| Sponsor: | Lantheus Medical Imaging | Protocol Number: | DEF-314 |
|---|---|---|---|

# Statistical Analysis Plan

## *Lantheus Medical Imaging, Inc.*

**Protocol: DEF-314**

**Investigational Product: DEFINITY®**

**A Phase III, Open-Label, Multicenter Trial to Evaluate Ejection Fraction, End-Diastolic and End-Systolic Volumes, by Unenhanced and DEFINITY®-enhanced 2D-Echo and Magnetic Resonance Imaging**


Author(s): Joseph Massaro, Ph.D.



Version Dates: Version 1.0 Draft 1: 07 February 2018
Version 1.0 Draft 2: 12 June 2018
Version 1.0 Draft 3: 15 August 2018
Version 1.0 Final: 06 October 2018

Pages: 35

# Contents

# Abbreviations

| | |
|---|---|
| A2C | Apical 2-chamber |
| A3C | Apical 3-chamber |
| A4C | Apical 4-chamber |
| AE | Adverse Event |
| BMI | Body Mass Index |
| CI | Confidence Interval |
| cm | Centimeters |
| CP | Conditional Power |
| CMR | Cardiac Magnetic Resonance Imaging |
| CRF | Case Report Form |
| ECG | Electrocardiogram |
| eCRF | Electronic Case Report Form |
| HEENT | Head, Eyes, Ears, Nose, and Throat |
| ITT | Intent-to-Treat |
| Kg | Kilogram |
| LVEF | Left Ventricular Ejection Fraction |
| MedDRA | Medical Dictionary for Regulatory Activities |
| m | Meter |
| MI | Medical Imaging |
| mITT | Modified Intent-to-Treat |
| mL | Millilitre |
| MRI | Magnetic Resonance Imaging |
| MUGA scan | Multiple-gated acquisition scan |
| PP | Per-Protocol |
| PT | Preferred Term |
| RMSE | Root Mean Square Error |
| SAE | Serious Adverse Event |
| SAP | Statistical Analysis Plan |
| SP | Safety Population |
| SD | Standard Deviation |
| SOC | System Organ Class |
| TEAE | Treatment Emergent Adverse Event |
| WHO | World Health Organization |

# 1 Introduction

This document presents the statistical analysis plan (SAP) for Lantheus Medical Imaging (LMI) Protocol No. DEF-314: A Phase III, Open-Label, Multicenter Trial to Evaluate Ejection Fraction, End-Diastolic and End-Systolic Volumes, by Unenhanced and DEFINITY®-enhanced 2D-Echo and Magnetic Resonance Imaging.

This analysis plan is based on the protocol dated 15 August 2018.

The purpose of the SAP for this study is to provide a framework in which answers to the protocols' objectives may be achieved in a statistically rigorous fashion, without bias or analytical deficiencies. Specifically, this SAP has the following purpose: To prospectively (a priori) outline the types of analyses and presentations of data that will form the basis for conclusions to be reached that will answer the studies' objectives outlined in the protocol, and to explain in detail how the data will be handled and analyzed, adhering to commonly accepted standards and practices of biostatistical analysis in the clinical trial industry.

# 2 Study Objectives

The objectives of this study are:

Primary objective:

- Demonstrate improvement in accuracy in left ventricular ejection fraction (LVEF) assessment using DEFINITY® contrast-enhanced over unenhanced echocardiography.

Secondary objectives:

- Demonstrate improvement in accuracy in LVEF assessment using DEFINITY® contrast-enhanced over unenhanced echocardiography in subjects with suboptimal echocardiograms.
- Demonstrate a reduction in inter-reader variability for the assessment of LVEF using DEFINITY® contrast-enhanced versus unenhanced echocardiography.
- Demonstrate a reduction in inter-reader variability for the assessment of end-diastolic/systolic volumes using DEFINITY® contrast-enhanced versus unenhanced echocardiography.
- Demonstrate a reduction in inter-reader variability for the assessment of LVEF using DEFINITY® contrast-enhanced versus unenhanced echocardiography in subjects with suboptimal echocardiograms.
- Demonstrate a reduction in inter-reader variability for the assessment of end-diastolic/systolic volumes using DEFINITY® contrast-enhanced versus unenhanced echocardiography in subjects with suboptimal echocardiograms.

## 2.1 Primary endpoint and analyses

The primary endpoint of this study is left ventricular ejection fraction (LVEF) accuracy. The primary analysis is to compare LVEF accuracy from unenhanced imaging to imaging with DEFINITY® contrast enhancement using cardiac magnetic resonance imaging (CMR) as the truth standard.

## 2.2 Secondary endpoints and analyses

The secondary endpoints and analyses of this study are:

- Demonstrate improvement in accuracy in LVEF assessment using DEFINITY® contrast-enhanced over unenhanced echocardiography in subjects with suboptimal echocardiograms.
- Demonstrate a reduction in inter-reader variability for the assessment of LVEF using DEFINITY® contrast-enhanced versus unenhanced echocardiography.

- Demonstrate a reduction in inter-reader variability for the assessment of end-diastolic/systolic volumes using DEFINITY® contrast-enhanced versus unenhanced echocardiography.
- Demonstrate a reduction in inter-reader variability for the assessment of LVEF using DEFINITY® contrast-enhanced versus unenhanced echocardiography in subjects with suboptimal echocardiograms.
- Demonstrate a reduction in inter-reader variability for the assessment of end-diastolic/systolic volumes using DEFINITY® contrast-enhanced versus unenhanced echocardiography in subjects with suboptimal echocardiograms.

## 2.3 Safety endpoints

Enrolled subjects will be followed for adverse events (AEs), serious adverse events (SAEs) and changes in concomitant medications from the time the Informed Consent (IC) is signed through 72±24 hours after completion of DEFINITY® administration.

# 3 Study Design

## 3.1 Discussion of Study Design

This is a Phase 3, prospective, open-label, multicenter study to evaluate LVEF measurement accuracy and reproducibility of DEFINITY® contrast-enhanced and unenhanced echocardiography as compared with non-contrast cardiac magnetic resonance imaging (CMR) used as the truth standard. Approximately one-hundred fifty (150) subjects will be enrolled over approximately 10 months at approximately 10 centers located in the United States. Subjects will undergo unenhanced and DEFINITY®-enhanced echocardiograms and CMR. The study population will consist of male and female subjects 18 years of age or older.

Subjects will be screened for enrollment if they have undergone a 2D echocardiogram with or without contrast or other methods (e.g. CMR, MUGA scan) within 6 months prior to enrollment (Day 0). Subjects will be stratified to achieve an even distribution within four pre-defined LVEF groups (>50, 41-50, 30–40, <30%). Subjects with optimal and sub-optimal echocardiograms (based on the investigator opinion) will be enrolled. An echocardiogram is considered sub-optimal if 2 or more segments of the ventricular border are classified as not adequately visualized.

