Division of Imaging and Radiation Medicine

NDA Supplement Review – Clinical

NDA #	NDA 021064 S-033	RPM	Modupe Fagbami
Drug	Definity (perflutren lipid microsphere)	Clinical reviewer	Shane Masters
Applicant	Lantheus Medical Imaging	Submission date	5/1/2023
SD #	972	Goal date	3/1/2024

Background:

Definity (perflutren lipid microsphere) is an ultrasound contrast agent indicated in adult patients with suboptimal echocardiograms to opacify the left ventricular chamber and to improve the delineation of the left ventricular endocardial border. The drug is administered intravenously in the form of microbubbles (b) (4) diameter that provide numerous gas-fluid interfaces to reflect sound waves.

Two other ultrasound contrast agents are marketed for a left ventricular opacification/endocardial border delineation indication in the United States, Lumason (sulfur hexafluoride lipid-type A microspheres) and Optison (perflutren protein-type A microspheres). With regards to this indication, Lumason is labeled for adult and pediatric patients of all ages, while Optison is labeled for adult patients.

The Applicant has submitted an efficacy supplement seeking to extend the current adult indication to pediatric patients of all ages.

Regulatory History:

Highlights of the regulatory history relevant to this supplement are presented in Table 1 below.

Table 1. Summary of Relevant Regulatory History

Date	Event Summary
1/22/2001	Deferral of pediatric studies granted for all ages
7/31/2001	Initial approval of Definity in adults for use in patients with suboptimal echocardiograms to opacify the left ventricular chamber and to improve the delineation of the left ventricular endocardial border
3/30/2009	DMP 115-419 report received in IND 048626
9/29/2010	Submission of efficacy supplements S-011 (b) (4) for safety study results, DMP 115-419, and stress echocardiograpy in adults

7/28/2011	Complete response for S-011 (b) (4) "The submitted pediatric study data (DMP 115-419) are insufficient to establish the efficacy of Definity among pediatric patients, primarily because the non-contrasted baseline echocardiograms were adequate for interpretation."
	(b) (4)
12/30/2022	Written response only pre-supplement meeting comments. "While subject to review upon submission of an NDA supplement, we believe it may be reasonable to extrapolate effectiveness for Definity from adults based on pharmacodynamic and/or dose-finding/dose-response data obtained in children."

Review:

Table 2. Listing of Studies Relevant to This Supplement

Trial	Trial Design	Dosing	No. of patients enrolled	Study Population	No. of Centers and Countries
DMP 115-419	Prospective	Sequential boluses of undiluted Definity; 2, 3, 5 µL/kg	40	Age 1 mo – 18 yr; scheduled for routine echocardiogram	1 (Canada)
Kutty 2016	Retrospective	Infusion of 3% dilution at 4-6 mL/min	113	Age <21 yr; contrast echocardiogram performed for known or suspected heart disease	1 (United States)
Fine 2021	Prospective	Slow bolus of 2.5% dilution; dose equivalent to 0.75 mL undiluted for >60 kg, 20 µL/kg for ≤60 kg	36	Age 10 - 21 yr; heart transplant with clinical indication for coronary angiography or within 6 months after	2 (United States and Canada)

Review strategy

The Applicant submitted 7 studies in support of this supplement. One of them, DMP 115-419 was funded by the Applicant and was submitted to NDA 021064 in SD 203. It is reviewed for its ability to support extrapolation of effectiveness from adult patients and for safety. The remaining 6 studies were identified from a systematic search of the scientific literature. Two of these studies enrolled younger patients, though not necessarily only patients meeting the regulatory definition of pediatric. These studies are reviewed for safety. The remaining 4 enrolled patients of all ages, had limited numbers of pediatric patients, and were not considered as adding significant support. Notably, these studies either did not report safety findings or did not report adverse events in the enrolled pediatric patients.

