

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**021064Orig1s011**

**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: 21-064/S-11  
Drug Name: DEFINITY (Peflutren Lipid Microsphere) Injectable Suspension  
Indication(s): Left ventricular opacification (LVO) and enhanced LV endocardial border delineation (LVEBD) in patients with suboptimal echocardiograms  
Applicant: Lantheus Medical Imaging  
Date(s): September 29, 2010 (Submission Receipt Date)  
Review Priority: Standard  
Biometrics Division: Division of Biometrics 7 (DB7)  
Statistical Reviewer: Janelle K. Charles, PhD  
Mathematical Statistician, DB7  
Secondary Reviewers: LaRee Tracy, MA, PhD  
Team Leader, DB7  
Mark Levenson, PhD  
Deputy Director, DB7  
Medical Division: Division of Medical Imaging Products  
Clinical Team: Ross Filice, MD, Medical Officer  
Libero Marzella, MD, Team Leader  
Project Manager: Frank, Lutterodt, MS

Keywords: ultrasound contrast agent, stress echocardiography, retrospective data, missing data

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## 1. EXECUTIVE SUMMARY

This statistical review primarily focuses on the data and analyses [REDACTED] (b) (4)

[REDACTED]. The study was submitted by Lantheus Medical Imaging (LMI) as part of a supplemental New Drug Application (sNDA) supporting proposed label changes for DEFINITY.

The proposed label changes include [REDACTED] (b) (4)

[REDACTED] removal of the statement that the safety and efficacy of DEFINITY during stress echocardiography has not been established from the Indications and Usage. Presently, the Indications and Usage states the following:

*Activated DEFINITY (Perflutren Lipid Microsphere) Injectable Suspension is indicated for use in patients with suboptimal echocardiograms to opacify the left ventricular chamber and to improve the delineation of the left ventricular endocardial border.*

*The safety and efficacy of DEFINITY with exercise stress or pharmacologic stress testing have not been established.*

LMI proposed Indications and Usage section reads:

*Activated DEFINITY (Perflutren Lipid Microsphere) Injectable Suspension is indicated for use in patients with suboptimal echocardiograms to opacify the left ventricular chamber and to improve the delineation of the left ventricular endocardial border.*

[REDACTED] (b) (4)

The reviewer disagrees with the sponsor's conclusion and views results from the statistical comparisons invalid. There are numerous statistical issues, some of which are summarized below, that need to be considered when interpreting the study findings.

[REDACTED] (b) (4)

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## 2. INTRODUCTION

### 2.1 Overview

DEFINITY (Perflutren Lipid Microsphere) is an intravenous ultrasound contrast agent originally approved for marketing in the United States in 2001. This product is indicated for use in patients with suboptimal echocardiograms to opacify the left ventricular chamber and to improve the delineation of the left ventricular endocardial border. The current Indications and Usage section of the product label states that, “The safety and efficacy of DEFINITY with exercise stress or pharmacologic stress testing have not been established”. The New Drug Application (NDA) holder for DEFINITY, Lantheus Medical Imaging (LMI), submitted a supplemental NDA

(b) (4) to exclude the statement regarding that the safety and efficacy in stress has not been established. (b) (4)



[Redacted] (b) (4)

NOTE: FDA met with LMI in August 2009 to discuss plans to submit information from the sponsor-conducted trials and published literature as part of a supplemental NDA [Redacted] (b) (4). [Redacted] FDA provided the following comment, "... we encourage the conduct of adequate and well controlled phase 3 trials to support safety and efficacy for the proposed new indication". FDA also provided LMI with comments pertaining to the use of the sponsor-proposed study for exploratory analyses.

***Reviewer's Comment: Despite FDA recommendations to conduct an adequate and well-controlled randomized clinical trial to evaluate DEFINITY this submission only includes information*** [Redacted] (b) (4).

The purpose of this statistical review is to analyze and assess the data provided specific to the [Redacted] (b) (4). The statistical efficacy review, Section 3.2, primarily focuses on the [Redacted] (b) (4). Brief statistical comments on [Redacted] (b) (4) are also provided in this section. The statistical safety review, Section 3.3, provides comments based on the following [Redacted] (b) (4):

1. [Redacted] (b) (4)
2. [Redacted] (b) (4)

A brief summary of additional information submitted in support of the safety of DEFINITY from postmarketing studies is also included in section 3.3.

**Reviewer's Comments:**

1. *Defer to clinical review by Dr. Ross Filice for a detailed safety review.*
2. [Redacted] (b) (4)

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### Postmarketing Studies

This section contains brief statistical comments for the three postmarketing safety studies included in this supplemental NDA.

DMP 115-415 was prospective, open-label, non-comparative, non-randomized Phase 4 surveillance registry study in 1053 patients undergoing DEFINITY enhanced echocardiography. The echocardiography procedures included rest only, stress only, or a combination of both rest and stress.

### **Reviewer's Comments:**

- 1. In the approval letter, the FDA recommended a planned sample size of 1000 patients for this post-marketing study requirement. This sample size was not based on a particular study endpoint nor was it based on a pre-specified statistical hypotheses or power calculation.***
- 2. LMI stated 'with the exception of the hepatic impairment subgroup, none of the patient subgroups demonstrated a statistically significant AE occurrence rate' (page 56 of CSR). Given that this study was non-comparative, non-randomized and not powered to detect differences in patient subgroups, statistically significant differences cannot be concluded.***

- 3. LMI stated ‘none of the history subgroups demonstrated a statistically significant difference in the occurrence of treatment-emergent AE as compared to the overall population...’(page 66 of CSR). As stated above, conclusions regarding statistical significance are invalid given study design limitations.***

DMP 115-416 was a prospective open-label, non-comparative, nonrandomized, Phase 4 clinical study in patients with normal or elevated pulmonary artery diastolic pressure, PASP, receiving DEFINITY following right heart catheterization. No echocardiographic images were acquired during this study.

