U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Science (OTS)
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	19-785 SE018
Drug Name:	Cardiolite® - Technetium Tc99m Sestamibi for injection
Indication(s):	Cardiac Imaging - Pediatric Study Reports for Pediatric Exclusivity
Applicant:	Bristol Myers Squibb-Medical Imaging
Date(s):	Date of Submission: Letter Date 29-October-2007 Stamp Date 29-October-2007 PDUFA Goal Date 30-April-2008
Review Priority:	Priority
Biometrics Division:	Division of Biometrics V
Statistical Reviewer:	Satish C. Misra, Ph. D.
Concurring Reviewers:	Jyoti Zalkikar, Ph. D., Statistical Team Leader Aloka Chakravarty, Ph. D., Director, Division of Biometrics V
Medical Division:	Division of Medical Imaging and Hematology Products
Clinical Team:	Robert J. Yaes, M.D., Clinical Reviewer
Project Manager:	Tiffany Brown

Keywords: Confidence Intervals, Sensitivity, Specificity, Positive Predictive Value, Open Label, Non-randomized

Table of Contents

LIST OF TABLES

1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

Cardiolite® Kit for the Preparation of Technetium Tc99m Sestamibi for Injection, is a myocardial perfusion agent and was approved as an imaging agent for use in adults on December 21, 1990. Cardiolite® is indicated for detecting coronary artery disease (CAD) by localizing myocardial ischemia (reversible defects) and infarction (non-reversible defects). Cardiolite® is also indicated for evaluating myocardial function and developing information for use in patient management decisions. The sponsor, Bristol-Myers Squibb Medical Imaging (BMS MI) Company, is not seeking any addition to currently approved indications.

The sponsor conducted and submitted the results of 3 studies to satisfy the requirements specified in the Written Request (WR) for Pediatric Studies, to support pediatric exclusivity. The Pediatric Exclusivity Board of FDA determined that the sponsor met all WR requirements.

The pediatric patients with Kawasaki Disease (KD) in the trial were followed for short-term cardiac outcomes at 6 months in a prospective Cardiolite® 301 study. This was a phase III, open-label, non-randomized, international, multi-center study. An interim 6-month clinical study report per FDA's Written Request (WR) was submitted. The 6-month data is not supportive of the ability of Cardiolite® to predict the risk of cardiac events in pediatric patients with Kawasaki Disease (KD). The sponsor plans to assess this endpoint periodically during the long-term follow-up primarily via telephone contacts, and submit final report at the end of 10-years follow-up.

Cardiolite® 302 study was a phase 3, retrospective, case-history, international, multicenter of pediatric Kawasaki Disease (KD) patients.

Low estimates of sensitivity and positive predictive value with wide confidence intervals were observed for both the prospective Cardiolite® 301 study and retrospective Cardiolite® 302 study. Based on the current data available, no evidence of diagnostic efficacy or clinical utility of Cardiolite® scan was found in the three clinical studies of children and adolescents with Kawasaki disease. The effectiveness in the pediatric population has not been established.

1.2 Brief Overview of Clinical Studies

The sponsor conducted and submitted the results of 3 studies to satisfy the requirements specified in the Written Request (WR) for Pediatric Studies in support of pediatric exclusivity. Study DUP 843-201 was a phase I-II, open-label, multi-center trial to determine the dosimetry and safety of Technetium tc99m Sestamibi in pediatric subjects. Study Cardiolite® 301 was a phase 3, open label, nonrandomized, international, multi-center study to evaluate the efficacy and Safety of Cardiolite® Myocardial Perfusion Imaging in Pediatric Subjects with Kawasaki Disease. Study Cardiolite® 302 was a case history, international, multi-center study to evaluate the efficacy and safety of Cardiolite® Single Photon Emission Computed Tomography (SPECT) Myocardial Perfusion Imaging (MPI) in Pediatric Patients with Kawasaki Disease. In this review only studies 301 and 302 will be discussed.