DMP 115-419

DMP 115-419 is a prospective, single arm study intended to determine dosing for left ventricular opacification, endocardial border delineation, and Doppler signal enhancement using Definity in children. It enrolled patients aged 1 month to 18 years who were undergoing routine echocardiographic imaging for any indication and who had, or had clinical need for, intravenous access. Exclusions included significant pulmonary disease, pulmonary hypertension, renal failure, pregnancy, and breast feeding. Patients were enrolled in 4 age groups, 1 month to 1 year, 1 – 5 years, 6 – 10 years, and 11 – 18 years.

Each patient was to receive 3 intravenous bolus injections of Definity in ascending dose sequence of 2 µL/kg, 3 µL/kg, and 5 µL/kg.[1] Echocardiographic imaging was performed after each injection, and injections were separated by at least 7 minutes. Patients who had contrast considered excessive were not to receive additional doses. Imaging was performed by a single sonographer in apical 4 chamber, apical 2 chamber, apical 5 chamber, and suprasternal views using a 4-2 MHz probe and mechanical index <0.3.

Images were evaluated by one local investigator in an unblinded manner. A secondary reader blinded to the first reader's interpretation evaluated imaging from 20 randomly selected patients to assess interobserver variability. These same patients were re-evaluated by the initial reader for intraobserver variability. Left ventricular opacification was assessed on a 5 point scale consisting of no contrast, weak or minimal contrast, adequate contrast, full contrast, and excessive contrast. Duration of contrast was the time from clearance of excessive contrast to when contrast was no longer adequate. Left ventricular endocardial border delineation was scored on a segmental basis using a 12 segment model as evaluable, non-evaluable, or not applicable (i.e., segment not in selected image).

The primary analysis specified in the statistical analysis plan was the number and percent of patients with improved border delineation, defined as more segments assessed as evaluable compared to baseline, for each dose.

The study enrolled 40 patients. The mean age was 6.7±5.6 years, the median age was 6.2 years, and the range was 0.1 to 17.3 years. Female patients comprised 40% of the enrollment. Racial distribution was 73% White, 8% Black/African American, and 19% other. Congenital heart defects were present in 50% of patients and 23% of patients had a heart transplant. All patients received all 3 protocol-defined doses of Definity. One patient had all segments assessed as 'not applicable' for endocardial border delineation and therefore could not contribute to the imaging analyses, though the Applicant continued to use 40 patients as the denominator in calculations.

Most patients had evaluable left ventricular endocardial borders at baseline without Definity (

[1] For reference, the adult intravenous bolus dose of Definity is 10 µL/kg. A second 10 µL/kg bolus may be administered 30 minutes after the first if needed.

Table 3), with 83% to 95% of patients being evaluable depending on echocardiographic view and cardiac segment. This markedly limited the potential of the study to show an improvement in border delineation, and no convincing improvement was seen for any dose. Analysis of these results by age group did not reveal clinically meaningful differences.

Table 3. Number of Patients with Evaluable Left Ventricular Endocardial Border by Segment and Definity Dose (N=40 Patients)

View or Segment	Pre-contrast	2 µL/kg Definity	3 µL/kg Definity	5 µL/kg Definity
Apical 4 chamber				
Basal septum	38	35	39	38
Mid septum	38	35	39	38
Apical septum	37	34	39	38
Apical lateral	36	34	39	38
Mid lateral	38	35	39	38
Basal lateral	38	34	38	38
Apical 2 chamber				
Basal inferior	37	29	32	35
Mid inferior	37	30	32	35
Apical inferior	35	30	30	35
Apical anterior	34	30	31	35
Mid anterior	33	29	32	35
Basal anterior	36	29	32	35

Source: Table 14.2.2.1 of DMP-115-419 clinical study report

As shown in Table 4 and Table 5, all tested doses resulted in opacification of the left ventricular cavity, with the lowest dose of 2 µL/kg resulting in 73% - 93% of patients having opacification graded as adequate or full. As the dose increased, there was a trend to increased number of patients with adequate or full opacification, but also some patients had opacification that was considered excessive. This was less pronounced on the apical 2 chamber views than the apical 4 chamber views, likely due to the imaging protocol starting with apical 4 chamber. Analysis of these results by age group did not reveal clinically meaningful differences.