Each patient will undergo an unenhanced ultrasound examination and a DEFINITY® contrast-enhanced examination on the same day. A minimum of 360 seconds of images will be collected during both the unenhanced and the DEFINITY® contrast-enhanced examinations.

Subjects will remain at the clinical site for at least 30 minutes of observation after the end of the administration of DEFINITY®. A safety follow-up telephone call will be conducted for all subjects at approximately 72±24 hours after completion of the imaging sessions.

Enrolled subjects will be followed for adverse events (AEs), serious adverse events (SAEs), and changes in concomitant medications from the time the Informed Consent is signed through the safety follow-up telephone call.

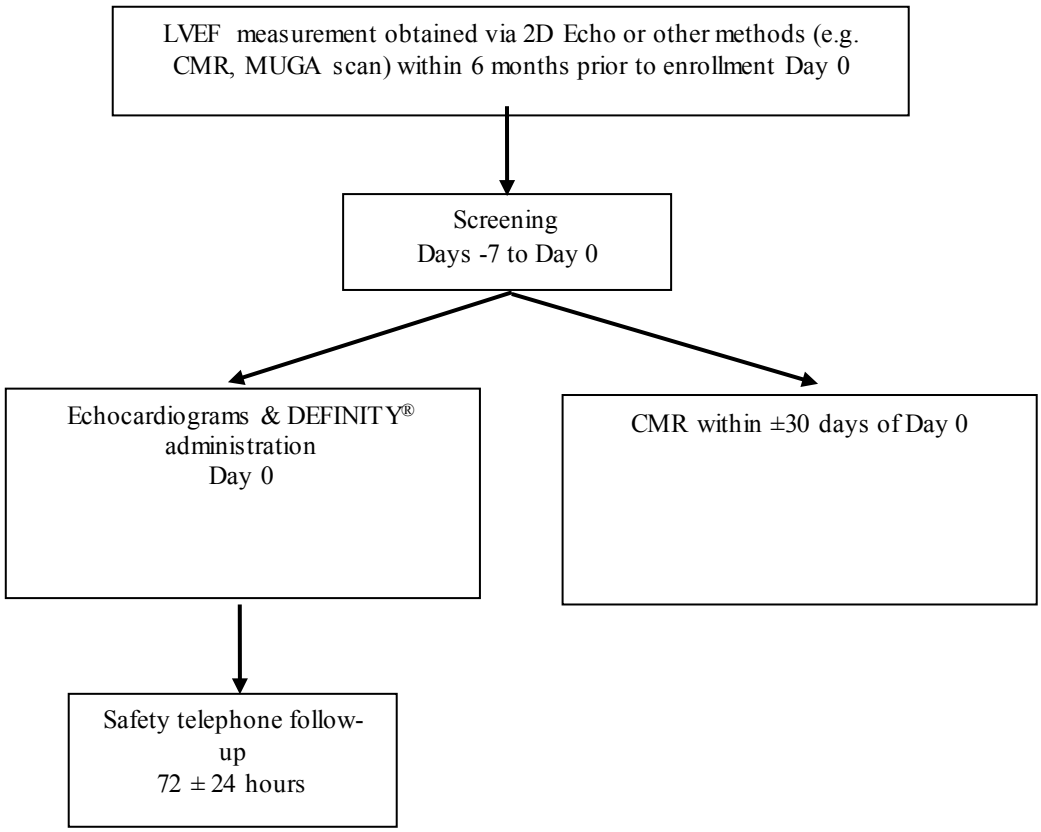
Unenhanced and DEFINITY®-enhanced echocardiograms will be performed with standard apical 2 chamber, apical 3 chamber, and apical 4 chamber (A2C, A3C, and A4C, respectively) views using harmonic imaging. Images will be recorded in standard digital format, masked to subject identifiers, and sent to a central imaging core laboratory for analysis. There, 3 experienced independent blinded readers will interpret the results according to the Image Review Charter. Additional analyses will also be performed as described in the Image Review Charter. Each reader's independent interpretation will be recorded in a database.

CMR images will also be collected and independently read by 3 experienced blinded readers at a central imaging core laboratory.

The figure below displays an overview of study events. The table that follows is a schedule of events:

All screening assessments will occur within 7 days prior to enrollment/DEFINITY® administration (Day 0). CMR studies will occur within ± 30 days of DEFINITY® administration. Safety monitoring will continue up to 72±24 hours post-DEFINITY® administration. The expected duration of subject participation is not more than 41 days. Subjects will be enrolled over a 10-month period.

**Figure: Schedule of Events**



## 3.2 Schedule of Procedures

| Study Procedures | Screening/Baseline[1] | Echo Imaging Session Day 0 | Telephone Follow-up | CMR Imaging Session |
|---|---|---|---|---|
| Informed consent | X | | | |
| Inclusion/Exclusion | X | | | |
| Medical history | X | | | |
| Physical exam | X | | | |
| Body weight and height | X | | | |
| Vital Signs | X | | | |
| Urine pregnancy test[2] | X | X | | |
| Resting unenhanced echocardiogram | | X | | |
| DEFINITY® administration and resting echocardiogram[3] | | X | 72 ± 24 hours after imaging session completion | Within ±30 days of imaging session |
| Concomitant medications | X | X | X | |
| Safety assessments (AEs, SAEs)[4] | ← | → | | |

[1]Procedures may be conducted up to 7 days prior to administration of study drug (Day 0).

[2]A urine pregnancy test will be performed at screening and within 24 hours prior to dosing study drug.

[3]Patient will remain at the clinical site for observation until at least 30 minutes after the end of study drug administration.

[4]AEs will be recorded from at the time the ICF is signed until the 72 ± 24 hour telephone follow-up.

### *3.2.1* Screening

All Screening/Baseline assessments will occur within 7 days prior to administration of study drug (Day 0);

- Determine eligibility according to the inclusion/exclusion criteria;
- Informed consent has been obtained;
- General medical history has been obtained;
- Concomitant medications collected;
- Physical examination: A physical examination will be performed at screening and will include height (cm), weight (kg), general appearance, and normal/abnormal assessment and description of abnormalities for body systems (head, ears, eyes, nose and throat [HEENT]); neck; cardiovascular; lungs; abdomen; lymph nodes; extremities; neurological; skin; musculoskeletal; and other). All physical examination abnormalities will be recorded on the electronic case report form (eCRF);
- Vitals signs including heart rate, respiratory rate and systolic and diastolic blood pressure will be collected at the Screening visit only;
- Urine pregnancy test: A urine sample for pregnancy testing will be obtained for all women of childbearing potential;
- Adverse event collection.