1.3 Statistical Issues and Findings

There were no requirements of formal hypotheses testing. Therefore, statistical evaluation is limited to pre-specified estimation of performance characteristics, such as sensitivity and positive predictive value and associated 95% confidence intervals for prospective study 301 and retrospective study 302.

2. INTRODUCTION

2.1 Background

Cardiolite® Kit for the Preparation of Technetium Tc99m Sestamibi for Injection, is a myocardial perfusion agent and was approved as an imaging agent for use in adults on December 21, 1990. Cardiolite® is indicated for detecting coronary artery disease by localizing myocardial ischemia (reversible defects) and infarction (non-reversible defects). Cardiolite® is also indicated for evaluating myocardial function and developing information for use in patient management decisions. The sponsor is Bristol-Myers Squibb Medical Imaging (BMS MI) Company.

The Pediatric Advisory Subcommittee (PAS) of the Anti-Infective Advisory Committee, in February 2004, concluded that pediatric population would benefit from studies utilizing Tc99m myocardial perfusion imaging (MPI) agents such as Cardiolite®. The FDA issued a Written Request (WR) for Pediatric Studies in December 2004 that defined 3 pediatric studies that would include patients with Kawasaki disease (KD).

The Sponsor submitted Pediatric Study Reports in the form of a sNDA to request Pediatric Exclusivity. This submission contains information about studies the sponsor conducted to fulfill the pediatric written request (WR) dated 17 Dec 2004.

2.2 A brief synopsis of Written Request (WR)

The amended WR dated July 27, 2007 required the following 3 studies:

Study 1: Pediatric Radiation Dosimetry Determination and Pharmacokinetic (Biodistribution): The objective of this study was to determine the dosimetry, pharmacokinetics (biodistribution in blood and urine) and safety of Technetium Tc99m Sestamibi including biodistribution, dosimetry and safety in pediatric patients. The study may be an open-label, non-randomized, multi-center trial in pediatric patients who have been scheduled to undergo rest or exercise stress Technetium Tc99m Sestamibi cardiac imaging. The age groups identified for this Study were (i) 4 years to < 12 years and (ii) ≥ 12 years to < 17 years. A minimum of 24 patients were required be evaluated for safety and for either dosimetry, or pharmacokinetics (biodistribution in blood and urine), evenly distributed between the two age groups.

Study 2: Pediatric Diagnostic Efficacy and Safety Study (Prospective Study): The objective of this study was to determine the diagnostic efficacy and safety of Technetium Tc99m Sestamibi in pediatric patients with Kawasaki Disease, by using clinical outcomes as the truth standard. This study may be an open-label, non-randomized, multi-center diagnostic efficacy and safety trial in pediatric patients with Kawasaki Disease (KD). The primary endpoint will consist of a summary determination of the sensitivity and specificity for the imaging detection of patients at high risk for cardiac events. All patients will be followed for short-term cardiac outcomes at 6 months and followed yearly to evaluate long-term cardiac outcomes over a 10 year period. Cardiac outcomes at 6 months will form the basis for the study's analytical results (an interim study report). A final report will be submitted upon completion of the 10 year period for all patients, exclusive of premature discontinuation due to death or any subject's termination of participation. The age groups identified for this Study were (i) 4 years to < 12 years and (ii) ≥ 12 years to < 17 years. A minimum of 60 evaluable patients in the study with at least 20 in each age group were required in this study.

Study 3: Pediatric Diagnostic Efficacy and Safety Study (Retrospective Study): The objective of this study was to determine the diagnostic efficacy and safety of Technetium Tc99m Sestamibi in pediatric patients with Kawasaki disease, by using X-ray angiography as the truth standard. This study was to collect data retrospectively from multiple clinical sites to evaluate the performance (sensitivity and specificity) of Tc99m Sestamibi cardiac imaging in patients with known Kawasaki disease, by using X-ray angiography as the truth standard. Pediatric patients with known or suspected Kawasaki disease ("classical" or "incomplete") from the proposed clinical sites were to be screened for enrollment. Statistical analysis was required to be done on images from patients who had had both stress (exercise or pharmacological) and rest MPI in addition to X-ray angiography. The age groups identified for this Study was 1 month to < 17 years. A minimum 60 eligible patients (KD; rest-stress, stress-rest, or stress only Tc99m sestamibi cardiac MPI; and X-ray angiogram within 90 days) were required to be enrolled.