Table 4. Number of Patients with Each Left Ventricular Opacification Score on Apical 4 Chamber Views by Definity Dose (N=40 Patients)

Contrast Score	Pre-contrast	2 µL/kg Definity	3 µL/kg Definity	5 µL/kg Definity
No contrast	33	0	0	0
Weak or minimal	1	3	0	0
Adequate	0	4	3	1
Full	1	33	35	34
Excessive	0	0	2	4

Source: Table 14.2.2.3 of DMP-115-419 clinical study report

Table 5. Number of Patients with Each Left Ventricular Opacification Score on Apical 2 Chamber Views by Definity Dose (N=40 Patients)

Contrast Score	Pre-contrast	2 µL/kg Definity	3 µL/kg Definity	5 µL/kg Definity
No contrast	31	0	0	0
Weak or minimal	0	3	0	0
Adequate	0	3	2	2
Full	1	26	30	32
Excessive	0	0	0	2

Source: Table 14.2.2.3 of DMP-115-419 clinical study report

The duration of left ventricular opacification lengthened as dose increased (Table 6). A possible slight trend to lower duration of opacification may have been observed in the youngest patients, but the clinical significance of this is doubtful.

Table 6. Duration of Useful Left Ventricular Opacification in Minutes

Parameter	Age 1 mo – 1 yr (N=10)	Age 1 yr – 5 yr (N=9)	Age 6 yr – 10 yr (N=10)	Age 11 yr – 18 yr (N=11)	All ages (N=40)
2 µL/kg					
Mean (SD)	1.3 (0.6)	1.9 (0.7)	2.1 (0.7)	2.2 (1.3)	1.9 (0.9)
Median	1.5	1.9	2	2.2	2
Range	0.2 – 2	1 – 3.3	1 – 3	0.6 – 4.6	0.2 – 4.6
3 µL/kg					
Mean (SD)	1.8 (1)	3.2 (2.3)	2.8 (1.2)	3.1 (1.7)	2.7 (1.6)
Median	2	2.5	3	2.7	2.4
Range	0.2 – 3.1	1 – 7.9	1 – 4.3	1.6 – 7.3	0.2 – 7.9
5 µL/kg					
Mean (SD)	2.7 (1.4)	3.8 (1.6)	4.7 (2.1)	4.4 (2.3)	3.9 (2)
Median	3.4	3.5	4.3	4.8	3.9
Range	0 – 4.1	2 – 7.4	1 – 8.3	1 – 8.3	0 – 8.3

Source: Table 14.2.2.4 of DMP-115-419 clinical study report
Note: Useful contrast duration was measured as the time from at least adequate contrast (after excessive contrast cleared if observed) to when contrast was no longer adequate to define the endocardial borders.
Abbreviations: mo = months, SD = standard deviation, yr = years

Patients were monitored for safety throughout the echocardiogram, including pre-contrast baseline, and for 30 minutes after the last injection of Definity. Monitoring of adverse events, oxygen saturation, respiratory rate, and ECG was continuous. Blood pressure and heart rate were assessed before, during, and after each injection of Definity. In sedated patients (40% of enrolled patients) and younger patients, investigator observation was the primary method of adverse event ascertainment. ECG data were not collected for later analysis.

No adverse events were reported in the study.

No changes in vital signs or ECG were assessed as clinically significant by the investigator. Review of the vital sign data shows multiple patients with substantial transient increases in heart rate and blood pressure, generally beginning after administration of 3 µL/kg Definity and decreasing after administration of 5 µL/kg Definity. These increases were attributed by the investigator to use of dobutamine stress.

Laboratory data were not collected in the study.

Kutty 2016

Kutty 2016 is a retrospective study intended to evaluate institutional data on safety and effectiveness of contrasted ultrasound in younger patients. It included patients aged less than 21 years who had an echocardiogram with Definity and known or suspected heart disease between January 2005 and June

2015. Definity was diluted to 3% and infused at 4 to 6 mL/min.[2] The administered volume is not reported.

A total of 113 patients were included in the study. The mean age was 17.8±3 years and the range was 5 to 21 years. Female patients comprised 45% of the enrollment. Racial distribution was not reported. Congenital heart defects were present in 30% of patients. Rest echocardiograms were obtained in 35% of patients, while the remaining 65% had imaging at rest and stress.