### *3.2.2* Echocardiography Imaging Session

Subjects providing informed consent and meeting the inclusion criteria and none of the exclusion criteria will next undergo the following assessments during the Echocardiography Imaging Session:

- Urine pregnancy test: A urine sample for pregnancy testing will be obtained for all women of childbearing potential within 24 hours prior to dosing the study drug.
- A bedside resting transthoracic echocardiogram will be performed according to standardized instructions provided in the protocol and in the Study Imaging Manual.
- After unenhanced imaging has been conducted, the study drug (DEFINITY®) will be administered as described in the Dose Preparation and Administration Guide.
- After study drug administration and subsequent image optimization, the same A2C, A3C, and A4C views will be obtained as instructed in the Study Imaging Manual.
- Subjects will remain at the site for observation until at least 30 minutes after the end of the administration of study drug.
- Concomitant Medications collected.

- Adverse event collection.

### *3.2.3* Telephone Assessment

- A safety follow-up telephone call will be conducted for all subjects at approximately 72±24 hours after completion of the imaging sessions. Concomitant medications and adverse events will be solicited on this call.

### *3.2.4* Cardiac Magnetic Resonance Imaging

- Within +/- 30 days of imaging session, subjects will receive a non-contrast enhanced CMR examination as described in the Study Imaging Manual.

  Instructions for MRI data transfer and storage at the central imaging core laboratory is provided in the Study Imaging Manual.

## 3.3 Efficacy Evaluations

Three blinded independent readers will perform all efficacy assessments following the methodology described in the Imaging Review Charter. Analyses discussed below will be conducted separately for each reader.

The primary endpoint of this study is left ventricular ejection fraction (LVEF) accuracy. The primary analysis is to compare LVEF accuracy from unenhanced imaging to imaging with DEFINITY® contrast enhancement using cardiac magnetic resonance imaging (CMR) as the truth standard.

The secondary endpoints and analyses of this study are:

- Demonstrate improvement in accuracy in LVEF assessment using DEFINITY® contrast-enhanced over unenhanced echocardiography in subjects with suboptimal echocardiograms.
- Demonstrate a reduction in inter-reader variability for the assessment of LVEF using DEFINITY® contrast-enhanced versus unenhanced echocardiography.
- Demonstrate a reduction in inter-reader variability for the assessment of end-diastolic/systolic volumes using DEFINITY® contrast-enhanced versus unenhanced echocardiography.
- Demonstrate a reduction in inter-reader variability for the assessment of LVEF using DEFINITY® contrast-enhanced versus unenhanced echocardiography in subjects with suboptimal echocardiograms.
- Demonstrate a reduction in inter-reader variability for the assessment of end-diastolic/systolic volumes using DEFINITY® contrast-enhanced versus unenhanced echocardiography in subjects with suboptimal echocardiograms.

## 3.4 Adverse Events

An AE is defined as any new untoward medical occurrence or worsening in severity or frequency of a pre-existing medical condition in a study patient, which does not necessarily have a causal relationship with investigational product. AEs occurring from the time the informed consent is signed until the 72±24 hour telephone follow-up will be reported. Included in the AE data collection are start date and time, severity (Mild/ Moderate/ Severe), relationship (Not Related/ Related to DEFINITY®/ Related to Study Procedure), outcome (Resolved/ Resolved with Sequelae/ Ongoing/ Death/ Unknown), end date and time, treatment action taken (Yes/No), serious (Yes/ No), resulted in death and date of death if applicable, is life threatening, requires hospitalization or prolonged hospitalization, results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect, other significant medical event).

## 3.5 Concomitant Medication

All medications (over the counter or prescription only medication) are permitted during this study at the discretion of the Investigator and will be captured in the database. Enrolled subjects will be followed for changes in concomitant medication use from the time the Informed Consent is signed through 72±24 hours after completion of DEFINITY® administration. Included in data collection are the indication, dose, dose units, frequency, route, start date, stop date or indicator of ongoing at end of study.

## 3.6 Study Analysis Populations

The following analysis populations are defined:

### *3.6.1* Safety Population

The Safety Population (SP) will include all subjects who have signed informed consent and who have received any amount of DEFINITY® in the study. This is the primary analysis population for the safety analysis.

### *3.6.2* Intent-to-Treat Population

The Intent-to-Treat (ITT) will include all subjects who have signed informed consent.

### *3.6.3* Modified Intent-to-Treat Population

The Modified Intent-to-Treat (mITT) population will include all ITT subjects who complete unenhanced imaging and DEFINITY® enhanced imaging. This is the primary analysis population for the efficacy endpoints.

### *3.6.4* Per-Protocol Population

The Per-Protocol (PP) population will include modified ITT subjects who a) did not violate inclusion and exclusion criteria that would likely have an effect on the primary outcome, b) do not have major protocol violations; c) have LVEF data on both unenhanced and DEFINITY®-enhanced images for at least one reader; (d) have CMR LVEF.

Efficacy analyses will be conducted for both modified ITT and PP population sets, differences in results using the two populations will be carefully examined descriptively.

### *3.6.5* Other Population Defined for Tables and Listings

For the purposes of tables and listings population includes:

- All screened subjects.

## 3.7 Withdrawn Subjects

The investigator may withdraw a subject from the study for any of the following reasons:

- Subject withdraws consent.
- Subject is lost to follow up.
- Subject has an AE that, in the opinion of the Investigator, requires the subject's discontinuation.
- Discretion of the Investigator.
- The Sponsor or Investigator terminates the study.

All events that result in discontinuation of study treatment will be appropriately recorded and reported. In addition, for all subjects who discontinue prematurely, an evaluation which reflects the status of the patient at premature termination, along with a final assessment and the reasons for termination, will be recorded on the eCRF.

## 3.8 Randomization

There is no randomization for this trial as all subjects will be receiving DEFINITY®.

## 3.9 Blinding

Blinding to treatment is not applicable for this single arm open-label trial.

## 3.10 Sample Size

The primary analysis is to demonstrate an improvement in LVEF accuracy from unenhanced imaging to imaging with DEFINITY® contrast enhancement using CMR as the truth standard.

For each patient, the absolute value of the difference of DEFINITY® LVEF minus CMR LVEF will be calculated. Similarly, the absolute value of the difference of unenhanced imaging LVEF minus CMR LVEF will be calculated for each patient. The primary analysis is to assess the significance of the difference between DEFINITY® and unenhanced echo with respect to the mean "absolute value of the difference vs. CMR". These means will be compared with a paired t-test at a two-sided 0.05 level of significance. Specifically, the null and alternative hypotheses are:

$$H0: \mu D = \mu U \text{ vs. } H1: \mu D \neq \mu U$$

where μD and μU are the mean of the DEFINITY® unenhanced echo absolute value of the difference vs. CMRs, retrospectively. A sample size of 150 enrolled subjects has 90% power to reject the null hypothesis in favor of the alternative if the true difference μD - μU is at least 2.75 (in favor of DEFINITY®) with a standard deviation of 10 or less and allows for approximately 5% premature withdrawal. Power was calculated using the PASS 15 software.