For studies 2 and 3, the point estimates of performance characteristics, such as sensitivity and specificity along with 95% Confidence Intervals (CI) were required to be provided. There was no requirement for hypotheses testing.

For all studies, safety was required to be assessed with collection of adverse events and serious adverse events and, for studies 1 and 2, hematologic, chemistry, and routine urinary laboratory parameters must also be documented.

The sponsor submitted clinical study reports for 3 studies per requirement of WR in 31 volumes of paper submission. The scope of this report is to provide an assessment of performance characteristics of Cardiolite® for prospectively designed study 301 and retrospective study 302.

2.3 Data Sources

The submission consisted to 31 volumes of paper submission, and had no electronic datasets. As a result of Information Request faxed to the sponsor on December 12, 2007 requesting BMS MI to submit the SAS datasets for the review of application, the sponsor submitted CD-ROM containing the SAS datasets for prospective study 301 only dated December 17, 2007.

3. STATISTICAL EVALUATION

The sponsor submitted the data electronically for study 301 on a CD. This reviewer analyzed these data and verified sponsor's results. However, electronic data for study 302 were not provided, and therefore, sponsor's results could not be verified.

3.1 Evaluation of Efficacy for prospective study 301

The study 301was a prospective evaluation of efficacy and safety of Cardiolite® in pediatric subjects with Kawasaki Disease (KD).

- **Study Design:** A phase III, open-label, non-randomized, international, multi-center study to evaluate the efficacy and safety of Cardiolite® myocardial perfusion imaging (MPI) in pediatric subjects with Kawasaki Disease (KD) scheduled to undergo invasive (angiography) or non-invasive echocardiography or myocardial perfusion imaging cardiac testing to evaluate the presence of ischemic heart disease over a 22-month period (6-month analysis interim report).

- **Primary Objective:** The primary objective was to determine the predictive value of Cardiolite® rest and stress MPI to define a pediatric population with KD at high and low risk of developing cardiac events.

- **Efficacy Evaluable (EE) Subjects:** Subjects who received at least 1 dose of Cardiolite® with an evaluable stress MPI image.

- **Number of Subjects and Demographics:** A total of 450 subjects were enrolled, and 445 (329 children in the age group 4 years to < 12 years, and 116 adolescent in the age group ≥ 12 years to < 17 years) were treated with at least 1 dose of Cardiolite®. Table 1 below provides a breakdown of these 445 treated subjects.

Table 1: Number of Subjects and Demographics - Study 301

Number Treated	445
Male (%)	301 (68%)
Asian	275 (62%)
White	135 (30%)
Other	45 (8%)
Efficacy Evaluable	425 (96%)
Subjects at 6 months at 6-months follow-up*	415 (93%)

* (6 children, 4 adolescent discountinued)

- **Truth and Imaging Standards:** The truth standard for this interim 6-month analysis was cardiac events for 6 months of follow-up. The images were assessed by three independent blinded readers and the majority reads formed a basis for classification of

MPI test status based on Summed Stress Score (SSS) (Normal or Negative if SSS < 4; Abnormal or Positive if SSS $\geq$ 4).

- **Efficacy Results:** The sponsor submitted the results of the interim 6-month analysis for study 301. There were 425 efficacy evaluable (EE) subjects who received at least 1 dose of Cardiolite® with an evaluable stress MPI image. 10 Subjects (6 children, 4 adolescent) discontinued (2.4%) before 6-month follow-up resulting in 415 subjects at 6 months. The number of cardiac events in the first 6-months of follow-up was small. There were no subjects in the study with any hard cardiac events. Hard cardiac events included only myocardial infarction [MI] and cardiac death. Other events included percutaneous coronary intervention [PCI] (2 events) or coronary artery bypass graft surgery [CABG]) (1 event). Subjects with more than one event were counted once. A summary of the efficacy evaluable subjects for Cardiolite® imaging as compared to cardiac events (truth) at 6-month is given in Table 2. The positive predictive value (PPV) was 0% with 95% confidence interval ranging from 0 to 8% and sensitivity was also 0% with 95% confidence interval ranging from 0 to 71%.