***Reviewer’s Comment:*** *This study was a small non-comparative, non-randomized study in patients with normal or elevated pulmonary hemodynamic pressure. The study sample was not obtained from a random sampling procedure. While the sponsor states that this was a small study, which was not powered to detect differences in the change from baseline measurements for the PASP groups, the sponsor provides some conclusions of statistical significance. The reviewer urges caution in interpreting these results of statistical significance.*

DEFINITY-418 was a retrospective observational database cohort study of mortality in critically ill hospitalized patients undergoing echocardiography with or without DEFINITY. This study utilized propensity score matching to balance differences in baseline characteristics and obtain comparable treatment groups

**Reviewer’s Comments:**

- 1. DMIP consulted DB7 in October 2009 to conduct a review of the data and study report for DEFINITY-418 study. The detailed statistical review is available in DARRTS.***
- 2. The data for this safety were not included in this submission as it exceeds the requirements for electronic submission. This data was submitted to FDA on CD in September 2009.***
- 3. This study excluded patients who received stress echocardiography only; it is possible that patients underwent both rest and stress echocardiography. The data provided does not account for type of echocardiography that patients underwent.***
- 4. The data reported were limited with respect to time to death following echocardiography and therefore lack in specificity necessary to assess exposure and outcome.***
- 5. This study relied on inpatient claims to identify patient characteristics and outcomes. No validation of specific ICD9 diagnostic codes was performed as part of this study***

*raising concerns regarding the sensitivity, specificity and predictability of the reported results.*

#### **4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS**

##### **4.1 Gender, Race, Age, and Geographic Region**

(b) (4)



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## **SIGNATURES/DISTRIBUTION LIST**

Primary Statistical Reviewer: Janelle K. Charles  
Date: June 29, 2011

Concurring Reviewer(s): LaRee Tracy, Mark Levenson

Statistical Team Leader: LaRee Tracy

Biometrics Division Director: Aloka Chakravarty

cc:

Project Manager: Frank Lutterodt

Medical Officer: Ross Filice

Medical Team Leader: Libero Marzella

DMIP Division Director: Dwaine Rieves

HFD-750/Primary Statistical Reviewer: Janelle K. Charles

HFD-750/Statistical Team Leader: LaRee Tracy

HFD-750/ Biometrics Deputy Director: Mark Levenson

HFD-750/Biometrics Division Director: Aloka Chakravarty

Office of Biostatistics: Lillian Patrician

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/s/  
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JANELLE K CHARLES  
06/29/2011

LAREE A TRACY  
06/29/2011

MARK S LEVENSON  
06/30/2011

## STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

**NDA Number: 21-064**

**Applicant:** Lantheus Medical  
Imaging

**Stamp Date:** September 29,  
2010

**Drug Name: DEFINITY**

**NDA/BLA Type: sNDA**

On **initial** overview of the NDA/BLA application for RTF:

|   | Content Parameter   | Yes | No | NA | Comments               |
|---|---|-----|----|----|------------------------|
| 1 | Index is sufficient to locate necessary reports, tables, data, etc.   | ✓   |    |    |                        |
| 2 | ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)                  | ✓   |    |    |                        |
| 3 | Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).                 |     | ✓  |    | See below <sup>1</sup> |
| 4 | Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets). | ✓   |    |    | See below <sup>2</sup> |

### IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? Yes

If the NDA/BLA is not fileable from the statistical perspective, state the reasons and provide comments to be sent to the Applicant.

1. The submission for study [REDACTED] <sup>(b) (4)</sup> does not contain results for efficacy analyses in patient demographic subgroups, that is, age, gender, and race. In addition, there were no safety assessment results by race for DEFINITY 504. We request that the sponsor submit the statistical methods and results for the primary efficacy and safety analyses by patient subgroup (i.e. race, age and gender).
2. The original data definition files lacked in detail and description pertaining to several categorical variables provided in the primary efficacy and safety data sets. The Agency requested that the sponsor submit detailed data definition files including all codes or definitions for the categorical variables included in all study datasets contained in the submission. In addition, there were several variables in the data sets provided that contained a number of blank entries. The Agency also requested that the sponsor specify the codes or symbols used for missing values in the data definition files. Upon request, the sponsor promptly provided updated and well populated data definition files.

## STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

| <b>Content Parameter (possible review concerns for 74-day letter)</b>   | <b>Yes</b> | <b>No</b> | <b>NA</b> | <b>Comment</b>         |
|---|------------|-----------|-----------|------------------------|
| Designs utilized are appropriate for the indications requested.   | ✓          |           |           | See below <sup>1</sup> |
| Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.  | ✓          |           |           |                        |
| Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available. |            |           | NA        |                        |
| Appropriate references for novel statistical methodology (if present) are included.   |            |           | NA        |                        |
| Safety data organized to permit analyses across clinical trials in the NDA/BLA.   | ✓          |           |           |                        |
| Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.   |            |           | NA        |                        |

1. The submission includes a literature review; we view this review as supportive evidence.

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Reviewing Statistician Date

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Supervisor/Team Leader Date

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/s/  
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JANELLE K CHARLES  
11/29/2010

LAREE A TRACY  
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