# 4 Statistical Methodology

## 4.1 Planned Analyses

A contract research organization (CRO) will be responsible for data management and statistical analysis. All statistical analyses will be performed using SAS (SAS Institute, Inc., Cary, NC) version 9.4 or higher. Patient data listings and tabular presentations of results will be provided. Presentation of summary statistics for continuous variables will include N, mean, median, and standard deviation, as well as the minimum and maximum values. For categorical variables, the number and percent of subjects in each category will be calculated; the number of subjects with missing data will be presented under a "Missing" category. Unless otherwise stated, subjects with missing values will be included in the denominator count when computing percentages. Results will be presented to 1 decimal place when applicable. All statistical tests will be two-sided employing a significance level of 5% unless otherwise specified. Further details of the criteria and conduct of the statistical analyses are below.

Demographic and efficacy analyses will be carried out using the modified intent-to-treat (mITT) population as the main analysis population; it will also be carried out on the per-protocol (PP) population. The safety analysis will be carried out on the Safety Population (SP).

The primary analysis will be performed on subjects with non-missing LVEF for DEFINITY®-enhanced echocardiography imaging, unenhanced imaging, and the truth standard, cardiac magnetic resonance. A supportive analysis will be run where missing LVEF is multiply imputed using the fully conditional specification (FCS) multiple regression, as detailed below. Otherwise, there will be no imputation of missing data.

## 4.2 Interim Analysis

This study will utilize an adaptive design that allows one interim sample size re-estimation after a minimum of 75 subjects have been enrolled and imaged. Further details are described below in the section describing the primary analysis.

## 4.3 Disposition of Subjects

Subject disposition data will include the number and percentage of ITT subjects who were enrolled in the trial, who received DEFINITY®, who completed the trial, and who discontinued the trial will be presented. The number and percentage of ITT subjects who discontinued the trial will also be presented by reason of discontinuation. The number and percentage of subjects in each analysis population will be presented. All percentages will be based on the total number of ITT subjects.

## 4.4 Baseline and Demographic Characteristics

All baseline and demographic characteristics will be summarized overall. This will include age at Screening, age group at Screening, gender, ethnicity, race, height, weight, body mass index (BMI), and active and past medical history. Descriptive statistics will be provided for each quantitative (continuous) variable; frequencies and percentages of subjects will be provided for each qualitative variable.

**Notes:**

- Age will be calculated as (year of screening date – year of birth) and presented to 1 decimal place. No rounding will be carried out prior to summarising age.
- Age group will be categorized as < 65 years and ≥ 65 years.
- BMI will be calculated as weight (kg)/height$^2$(m).
- Medical history data will be collected by body system for all enrolled subjects. The details of history by body system are collected as open text. Medical history will be coded according to Medical Dictionary for Regulatory Activities (MedDRA) version 20.0; the number and percentage of subjects within each system organ class (SOC) and preferred term (PT) will be presented; a patient experiencing a medical history within more than one SOC or PT will be counted only once within that SOC and PT, respectively.
- Active medical history is defined as histories marked as ongoing at time of screening.
- Past medical histories are defined as histories marked as resolved at time of screening (ongoing not selected).

## 4.5 Exposure

DEFINITY® will be administered as a diluted bolus injection. 1.3 mL of activated DEFINITY® will be diluted with 8.7 mL of preservative-free saline to evenly distribute microspheres. An initial injection of up to 3 mL of diluted DEFINITY® will be administered with subsequent injections of 1 to 2 mL, as needed. Information about the administration of DEFINITY® is collected in the eCRF. Exposure to DEFINITY® study drug will be summarized as described below:

The number and percentage of ITT subjects who are administered DEFINITY® will be presented. Summary statistics of the dose administered (mL) will be summarized for the safety population.

## 4.6 Concomitant Medication

Medications are coded using World Health Organization (WHO) Drug dictionary, version Q3-2016. The number and percentage of subjects with prior and concomitant medication will be presented overall by, WHO therapeutic area and WHO preferred drug name. Prior medications

are those that started and stopped before exposure to contrast agents; concomitant medications are all medications taken during the study period, including those started before but on going at first administration.

Medications for each subject will be assigned as prior or concomitant by comparing the start and stop date of medication and the date of each dose. Where a medication start date is partially or fully missing, and it is unclear as to whether the medication is prior or concomitant, it will be assumed that it is concomitant.

## 4.7 Efficacy / Primary and Secondary Analysis

All efficacy parameters will be summarized and presented in tables based on the Modified Intention-to-Treat population and reanalysed using the Per Protocol population.

### *4.7.1* Primary endpoint

The primary endpoint of this study is LVEF accuracy. The primary analysis is to compare LVEF accuracy from unenhanced imaging to that derived from imaging with DEFINITY® contrast enhancement using cardiac magnetic resonance imaging (CMR) as the truth standard.

### *4.7.2* Primary analysis for the primary endpoint

The primary analysis is to demonstrate an improvement in LVEF accuracy from unenhanced imaging to that derived from imaging with DEFINITY® contrast enhancement using CMR as the truth standard.

For each patient, the absolute value of the difference of DEFINITY® LVEF minus CMR LVEF will be calculated. Similarly, the absolute value of the difference of unenhanced imaging LVEF minus CMR LVEF will be calculated for each patient. The primary analysis is to assess the significance of the difference between DEFINITY® and unenhanced echo with respect to the mean "absolute value of the difference vs. CMR". Specifically, the null and alternative hypotheses are:

$$H0: \mu D = \mu U \text{ vs. } H1: \mu D \neq \mu U$$

or i.e.,

$$H0: \mu U - \mu D = 0 \text{ vs. } H1: \mu U - \mu D \neq 0$$

where μD and the μU are the mean of the DEFINITY® and unenhanced echo absolute value of the difference vs. CMR, retrospectively. The null hypothesis will be tested at a two-sided 0.05 level of significance using a paired t-test derived from the sample point estimates of the mean and standard deviation of the difference between unenhanced echo's and DEFINITY's® "absolute value of the difference vs. CMR".

The analyses will be conducted separately for each of the three blinded readers of the DEFINITY® enhanced and unenhanced images; the criterion for success is that the null hypothesis is rejected in favor of DEFINITY® for at least 2 of the 3 blinded readers for all subjects. CMR LVEF is interpreted by a single reader; this is the CMR LVEF that will be used as the comparator for each of the three blinded readers.

The primary analysis will be performed on mITT subjects with non-missing LVEF for DEFINITY®, unenhanced echocardiography, and the truth standard. A supportive analysis will be run where a missing echocardiography or CMR LVEF is multiply imputed using the fully conditional specification (FCS) multiple regression.

