Sensitivity = 80% vs. H1: Sensitivity >80%
H0: Specificity = 80% vs. H1: Specificity >80%

Sample sizes resulted in each test having 80% power given the true values for sensitivity and specificity were expected to be 89% and 95%, respectively.

Reviewer Comments:

[1] In Study MBG308, of the 250 patients included in the total dosed population, 159 patients who were classified as having active tumor were included into the results of the primary analyses of sensitivity and specificity.

3.1.5 STATISTICAL METHODOLOGIES

3.1.5.1 Sponsor's Protocol/Statistical Analysis Plan

3.1.5.1.1 Study MBG308

The primary efficacy endpoint was analyzed through the primary statistical measures sensitivity and specificity of 123I-mIBG planar scintigraphy, as well as the secondary measures of accuracy, PPV, and NPV. Secondary analyses of the same measures were performed for the subset of subjects from the ITD population for whom a 123I-mIBG SPECT scintigraphy was available and were based on a combined read of the planar and SPECT evaluations.

The results from the 3 independent readers of the 123I-mIBG imaging were compiled and presented as independent measures in the clinical study report. For each reader, sensitivity and specificity of ^{123}I-mIBG in diagnosing phaeochromocytoma and neuroblastoma on a subject level were calculated.

For each reader, the primary analyses tested the hypothesis: H0: pa= 0.80 vs. H1: pa≥0.80, where pa denotes either sensitivity or specificity. The primary efficacy endpoint was considered to be

achieved if lower bounds for 95% confidence intervals (CIs) computed for both sensitivity and specificity were 80% or greater for 2 out of 3 readers.

The testing of the hypothesis: H0: pa=0.80 vs. H1: pa≥0.80 was performed using the SAS binomial option of the frequency procedure (PROC FREQ; TABLES var / BINOMIAL; EXACT/BINOMIAL). This code also performed the calculation of sensitivity and specificity and their exact and asymptotic CIs.

3.1.5.1.2 Study MBG304

The primary efficacy measures in study MBG304 were the sensitivity and specificity of 123I-mIBG in correctly diagnosing subjects with neuroblastoma and those with phaeochromocytoma. For each efficacy measure and tumor type, the planned meta-analysis was not performed if less than 4 studies were eligible. However, measures and the 95% confidence intervals (CIs) of each qualified study were presented. The same principle applied to secondary efficacy measures as well. More detail of description of the probability models and methods of analysis such as efficacy measures of the individual study and efficacy measures of study combined can be found in the appendix in the end of this review.

3.1.6 SPONSOR'S RESULTS AND STATISTICAL REVIEWER'S COMMENTS/FINDINGS

3.1.6.1 Data Sets

3.1.6.1.1 Study MBG308

The primary efficacy population for study MBG308 is the intent-to-diagnosis (ITD) population consisted of subjects injected with 123I-mIBG who had a diagnosis according to the SOT other than indeterminate.

The following tables show some results of demographic data of patients in study MBG308.

Table 1: Sponsor's Summary of Demographic Data by Tumor types in Study MBG308

	Total (N=251)	Neuroblastoma (N=100)	Phaeochromocytoma (N=151)
Age (yrs)			
N	251	100	151
Mean (SD)	31.4 (24.9)	4.7 (6.9)	49.0 (14.7)
Min, Max	0.08, 88.0	0.08, 58.0	17.0, 88.0
Gender (n [%])			
Male	119 (47.4)	57 (57.0)	62 (41.1)
Female	132 (52.6)	43 (43.0)	89 (58.9)

Race (n[%])			
White	220 (87.7)	88 (88.0)	132 (87.4)
Black	12 (4.8)	4 (4.0)	8 (5.3)
Asian	3 (1.2)	0	3 (2.0)
Other*	16 (6.4)	8 (8.0)	8 (5.3)

**[source: Table 6 in Section 10.3 of Clinical Study Report MBG308]*

Table 2: Reviewer's Summary of Demographic Data by Tumor types in Study MBG308

	Total (N=250)	**Neuroblastoma (N=100)**	**Phaeochromocytoma (N=150)**
Age (yrs)			
N	251	100	150
Mean (SD)	31.4 (24.9)	4.7 (6.9)	49.2 (14.5)
Min, Max	0.08, 88.0	0.08, 58.0	17.0, 88.0
Gender (n [%])			
Male	119 (47.4)	57 (57.0)	62 (41.1)
Female	132 (52.6)	43 (43.0)	88 (58.9)
Race (n[%])			
White	220 (87.7)	88 (88.0)	131 (87.4)
Black	12 (4.8)	4 (4.0)	8 (5.3)
Asian	3 (1.2)	0	3 (2.0)
Other*	16 (6.4)	8 (8.0)	8 (5.3)

Reviewer's Comment:

[1] Among 251 patients who were administered ^{123}I*m*IBG, 250 subjects were evaluable for efficacy (one subject was withdrawn due to a protocol violation). The slightly difference between the sponsor's summary and the reviewer's summary in Table 1 and Table 2 are due to the slightly difference in total numbers of patient.