Table 2: Summary of Results–Study 301- Efficacy Evaluable Subjects (Cardiac Events as Truth Standard)

MPI Test Status	Cardiac Event		
	Yes	No	Total
Abnormal	0	43	43
Normal	3	369	372
Total	3	412	415

Performance Characteristics:

Parameter	Estimate (%)	95% Confidence Interval (%)
Sensitivity	0%	(0, 71%)
Specificity	90%	(86, 92%)
Positive Predictive Value (PPV)	0%	(0, 8%)
Negative Predictive Value (NPV)	99%	(98, 100%)

- **Further Analysis:** The three cardiac events occurring in this study 301 were further examined. All the 3 subjects who had cardiac events and classified by Cardiolite® MPI test as normal came from US centers and 2 from the same center. The results are given in Table 3.

Table 3: Details of 3 Cardiac Events Classified Normal by MPI Test - Study 301

ID	Sex	Age	Race	Event Description
008-001	M	13	White	Percutaneous Coronary Intervention (PCI) rotoblator procedure performed 1 week after investigational MPI
008-003	F	11	White	Percutaneous Coronary Intervention with stent implantation approximately 3 months later
083-014	M	7	Asian	Coronary Artery Bypass Graft (CABG) 5 months after investigational MPI

3.3 Conclusion for prospective study 301

The 6-month data is not supportive of the ability of Cardiolite® to predict the risk of cardiac events in pediatric patients with Kawasaki Disease (KD). The sponsor plans to assess this endpoint periodically during the long-term follow-up primarily via telephone contacts, and submit final report at the end of 10-years follow-up.

Based on the current data available, the diagnostic efficacy of Cardiolite® to predict the risk of cardiac events in pediatric patients with Kawasaki Disease (KD) has not been established and the data suggest that pediatric KD subjects may be un-necessarily exposed to an agent not beneficial to them.

3.4 Evaluation of Efficacy for retrospective study 302

The study 302 was a retrospective evaluation of efficacy and safety of Cardiolite® in pediatric subjects with Kawasaki Disease (KD).

- **Study Design:** This was a phase 3, retrospective, case-history, international, multicenter of pediatric Kawasaki disease (KD) patients who completed a rest stress, stress rest, or stress only Cardiolite® single photon emission computed tomography (SPECT) myocardial perfusion imaging (MPI) study within 10 years of 30 June 2006. Patient medical records and/or clinic charts were abstracted during a l4-month period ending 28 March 2007.

- **Primary Objective:** The primary objective was to evaluate the performance (sensitivity and specificity) Of Cardiolite® SPECT MPI relative to coronary angiography in pediatric KD patients.

- **Efficacy Evaluable (EE) Subjects:** Subjects who met the study criteria (both evaluable angiographic images and evaluable Cardiolite® MPI images)

- **Number of Subjects and Demographics:** A total of 428 Cardiolite® scan subjects were screened, 86 subjects had at least 1 Cardiolite® MPI and 1 angiogram within 90 days ranging in age from 1 month to 16 years. Table 4 below provides a breakdown of these 86 subjects.

Table 4: Number of Subjects and Demographics - Study 302

Number qualified for inclusion in study	86
Male (%)	61 (71%)
Asian	53 (62%)
White	21 (24%)
Other	12 (14%)
Efficacy Evaluable	72 (84%)

- **Truth and Imaging Standards:** The truth standard for this retrospective study was results of angiographic images using x-ray angiography. Each coronary artery was evaluated and patients ≥ 1 coronary artery demonstrating a ≥ 50% stenosis were classified as abnormal for coronary artery disease (CAD) based on angiographic analysis.. The MPI images were assessed by using Summed Stress Score (SSS) (Normal or Negative if SSS < 4; Abnormal or Positive if SSS ≥ 4).