**Interim Analysis:** This study will utilize an adaptive design that allows one interim sample size re-calculation after a minimum of 75 subjects have been enrolled and followed. The pre-specified maximum allowable adjusted sample size following re-estimation will be 300 enrolled, or two times the initial planned sample size of 150 enrolled. The re-estimation of sample size will be conducted by an independent biostatistician following a pre-specified plan using the method of by Mehta and Pocock (2011).[1] Specifically, at the interim stage, the conditional power (CP) for obtaining a significant beneficial effect of DEFINITY® over unenhanced imaging with respect to the primary endpoint will be calculated for each blinded reader, using the protocol-specified planned sample size of 150 enrolled subjects (approximately 143 evaluable subjects assuming 5% premature withdrawal). This conditional power will be calculated under the assumption that the interim estimate of the mean unenhanced- DEFINITY® difference in LVEF accuracy is the true population mean difference. Specifically, the calculation of conditional power and sample size increase will be as follows:

Let μD be the true mean of the absolute value of the differences between the DEFINITY®-enhanced echo LVEF and the CMR LVEF, and let μU be the true mean of the absolute value of the differences between the unenhanced echo LVEF and the CMR LVEF. After 75 patients are enrolled and followed (which should lead to approximately 71 evaluable patients), an unblinded interim analysis will be conducted to determine whether sample size should be increased to maintain adequate conditional power of up to 90% for each reader. Conditional Power (CP) for rejecting the null hypothesis in favor of DEFINITY® by the planned final sample size of 143 evaluable patients is calculated as follows for each reader:

$$\text{CP} = P\left(Z > \frac{c_2\sqrt{i_2} - t_1\sqrt{I_1} - (I_2 - I_1)\Delta}{\sqrt{I_2 - I_1}}\right)$$

where

a. Z is a random standard random variate

b. $c_2$ is the $t$-critical value to be used in the final analysis = 1.97681 (one-sided 0.025 level of significance; with 142 df assuming the final evaluable sample size is 143, which is the number of evaluable subjects expected for the final analysis with 150 enrolled subjects with 5% premature withdrawal)

*c.* Δ is the assumption of the true difference "μU minus μD" where μD is the mean of the absolute value of the differences between the DEFINITY®-enhanced echo LVEF and the

CMR LVEF, and μU is the mean of the absolute value of the differences between the unenhanced echo LVEF and the CMR LVEF; Δ will be set to the interim sample's point estimate of μU minus μD (i.e., Δ will be set to $\bar{X}_U - \bar{X}_D$, where $\bar{X}_U$ and $\bar{X}_D$ are the sample mean point estimates of μU and μD, respectively).

d. $I_1$ is the observed "information" at the interim analysis; specifically, $I_1 = \frac{1}{s^2/n_1}$ where $s$ = the interim sample point estimate of the standard deviation of the difference between the unenhanced and DEFINITY® echo's "absolute value of the difference vs. CMR" and $n_1$ is the interim sample size.

e. $I_2$ is the anticipated "information" at the final analysis; specifically, $I_2 = \frac{1}{s^2/n_2}$ where $s$ is as defined in item d directly above and $n_2$ is the planned final evaluable sample size = 143.

f. $t_1$ is the interim paired t-statistic testing the null hypothesis, derived from the interim sample point estimates of the mean and standard deviation of the difference between the unenhanced and DEFINITY® echo's "absolute value of the difference vs. CMR".

The study will not be stopped for overwhelming efficacy or futility at this interim stage. Instead, based on Table 1 of Mehta and Pocock (2011),[1] the following algorithm will be carried out:

- If 36% < CP < 90% for all three readers: Let $n$ be the total protocol-specified enrolled sample size. Assume $n_a$ is the total enrolled sample size for reader 1 to reach 90% CP, $n_b$ is the total enrolled sample size for reader 2 to reach 90% CP, and $n_c$ is the total enrolled sample size for reader 3 to reach 90% CP. The final total number of enrolled subjects is min(max($n_a$, $n_b$, $n_c$), 2$n$). Each reader's final analysis will be based on min(max($na$, $nb$, $nc$), 2$n$) enrolled subjects.
- If 36% < CP < 90% for exactly two out of three readers, for example reader 1 and reader 2 where and reader 3's CP is not in the promising zone. The final total number of enrolled subjects will be the sample size with which both readers have more than 90% CP but not exceeding 2$n$, i.e. min(max($n_a$, $n_b$), 2$n$). Each reader's final analysis will be based on this min(max($n_a$, $n_b$), 2$n$) enrolled subjects.

The number of enrolled subjects is not changed from the final protocol-specified sample size in any other cases. That is, in all such other cases, each reader's final analysis will be based on the $n$ enrolled subjects.

The sponsor and investigators will remain blinded to the interim results for the duration of the ongoing study. After the interim analysis is carried out, the recommendation made to the sponsor will only be to keep sample size as is or to increase enrolled sample size to a given value; the reason for the recommendation will not be given to the sponsor.

### *4.7.3* Other analyses for the primary endpoint

The following will be carried out separately for each of the three blinded readers without imputation of missing LVEF.

Bias is the mean of the actual (not absolute value) per-subject differences between the imaged LVEF and CMR LVEF. The bias, the two-sided 95% confidence interval of the bias, the precision (standard deviation of the per-subject differences) and the root mean square error (RMSE) will be calculated for the LVEF derived from the DEFINITY®-enhanced images. The RMSE is the square root of the bias-squared + precision-squared and is considered a measure of overall accuracy. These analyses will be repeated for LVEF values derived from the unenhanced echocardiography vs. those from CMR. It is anticipated that the RMSE will be smaller for DEFINITY®-enhanced LVEF than for unenhanced LVEF.

DEFINITY®-enhanced and unenhanced echocardiography LVEF will each be assessed for measurement accuracy against the reference CMR using Bland-Altman analysis and Deming regression analysis. For the Bland-Altman analysis, a plot of the per-subject actual difference between DEFINITY®-enhanced echocardiography and CMR LVEF will be plotted vs. the per-subject sum of the two measurements. Limits of agreement (defined as the mean of the DEFINITY® vs. CMR difference) +/- 2 standard deviations (SDs) will be shown on the plot. The same analyses will be performed for unenhanced echocardiography using CMR as the reference standard.

Deming regression plots of LVEF vs. CMR LVEF will be generated for each of DEFINITY®-enhanced and unenhanced echocardiography. Unweighted Deming regression will be employed to estimate the regression slope and intercept with two-sided 95% confidence intervals of each assuming the measurement error is the same for CMR and each of the echocardiography error techniques.

The intra-class correlation coefficient (ICC) and its two-sided 95% confidence interval (CI) will be calculated for DEFINITY®-enhanced echo vs. CMR and for unenhanced echo vs. CMR. The ICCs and their two-sided confidence intervals will be calculated using between and within mean squares from an ANOVA model with method (echocardiography, CMR) and subject as the main effects and LVEF as the dependent variable. The ICC will be calculated using the SAS macro developed by Hamer (1990).[2]

### *4.7.4* Secondary endpoints

The secondary endpoints and analyses of this study are:

- Demonstrate improvement in accuracy in LVEF assessment using DEFINITY® contrast-enhanced over unenhanced echocardiography in subjects with suboptimal echocardiograms.
- Demonstrate a reduction in inter-reader variability for the assessment of LVEF using DEFINITY® contrast-enhanced versus unenhanced echocardiography.
- Demonstrate a reduction in inter-reader variability for the assessment of end-diastolic/systolic volumes using DEFINITY® contrast-enhanced versus unenhanced echocardiography.