3.1.6.1.2 Study MBG304

In study MBG304, efficacy variables were collected by the 2 independent literature reviewers. In study MBG304, there were 19 eligible articles. Of the 19 eligible articles, 7 applied 123I-*m*IBG in the diagnosis of neuroblastoma, 9 in phaeochromocytoma. Most of the studies described in those articles were conducted in Europe, with the remainder from the U.S. and Japan. Thirty-seven percent (37%) of the studies were initiated before the year of 1991 Seventy-four percent (74%) of the studies were completed within 24 months. As summary in the following table, the number of

subjects in the studies ranged from 19 to 284, with percentage male ranging from 18% to 70%. The mean age of subjects ranged from 6.9 months to 56 years.

3.1.6.2 Standard of Truth

In study MBG308, Of the 250 subjects included in the total dosed population, 159 subjects were classified as having active tumor, 52 subjects were classified as not having active tumor, and 39 subjects were classified as indeterminate. Therefore, the ITD population for the primary efficacy analyses consisted of 211 subjects.

Table 3: Standard of Truth (All-Dosed Population) in Study MBG308

		Active Tumor Present?			If Yes, Type of Tumor	
		Yes	No	Indeterminate	Phaeochro-mocytoma	Neuroblastoma
	N	n (%)	n (%)	n (%)	n (%)	n (%)
Total	**250**	159 (63.6)	52 (20.8)	39 (15.6)	92 (57.9)	67 (42.1)
Histology*	**50**	42 (84.0)	8 (16.0)	0	22 (52.4)	20 (47.6)
Expert Panel	**200**	117 (58.5)	44 (22.0)	39 (19.5)	70 (59.8)	47 (40.2)

[Source: Sponsor's study report section 11.2.2.]
Diagnosis was determined by "current" histopathology. Subjects in this group were not reviewed by the Expert Panel. Eight other subjects had "current" histopathology data but were reviewed by the Expert Panels for additional verification.

3.1.6.3 Primary Efficacy Analysis

The following tables summarize the sponsor's results of sensitivity and specificity results for confirming/excluding the diagnosis of neuroblastoma or phaeochromocytoma.

Table 4: sponsor's results of sensitivity and specificity in Study MBG308

	Reader A	Reader B	Reader C
Sensitivity			
N	159	159	159
Estimate	0.80	0.77	0.79
95% CI	0.73, 0.86	0.70, 0.84	0.71, 0.85
Specificity			
N	52	52	52
Estimate	0.77	0.73	0.69
95% CI	0.63, 0.87	0.59, 0.84	0.55, 0.81

[Source: Study Clinical Report Section 11.3 Table1 17]

Table 5: Sponsor's Summary of Primary Efficacy Measures-Sensitivity and Specificity of ^{123}I-mIBG Image by Tumor and Study in Study MBG304

Article ID	Subjects with Confirmed Disease	Sensitivity (%)	Exact 95% CI (%)	Disease-free Subjects	Specificity (%)	Exact 95% CI (%)
Neuroblastoma						
1005	33	100	(89, 100)			
1007	17	76	(50, 93)			
1020	19	89	(67, 99)			
1041	19	100	(82, 100)			
1046	88	94	(87, 98)			
1057	20	100	(83, 100)			
1082	27	100	(87, 100)			
Phaeochromocytoma						
1022	18	94	(73, 100)	40	100	(91, 100)
1036	29	100	(88, 100)	91	55	(44, 65)
1056	16	75	(48, 93)			
1058	18	83	(59, 96)	62	89	(78, 95)
1060	48	98	(89, 100)			
1085	59	90	(79, 96)			
2014				20	95	(75, 100)
2044				23	100	(85, 100)
2071				22	100	(85, 100)

[Source: Study Clinical Report Section 11.1.1 Table 7]

Table 6: Sponsor's Summary of Meta-Analysis for Primary Efficacy Measures by Tumor in Study MBG304

Efficacy Measures	Total Studies	Fixed Effect Model		Homogeneity Test* (p-value)	Random Effect Model**	
		Point Estimate (%)	95% CI (%)		Point Estimate (%)	95% CI (%)
Neuroblastoma						
Sensitivity	7	97	(95, 99)	Homogeneity (0.31)	-	-
Specificity	-	-	-	-	-	-
Phaeochromocytoma						
Sensitivity	6	96	(93, 99)	Heterogeneity	94	(90, 99)
				-0.07		
Specificity	6	95	(93, 97)	Heterogeneity	90	(80, 99)
				(<0.001)		