- **Efficacy Results:** Twelve out of 72 evaluable patients had an abnormal angiogram (≥ 50% stenosis), and 3 patients had positive Cardiolite® MPls (summed stress score (SSS) ≥ 4). Only 1 of these patients had both an abnormal angiogram and a positive Cardiolite® MPI. A summary of the efficacy evaluable subjects for Cardiolite® imaging as compared to angiographic images (truth) for this retrospective study is given in Table 5. The positive predictive value (PPV) was 33% with 95% confidence interval ranging from 1 to 91% and sensitivity was 8% with 95% confidence interval ranging from 0 to 38%.

Table 5: Summary of Results- Study 302- Efficacy Evaluable Subjects (Angiographic Images as Truth Standard)

MPI Test Status	Angiographic Images		
	Abnormal	Normal	Total
Abnormal	**1**	**2**	**3**
Normal	**11**	**58**	**69**
Total	**12**	**60**	**72**

Performance Characteristics:

Parameter	Estimate (%)	95% Confidence Interval (%)
Sensitivity	8%	(0, 38%)
Specificity	97%	(88, 100%)
Positive Predictive Value (PPV)	33%	(1, 91%)
Negative Predictive Value (NPV)	84%	(73, 92%)

3.5 Conclusion for retrospective study 302

The sensitivity and PPV of the retrospective study 302 study are 8% with 95% CI ranging from 0 to 38% and 33% with 95% CI ranging from 1 to 91% respectively. No conclusions can be drawn regarding the ability of Cardiolite® to predict the risk of cardiac events in pediatric patients with Kawasaki Disease (KD) for this retrospective Cardiolite® 302 study.

3.6 Evaluation of Safety

For study DUP 843-201 (Pediatric Radiation Dosimetry Determination and Pharmacokinetic (Biodistribution) Study), the overall incidence of AEs was 19%, and the incidence was higher in children (28%) than in adolescents (10%). One child experienced an SAE (asthma) and 1 child discontinued due to an AE (infusion site reaction). For Cardiolite® 301 prospective study, there was only 1 subject with a reported serious adverse event (overdose with no symptoms) and for Cardiolite® 302 retrospective study, five patients reported a total of 8 adverse events, and no serious adverse events were reported. There were no deaths. Cardiolite® appears to be safe and well tolerated.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

Additional analysis for the following subgroups pre-defined in the protocol for prospective study 301 is provided below.

4.1 Subgroup of Angiographic Images as Truth Standard for Study 301

A secondary objective of the prospective study 301 was to estimate the performance of Cardiolite® rest and stress MPI for the detection of myocardial ischemia in a subset of pediatric subjects who have undergone coronary angiography in terms of positive predictive value (PPV), sensitivity, specificity, and negative predictive value (NPV).

The truth standard for this subset was the results of angiographic images. Efficacy Evaluable (EE) Subjects included both evaluable angiographic images and evaluable Cardiolite® MPI images. There were 51 subjects (out of 415 efficacy evaluable subjects in study 301) who had angiography reports – 12 Subjects had a positive Cardiolite® MPI summed difference score (SDS) ≥ 2 and 11 subjects had coronary stenosis ≥ 50%. These results are given in the following Table 6. As seen from Table 6, the sensitivity of Cardiolite® MPI was 18% with 95% CI ranging from 2 to 52% and the PPV was 17% with 95% CI ranging from 2 to 48%.