- Demonstrate a reduction in inter-reader variability for the assessment of LVEF using DEFINITY® contrast-enhanced versus unenhanced echocardiography in subjects with suboptimal echocardiograms.
- Demonstrate a reduction in inter-reader variability for the assessment of end-diastolic/systolic volumes using DEFINITY® contrast-enhanced versus unenhanced echocardiography in subjects with suboptimal echocardiograms.

### *4.7.5* Methods of analysis for secondary outcomes

#### 4.7.5.1 Demonstrate improvement in accuracy in LVEF assessment using DEFINITY® contrast-enhanced over unenhanced echocardiography in subjects with suboptimal echocardiograms

The above primary endpoint analyses will be repeated in the subset of subjects with suboptimal echocardiograms. The study is not powered to reject the primary endpoint null hypothesis in Section 4.7.2, so the focus is more on the estimate of μD - μU, on Bland-Altman plots and on the Deming regression for each blinded reader. There will be no imputation of missing LVEF data for this analysis.

#### 4.7.5.2 Demonstrate a reduction in inter-reader variability for the assessment of LVEF using DEFINITY® contrast-enhanced versus unenhanced echocardiography.

The inter-reader variability among each pair of readers within each imaging modality will be estimated using an intra-class correlation coefficient (ICC) and its two sided 95% CI. The ICC assesses rating reliability by comparing the variability of different ratings of the same subject with the total variation across all ratings and all subjects. The inter-observer variability in the assessment of LVEF between two readers will be determined by percentage of error. The percentage of error will be calculated using the formula:

Percentage of error = SD between 2 measurements/mean of the 2 measurements x 100

The mean percentage of error and its 95% confidence interval will be calculated for each pair of readers within each imaging modality.

There will be no imputation of missing data for this analysis. The pairwise ICCs and percentages of error differences will be compared descriptively between contrast-enhanced and unenhanced echocardiography.

#### 4.7.5.3 Demonstrate a reduction in inter-reader variability for the assessment of end-diastolic/systolic volumes using DEFINITY® contrast-enhanced versus unenhanced echocardiography.

The above analyses used to assess inter-reader variability on LVEF will be carried out, but on end-diastolic/systolic volumes. There will be no imputation of missing data for this analysis.

#### 4.7.5.4 Demonstrate a reduction in inter-reader variability for the assessment of LVEF using DEFINITY® contrast-enhanced versus unenhanced echocardiography in subjects with suboptimal echocardiograms.

The above analyses used to assess inter-reader variability on LVEF will be carried out, but on the subgroup of subjects with suboptimal echocardiograms. There will be no imputation of missing data for this analysis.

#### 4.7.5.5 Demonstrate a reduction in inter-reader variability for the assessment of end-diastolic/systolic volumes using DEFINITY® contrast-enhanced versus unenhanced echocardiography in subjects with suboptimal echocardiograms.

The above analyses used to assess inter-reader variability on LVEF in subjects with suboptimal echocardiograms will be carried out, but on end-diastolic/systolic volumes. There will be no imputation of missing data for this analysis.

## 4.8 Safety Analysis

The safety analyses that are described below will be carried out on the Safety Population.

### *4.8.1* Adverse events

A treatment emergent adverse event (TEAE) is an adverse event that started or worsened in severity following the start of administration of DEFINITY®. A table of adverse events will be summarized including:

- Number of subjects having experienced at least one TEAE,
- Number of subjects having experienced at least one TEAE related to the DEFINITY®,
- Number of subjects having experienced at least one TEAE related to a study procedure,
- Number of subjects having experienced at least one severe TEAE,
- Number of subjects definitively removed from the contrast agent due to a TEAE,
- Number of subjects definitively removed from the contrast due to a TEAE related to the study contrast agent,

- Number of subjects definitively removed from the contrast due to a TEAE related to the study procedure,
- Number of subjects having experienced at least one serious TEAE,
- Number of subjects having experienced at least one serious TEAE related to the study contrast agent,
- Number of subjects having experienced at least one serious TEAE related to a study procedure,
- Number of subjects having experienced at least one severe serious TEAE,
- Number of subjects definitively removed from the contrast agent due to a serious TEAE,
- Number of subjects definitively removed from the contrast agent due to a serious TEAE related to the study contrast agent,
- Number of subjects definitively removed from the contrast agent due to a serious TEAE related to the study procedure,
- Number of subjects having experienced a fatal serious TEAE,
- Number of subjects having experienced a fatal serious TEAE related to the study contrast agent,
- Number of subjects having experienced a fatal serious TEAE related to a study procedure.

A summary table of TEAEs (number and % of subjects who experienced an adverse event and number of events) grouped by primary SOC and PT will be presented for the following categories of events:

- All TEAEs,
- All TEAEs related to the study contrast agent,
- All TEAEs related to a study procedure,
- All serious TEAEs,
- All serious TEAEs related to the study contrast agent,
- All serious TEAEs related to a study procedure,
- All severe TEAEs,
- All TEAEs leading to study discontinuation.

A summary table of TEAEs by SOC and PT will be also presented for each severity.

A subject with more than one occurrence of the same adverse event in a particular SOC and PT will be counted only once in the total of subjects experiencing adverse events in that particular SOC and PT, respectively. If a subject experiences the same adverse event at more than one

severity, or with more than one relationship category, the most severe rating or the stronger causal relationship will be given precedence.

Any missing severity or relationship of an AE should be replaced by the worst case as follows:

- If severity is missing, then the AE will be included in "severe" category.
- If relationship is missing, then the AE will be included as "related to the study contrast agent".

Time to onset and duration of events in days will also be listed where:

- Time to onset is defined as (AE start date – date of DEFINITY®).
- Duration of event is defined as (AE stop date - AE start date + 1).

**Note**: AEs with missing start dates will be included in the count of events, but a time will not be calculated.

AEs will be coded using MedDRA version 19.0.

### *4.8.2* Vital Signs

The vital sign measurements are only obtained at screening/baseline visit. The vital sign measurements (systolic and diastolic blood pressure, heart rate, and respiratory rate) at baseline will be summarized using descriptive statistics.

The number and percentage of subjects with potentially clinically significant vital sign values at baseline will be tabulated. Potentially clinically significant vital signs values are detailed below:

| | Parameter | Unit | Normal range | Potentially Clinically Significant |
|---|---|---|---|---|
| vital sign | Heart Rate | Beats per minute | 60-100 | 1) <50 bpm and >/=25% decrease from baseline<br>2) >100 bpm and >/=25% increase from baseline |
| | Systolic Blood Pressure | mmHg | 90~139 | 1) > 190 mmHg (entry is < 160 mmHg)<br>2) Systolic <80 mm Hg<br>Decrease from baseline >30 mmHg |
| | Diastolic Blood Pressure | mmHg | 60~89 | 1) 110 mmHg (entry is < 90 mmHg)<br>2) <50 mm Hg<br>3) Change from baseline of 20mmHg (increase or decrease) |

#### *4.8.3* Physical exam

Physical examination body system inspection results will be listed only. The physical exam is only conducted at Screening.