[Source: Study Clinical Report Section 11.1.1 Table 8]

Reviewer's Comment:

[1] The reviewer verified the results in Table 3. As shown in the Table 3, the lower bounds of the 95% confidence intervals (CI) for sensitivity for Readers A, B, and C were 73%, 70% and 71%, respectively and the lower bounds of the 95% CI for specificity for Readers A, B, and C were 63%, 59% and 55%, respectively. Therefore, these results failed to reject the null hypothesis that both sensitivity and specificity of 123I-*m*IBG were at least 80% by any readers.

3.2 EVALUATION OF SAFETY

Please see the clinical review by Dr. Yaes for the safety evaluation.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

This section will be focused on the reviewer's results of the exploratory subgroup analyses of sensitivity and specificity.

4.1 GENDER, RACE AND AGE

The following table is this reviewer's summary of subgroup analyses of sensitivity and specificity by age and race. Since the range of age in the group of neuroblastoma patients is 0.08 to 58 years with median age of 14.5 years old. The subgroup analysis by age (>=65 or <65) in neuroblastoma patients will not be performed.

Table 7: Result of Sensitivity and Specificity in Subgroups of Patients by Age, Gender and Race (FDA's Analysis)

Subgroup	Sample size	N1*	Sensitivity			N2**	Specificity		
Reader			A	B	C		A	B	C
Age< 65 (Phaeo)	125	78	79.5	76.9	76.9	28	75.0	71.4	57.1
Age>=65(Phaeo)	25	14	78.6	78.6	85.7	7	1.0	85.7	1.0
Male	119	77	81.8	77.9	84.4	22	68.2	63.6	63.6
Female	131	82	78.0	76.8	71.4	30	84.2	80.0	73.3
Caucasian	219	137	80.3	76.6	78.1	47	74.5	74.5	68.1
Non-Caucasian	31	22	77.3	81.8	81.8	5	1.0	60.0	80.0

**Number of patients with truth diagnosis based on standard of Truth.*
*** Number of patients with Negative based on standard of truth.*

Reviewer's Comment:

[1] The results of sensitivity and specificity by age, race and gender are similar to the results in ITD population.

4.2 OTHER SPECIAL/SUBGROUP POPULATIONS

The sponsor reported that the results of sensitivity and specificity from the subset of patients with current histopathology showed the observed sensitivity and specificity values closer to those expected for patients with definitive diagnoses as reported in the literature. The following Table shows the results of sensitivity and specificity for patients with current histopathology.

Table 8: Results of Sensitivity and Specificity by Presence of Current Histopathology

	Reader A	Reader B	Reader C
Sensitivity			
N	42	42	42
Estimate	0.86	0.83	0.83
95% CI	0.71, 0.95	0.69, 0.93	0.69, 0.93
Specificity			
N	8	8	8
Estimate	1.00	0.75	1.00
95% CI	0.63, 1.00	0.35, 0.97	0.63, 1.00

[Source: Study Clinical Report Section 11.3.1 Table1 18]

In addition, the results of sensitivity and specificity by tumor type are shown in the following table.

Table 9: Results of Sensitivity and Specificity by Tumor Type

	Neuroblastoma			Phaeochromocytoma		
	Reader A	**Reader B**	**Reader C**	**Reader A**	**Reader B**	**Reader C**
Sensitivity						
N	67	67	67	92	92	92
Estimate	0.81	0.78	0.79	0.79	0.77	0.78
95% CI	0.69, 0.89	0.66, 0.87	0.67, 0.88	0.70, 0.87	0.67, 0.85	0.68, 0.86
Specificity						
N	17	17	17	35	35	35
Estimate	0.71	0.71	0.76	0.80	0.74	0.66
95% CI	0.44, 0.90	0.44, 0.90	0.50, 0.93	0.63, 0.92	0.57, 0.88	0.48, 0.81

[Source: Study Clinical Report Section 11.3.1 Table1 19]

Reviewer's Comment:

[1] The results of sensitivity and specificity by presence of current histopathology and by tumor type shown in above tables are verified and consistent with the results in ITD population.

5 SUMMARY AND CONCLUSIONS

5.1 SPONSOR'S EFFICACY CONCLUSIONS AND REVIEWER'S CONCLUSIONS AND RECOMMENDATIONS

In this NDA, the sponsor submitted the results of study MBG308 and study MBG304 to seek an approval of ^{123}I-*m*IBG (Iobenguane I ^{123}) to be used as an imaging agent for the detection of primary or metastatic pheochromocytomas and neuroblastomas. This reviewer verified the sponsor's primary efficacy results of sensitivity and specificity from study MBG308. The sponsor claimed that observed sensitivity and specificity of ^{123}I-*m*IBG with corresponding lower bounds of the 95% confidence intervals (CI) as shown in the following table.