Table 6: Summary of Results - Study 301 Efficacy Subset (Angiographic Images as Truth Standard)

MPI Test Status	Angiographic Images		
	Abnormal	Normal	Total
Abnormal	2	10	12
Normal	9	30	39
Total	11	40	51

Performance Characteristics:

Parameter	Estimate (%)	95% Confidence Interval (%)
Sensitivity	18%	(2, 52%)
Specificity	75%	(59, 87%)
Positive Predictive Value (PPV)	17%	(2, 48%)
Negative Predictive Value (NPV)	77%	(61, 89%)

4.2 Age Groups for Study 301

Two age groups were pre-specified in this submission -- children in the age group 4 years to < 12 years, and adolescent in the age group ≥ 12 years to < 17 years). There were 329 children, and

116 adolescent. The performance characteristics of these two age groups are given in Tables 7 and 8.

Table 7: Summary of Results - Study 301 - Children (4 to < 12 Years) (Cardiac Events as Truth Standard)

MPI Test Status	Cardiac Event 4 years to < 12 years		
	Yes	No	Total
Abnormal	0	25	25
Normal	2	280	282
Total	2	305	307

Performance Characteristics:

Parameter	Estimate (%)	95% Confidence Interval (%)
Sensitivity	0%	(0, 84%)
Specificity	92%	(88, 95%)
Positive Predictive Value (PPV)	0%	(0, 14%)
Negative Predictive Value (NPV)	99%	(98, 100%)

Table 8: Summary of Results - Study 301 - Adolescent (≥12 to <17 Years) (Cardiac Events as Truth Standard)

MPI Test Status	Cardiac Event ≥12 years to <17 years		
	Yes	No	Total
Abnormal	0	18	18
Normal	1	89	90
Total	1	107	108

Performance Characteristics:

Parameter	Estimate (%)	95% Confidence Interval (%)
Sensitivity	0%	(0, 98%)
Specificity	83%	(75, 90%)
Positive Predictive Value (PPV)	0%	(0, 19%)
Negative Predictive Value (NPV)	99%	(9, 100%)

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

Please refer to the sections 1 and 2 for a discussion.

5.2 Conclusions and Recommendations

Cardiolite® Kit for the Preparation of Technetium Tc99m Sestamibi for Injection, is a myocardial perfusion agent and was approved as an imaging agent for use in adults on December 21, 1990. Cardiolite® is indicated for detecting coronary artery disease (CAD) by localizing myocardial ischemia (reversible defects) and infarction (non-reversible defects). Cardiolite® is also indicated for evaluating myocardial function and developing information for use in patient management decisions. The sponsor, Bristol-Myers Squibb Medical Imaging (BMS MI) Company, is not seeking any addition to currently approved indications.

The sponsor conducted and submitted the results of 3 studies to satisfy the requirements specified in the Written Request (WR) for Pediatric Studies, to support pediatric exclusivity. The Pediatric Exclusivity Board of FDA determined that the sponsor met all WR requirements.

The pediatric patients with Kawasaki Disease (KD) in the trial were followed for short-term cardiac outcomes at 6 months in a prospective Cardiolite® 301 study. This was a phase III, open-label, non-randomized, international, multi-center study. An interim 6-month clinical study report per FDA's Written Request (WR) was submitted. The 6-month data is not supportive of the ability of Cardiolite® to predict the risk of cardiac events in pediatric patients with Kawasaki Disease (KD). The sponsor plans to assess this endpoint periodically during the long-term follow-up primarily via telephone contacts, and submit final report at the end of 10-years follow-up.

Cardiolite® 302 study was a phase 3, retrospective, case-history, international, multicenter of pediatric Kawasaki Disease (KD) patients.

Low estimates of sensitivity and positive predictive value with wide confidence intervals were observed for both the prospective Cardiolite® 301 study and retrospective Cardiolite® 302 study. Based on the current data available, no evidence of diagnostic efficacy or clinical utility of Cardiolite® scan was found in the three clinical studies of children and adolescents with Kawasaki disease. The effectiveness in the pediatric population has not been established.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Satish Misra
4/16/2008 03:53:22 PM
BIOMETRICS

Jyoti Zalkikar
4/17/2008 04:34:04 PM
BIOMETRICS

Aloka Chakravarty
4/18/2008 11:44:00 AM
BIOMETRICS