#### *4.8.4* Study Center effects

The mean "absolute value of the difference vs. CMR" for each of DEFINITY® and unenhanced echocardiography, as well as the difference between the two treatments with respect to this mean, will be presented for each study center and each blinded reader. Within each blinded reader, and assessment of study center effect on the mean treatment difference will be assessed using one-way analysis of variance. For each blinded reader, a site difference that is not significant at the 0.15 level of significance, or a site difference that is significant but where for every site the mean treatment difference is more favorable for DEFINITY® than enhanced echocardiography, will support pooling subjects across sites for the primary analysis for that reader.

## 4.9 Protocol Violations

The finalization of protocol violations and excluded data will be made prior to the database lock.

#### *4.9.1* Violation criteria

Subjects who meet any of the following criteria will be listed and presented in the study report:

- Non-compliance with inclusion criteria.
- Non-compliance with exclusion criteria.
- Non-compliance with study contrast agent.
- Non-compliance with study procedures.
- Other.

Other reasons for violation may be added to this list and will be done so prior to database lock of the study.

#### *4.9.2* Protocol violations

Deviations from the protocol, as defined in the protocol, will be documented and monitored on an ongoing basis by the Sponsor, study monitors and project manager throughout the study period.

At the time of database lock, while the protocol violations are being reviewed, the Sponsor will forward all relevant documentation highlighting protocol violations to the study statistician. These violations will be included in the protocol violation document for agreement and will be listed with the protocol violations in the clinical study report.

## 4.10 Missing Values and Missing Visit Dates

Within each blinded reader, the primary hypothesis test on the primary endpoint will be performed on subjects with non-missing LVEF for DEFINITY®, unenhanced echocardiography, and the reference standard. A supportive analysis will be run where, within each blinded reader, missing LVEF is multiply imputed using the fully conditional specification (FCS) multiple regression prior to carrying out the primary endpoint analysis. The covariates in the imputation model will be study center, age, gender, body weight (kg), race and ethnicity; this will be done separately for each imaging method (DEFINITY® enhanced, unenhanced, and CMR reference standard). A total of 50 imputations will be generated; the paired t-test comparing mean bias between DEFINITY® and unenhanced (see primary endpoint null and alternative hypotheses above) will be performed separately on each of the 50 imputed datasets, and the t-test results will be combined across datasets using the usual multiple imputation techniques to create one overall paired t-test results on imputed data.

There is no intention to implement any procedure for replacing missing data for any analyses except the primary endpoint paired t-test. For all other analyses, the number of subjects with missing data will be presented under a "Missing" category. Unless otherwise stated, subjects with missing values will be included in the denominator count when computing percentages.

When continuous data are being summarized, only the non-missing values will be evaluated for computing summary statistics.

In case of missing date, replacement will be applied in order to be in a worst case:

- Concomitant medication start date:
    - in case of completely missing date, it will be estimated as the DEFINITY® administration date;
    - if the day and the month are missing:
        - if the year is the same as the year of the DEFINITY® administration date, it will be estimated by the DEFINITY® administration date;
        - if the year is different to the year of the administration date, it will be estimated as 1st January of that year;
    - if day only is missing:
        - if the month/year are the same as the month/year of the DEFINITY® administration date, it will be estimated by the DEFINITY® administration date;
        - if the month/year are different from the month/year of the DEFINITY® administration date, it will be estimated by the first day of the month;
- Concomitant medication end date (if ongoing is not ticked at the end of the study):
    - in case of missing date, it will be estimated by the End of Study date;
    - if the day and the month are missing:

  - if the year is the same as the year of the End of Study date, it will be estimated by End of Study date;
  - if the year is prior to the year of End of Study date, it will be estimated by as 31 December of that year;
- if day only is missing:
  - if the month/year are the same as the month/year of End of Study date, it will be estimated by the End of Study date;
  - if the year or month is different to the year or month of End of Study date, it will be estimated by the last day of the month.

- Start date of an adverse event:
  - In case of completely missing date, it will be estimated by the DEFINITY® administration date.

## 4.11 Deviations from SAP

Any deviations from the original statistical plan will be described and justified in the final clinical study report, whether written post interim or final analysis.

## 4.12 Changes in Conduct or Planned Analyses from the Protocol

There have been no changes in analyses from those defined in the protocol.

## 4.13 Algorithms/SAS Codes

- **Tables that need descriptive statistics – continuous variables:**

```
PROC UNIVARIATE DATA=dset NOPRINT;
    VAR var1 var2 var3 ...varn;
    BY byvar; (optional)
    OUTPUT OUT=outname
    N=n MEAN=mean MIN=min MAX=max MEDIAN=median STD=std;
RUN;
```

- **Tables that need frequency counts:**

```
PROC FREQ DATA=dset NOPRINT;
    BY byvar; (optional)
    TABLES var1*var2;
    OUTPUT OUT=outname;
RUN;
```

- **Tables that need 95% CIs within group for continuous variables:**

```
DATA outdata;
    SET outname;
    LCL=mean-(TINV(0.975,n-1)*(std/SQRT(n)));
    UCL=mean+(TINV(0.975,n-1)*(std/SQRT(n)));
RUN;
```

# 5 Tables and Listings

## 5.1 Table Format

All output will be produced using SAS version 9.4 or a later version.

In the top left portion of each table/listing, a *table/listing number* followed by the *title* of the table/listing will be presented. After the title line, optional *sub-title* or *population* information can be presented. Horizontal lines will appear before and after the column heading of the table/listing. *Footnotes* will be put under the main body of text at the bottom of the page.

The *sponsor name*, *protocol number,* programmers User ID, status of the table/listing (i.e. draft or final) and *SAS program name* will appear bottom left in a string and the *page number* will appear on the bottom right corner of each table/listing. The *date and time of creation* of table/listing will appear bottom left under the sponsor name. The source listing number will appear bottom left.

A *landscape layout* is proposed for both table and listing presentations.

The *left* and *right margins* of all tables and listings will be a minimum of 2.1 cm from the left and 1.9cm from the right. The *top and bottom margins* will be a minimum 2.92cm. *Header and footer* will be both 1.27 cm.

There is no special requirement of *font type* and *size*, but an *8-point* font size for tables and *7*or *8-point* for listings is proposed using *Courier New* font. A maximum SAS line size=141 and page size=44 for *8-point* font size, and line size=161 and page size=50 for *7-point* will be used so as to fit on both UK and US paper sizes.

In a listing, in the case that a subject's record has been continued to the next page, an appropriate identification (e.g., the subject ID number) must be presented at the beginning of that page.