Results of Sensitivity and Specificity in Study MBG308

	Reader A	Reader B	Reader C
Estimated Sensitivity (N=159)	0.80	0.77	0.79
95% CI	0.73, 0.86	0.70, 0.84	0.71, 0.85
Estimated Specificity (N=52)	0.77	0.73	0.69
95% CI	0.63, 0.87	0.59, 0.84	0.55, 0.81

As shown in the table, the lower bounds of the 95% CI of sensitivity and specificity are less than 80% for all readers. From this reviewer's point of view, these results from the study MBG308 failed to meet the primary objectives to demonstrate that ^{123}I-*m*IBG planar scintigraphy was sensitive and specific to the pre-specified levels of 80% in confirming or excluding the diagnoses of neuroblastoma and phaeochromocytomas. Whether ^{123}I-*m*IBG scintigraphic imaging can provide clinical value in diagnosis of phaeochromocytoma or neuroblastoma will be deferred to the clinical judgment.

APPENDIX

DESCRIPTION OF THE PROBABILITY MODELS AND METHODS OF ANALYSIS

(1) Efficacy measures of the individual study

If possible, the sensitivity and specificity of each individual study were calculated by disease using the definitions below.

Sensitivity=TP/D+, Specificity=TN/D-

Here TP was the number of subjects with positive mIBG results matching with the results of a reference standard and D+ was the number of subjects with confirmed disease; similarly, TN were those subjects with both negative findings on mIBG and a reference standard and D- indicated disease-free subjects. To be counted in the denominators of both equations, the subject's disease status must have been confirmed by an acceptable reference standard.

(2) Efficacy measures of study combined

Efficacy measures by disease type were pooled across studies using the fixed effect model which assumed that each individual study shared a common mean $\hat{p}_w$ (equation [1]) and used the inverse of the sample variance of each study as the weight (equation [2]).

$$\hat{p}_w = \sum_i w_i p_i \Big/ \sum_i w_i \quad (1)$$

$$w_i = \frac{1}{s_i^2} = \frac{1}{p_i(1-p_i)/n_i}, \quad (2)$$

Where i=1 to k individual study; pi was the point estimate (i.e. sensitivity or specificity) of i^{th} study, w_i was the inverse of the i^{th} sample variance and n_i was the sample size from i^{th} study.

The asymptotic variance of $\hat{p}_w$ was $1/\sum w_i$.

To avoid the possibility of zero variance for primary studies with 100% sensitivity or specificity, 0.5 and 1 were added to the numerator and denominator of p_i, respectively when calculating the pooled estimates. Next, variations (heterogeneity) among studies were examined using a formal statistic test Q and an informal check was done of the dot plot of CIs for the combined estimate and each individual study. The Q statistic was defined as:

$$Q = \sum_i w_i (p_i - \hat{p}_w)^2 \sim \chi^2_{k-1},$$

where i=1 to k individual study; pi was the point estimate (i.e. sensitivity or specificity) of ith study, wi (equation [2]) was the inverse of the ith sample variance and $\hat{p}_w$ (equation [1]) was the weighted average of pi across studies while using wi as the weight.

Again, to avoid the possibility of zero sample variance, 0.5 and 1 were added to the numerator and denominator of pi, respectively when calculating Q statistics.

If the observed value of Q was less than the 90 percentile of the χ^2_{k-1} distribution (p>0.10), the fixed-effect model of pooling study measures was used.

On the contrary, if there appeared to be study heterogeneity (p<0.10), both fixed-effect and the following random-effect model were calculated,

$$\hat{p}_W = \sum_i W_i p_i \Big/ \sum_i W_i, \quad W_i = \frac{1}{s_i^2 + s_A^2}, \qquad s_A^2 = \frac{Q-(k-1)}{\sum w_i - \sum w_i^2 \Big/ \sum w_i}$$

The variance of p^$_w$ was $1/\sum W_i$

If the presence of study heterogeneity was evident, the association between measures of primary studies and study specific characteristics were investigated to identify possible source of inconsistency.

SIGNATURES/DISTRIBUTION LIST

Primary Statistical Reviewer: Xiaoping (Janet) Jiang, Ph.D.
Date:

Concurring Reviewer: Jyoti Zalkikar, Ph.D., Team Leader
Aloka Chakravarty, Ph.D., Director
Date:

cc:
HFD-150/Dr. R. Yaes
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HFD-711/Dr. A. Mucci
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