## 5.2 Conventions

Unless otherwise specified, in summary tables of continuous variables, the minimum and maximum values will be displayed to the same number of decimal places as the raw data, the mean and median will be presented to one extra decimal place compared to the raw data, and the standard deviation will be displayed to two extra decimal places compared to the raw data. Wherever possible data will be decimal aligned.

Unless otherwise specified frequency tabulations will be presented by number and percentage, where the percentage is presented in brackets to 1 decimal place.

P-values, if applicable, will be presented to 3 decimal places. If a p-value is less than 0.05 but is greater than or equal to 0.01, then an asterisk (*) will be added next to this value. If a p-value is less than 0.01 but is greater than or equal to 0.001, then two asterisks (**) will be added next to this value. Finally, if the p-value is less than 0.001 then three asterisks (***) will be added next to this value and it will be presented as <0.001. If the rounded result is a value of 1.000, it will be displayed as >0.999. Any date information in the listing will use the *date9.* format, for example,

07MAY2002. In the listing, a unit associated with a variable will be presented only once within parentheses either below or next to that variable in the heading portion. If a parameter has multiple units, each unit will be displayed only once, as applicable.

All tables will have their source listing referenced in a footnote. Listings should be sorted by Sequence, and subject and have the source data received by data management referenced in a footnote. All tables and listings will be converted into Microsoft Word documents and collated into two complete documents.

## 5.3 Tables

### *5.3.1* Section 14.1: Demographic and baseline

Table 14.1.1 Subject Disposition (All screened population)
Table 14.1.2 Demographics (Modified ITT populations)
Table 14.1.3.1 Active Medical History (Modified ITT populations)
Table 14.1.3.2 Past medical history (Modified ITT populations)
Table 14.1.4 Exposure (Safety population)
Table 14.1.5.1 Prior medications (Safety population)
Table 14.1.5.2 Concomitant medications (Safety population)

### *5.3.2* Section 14.2: Primary

Table 14.2.1.1.1 LVEF – Subjects with Available Data (Modified ITT population)
Table 14.2.1.1.2 LVEF by Study Center – Subjects with Available Data (Modified ITT population)
Table 14.2.1.2.1 LVEF – All Subjects - Multiple Imputation (Modified ITT population)
Table 14.2.1.2.2 LVEF by Study Center – All Subjects - Multiple Imputation (Modified ITT population)
Table 14.2.1.3.1 LVEF – All Subjects (Per-Protocol population)
Table 14.2.1.3.2 LVEF by Study Center – All Subjects (Per-Protocol population)

### *5.3.3* Section 14.2: Secondary

Table 14.2.2.1 LVEF for Suboptimal Echocardiograms – Subjects with Available Data (Modified ITT population)
Table 14.2.2.2 LVEF for Suboptimal Echocardiograms – All Subjects (Modified PP population)
Table 14.2.3.1 Inter-Reader Variability - LVEF – Subjects with Available Data (Modified ITT population)
Table 14.2.3.2 Inter-Reader Variability - LVEF – All Subjects (Modified PP population)
Table 14.2.4.1 Inter-Reader Variability – End-Diastolic/Systolic Volumes – Subjects with Available Data (Modified ITT population)
Table 14.2.4.2 Inter-Reader Variability – End Diastolic/Systolic Volumes – All Subjects (Modified PP population)

Table 14.2.5.1 Inter-Reader Variability - LVEF for Suboptimal Echocardiograms – Subjects with Available Data (Modified ITT population)
Table 14.2.5.2 Inter-Reader Variability - LVEF for Suboptimal Echocardiograms - All Subjects (Modified PP population)
Table 14.2.6.1 Inter-Reader Variability – End-Diastolic/Systolic Volumes for Suboptimal Echocardiograms – Subjects with Available Data (Modified ITT population)
Table 14.2.6.2 Inter-Reader Variability – End Diastolic/Systolic Volumes for Suboptimal Echocardiograms – All Subjects (Modified PP population)

### *5.3.4* Section 14.3: Safety

#### 5.3.4.1 Adverse events

Table 14.3.1.1 Summary of Treatment Emergent Adverse Events
Table 14.3.1.2.1 Treatment Emergent Adverse Events by System Organ Class and Preferred Term
Table 14.3.1.2.2 Study Contrast Agent Related Treatment Emergent Adverse Events by System Organ Class and Preferred Term
Table 14.3.1.2.3 Procedure Related Treatment Emergent Adverse Events by System Organ Class and Preferred Term
Table 14.3.1.3.1 Serious Treatment Emergent Adverse Events by System Organ Class and Preferred Term
Table 14.3.1.2.2 Study Contrast Agent Related Serious Treatment Emergent Adverse Events by System Organ Class and Preferred Term
Table 14.3.1.2.3 Procedure Related Serious Treatment Emergent Adverse Events by System Organ Class and Preferred Term
Table 14.3.1.4 Severe Treatment Emergent Adverse Events by System Organ Class and Preferred Term
Table 14.3.1.5 Treatment Emergent Adverse Events Leading to Study Withdrawal by System Organ Class and Preferred Term
Table 14.3.1.6 Treatment Emergent Adverse Events by System Organ Class and Preferred Term Classified According to Severity

#### 5.3.4.2 Vital signs

Table 14.3.3.1 Vital signs
Table 14.3.3.2 Number (Percentage) of Subjects with Potentially Clinically Significant (PCS) Values in Vital Signs

All safety tables will be produced using the Safety Population.

## 5.4 Figures

## 5.4 Listings

Listing 16.2.1.1 Eligibility
Listing 16.2.1.2 Subject disposition
Listing 16.2.2.1 Inclusion/Exclusion descriptions
Listing 16.2.2.2 Inclusion/Exclusion criteria
Listing 16.2.2.3 Protocol violations
Listing 16.2.4.1 Subject demography
Listing 16.2.4.2 Medical history, including reported and coded terms
Listing 16.2.4.3 Prior medications, including reported and coded terms
Listing 16.2.4.4 Concomitant medications, including reported and coded terms
Listing 16.2.5.1 DEFINITY® Exposure
Listing 16.2.5.2 Visit Dates
Listing 16.2.6.1 LVEF
Listing 16.2.6.2 End Diastolic and Systolic Volumes
Listing 16.2.7.1 Adverse events, including reported and coded terms
Listing 16.2.7.2 Related adverse events
Listing 16.2.7.3 Adverse events leading to withdrawal
Listing 16.2.7.4 Serious adverse events
Listing 16.2.7.5 Deaths
Listing 16.2.8.1 Vital signs
Listing 16.2.8.2 Physical examination

# 6 Reference List

1. Mehta CR and Pocock SJ. Adaptive increase in sample size when interim results are promising: A practical guide with examples. Statist Med 2011;30:3267-3284.

2. Hamer RM. INTRACC.SAS Macro to Calculate Reliabilities for Intraclass Correlations [Internet]. SAS institute;1990 [cited 15 January 2018]. Available from https://github.com/friendly/SAS-macros/blob/master/intracc.sas.