Efficacy analysis in the study was largely descriptive and included uses of Definity that are not approved. These results are not considered relevant to this application.

According to the chart review, 13/113 (11%) patients reported 15 adverse events during Definity administration. This included chest pain (n=7 patients), fatigue (n=3), back pain, dizziness, headache, neck pain, and shortness of breath (n=1 each). All adverse events resolved without treatment and lasted <1 minute. Assessment for delayed adverse events was not routinely conducted. ECG abnormalities were reported in 17 patients during stress echocardiography, including ST segment depression (n=13), premature atrial contraction (n=2), premature ventricular contraction (n=1), and nonsustained ventricular tachycardia (n=1).

Fine 2021

Fine 2021 is a prospective, single arm study intended to assess feasibility of real time myocardial contrast echocardiography, a technique for assessing myocardial perfusion, in pediatric patients with heart transplant. It enrolled patients aged 10 to 21 years who were at least 1 year post-heart transplant and had a clinical indication for coronary angiography or had coronary angiography within 6 months. Patients with known intracardiac shunt, hypersensitivity to Definity, hospitalization within 3 months for myocardial infarction, acute decompensated heart failure, acute allograft rejection, or multiorgan transplant were excluded. Each patient received Definity as part of a dobutamine stress echocardiogram with perfusion imaging incorporating bubble destruction/replenishment. For patients weighing more than 60 kg, 0.75 mL Definity was diluted to 2.5% with normal saline. Patients weighing ≤60 kg received 20 µL/kg Definity diluted to 2.5%. The contrast was administered by slow intravenous bolus, intended to simulate an infusion.

A total of 36 patients were included in the study. The mean age was 13.5±4.3 years. Female patients comprised 42% of the enrollment. Racial distribution was not reported.

Efficacy analyses in this study were not directly relevant to the current application and are not evaluated here.

A total of 15 adverse events were reported in 12/36 (33%) patients. These included palpitations (n=7 patients), headache (n=6), dyspnea (n=1), and nausea (n=1). One patient could not complete imaging due to headache. No adverse events were considered serious by the investigators. While Definity was

[2] For reference, the recommended adult infusion dose is 1.3 mL Definity added to 50 mL saline (approximately 2.5% dilution) infused at 4 to 10 mL/min.

administered during both stress and rest, all adverse events occurred during the stress portion of the echocardiogram.

Summary of effectiveness

None of the presented studies are considered adequate and well-controlled studies that demonstrate effectiveness of Definity for use in pediatric patients with suboptimal echocardiograms to opacify the left ventricular chamber and to improve the delineation of the left ventricular endocardial border. In particular, DMP 115-419 did not study the population of intended clinical use as few of the enrolled patients had a suboptimal echocardiogram at baseline. This approach was taken because of feasibility, as it is uncommon for infants and children to have suboptimal echocardiograms.

It is appropriate to extrapolate effectiveness for the proposed indication in pediatric patients from adult data. The microbubbles that provide ultrasound contrast are restricted to the intravascular space upon intravenous injection and based on this mechanism and distribution, we expect that patient age will not affect the ability of Definity, when administered at an appropriate dose, to opacify the left ventricle or to aid in left ventricular endocardial border delineation. Study DMP 115-419 provided sufficient data to determine an appropriate pediatric dose, as concluded in the Clinical Pharmacology review. Importantly, it also supports the mechanistic justification for extrapolation from adult effectiveness data though the left ventricular opacification results.

Summary of safety

The safety database is composed of 189 patients aged 1 month to 24 years, all of whom had a clinical indication for echocardiography. Among these patients, the overall adverse event rate was 13%. The reported adverse events were compatible with those present in existing labeling for adults, and no new safety signal was identified.

We believe the presented safety data are adequate for this supplement, but note there were limitations to the data including:

- The infusion dosing of Definity in Kutty 2016 and Fine 2021 differed from the bolus dosing in DMP 115-419 and the proposed prescribing information. However, Definity is labeled for both bolus and infusion dosing in adults and we are not aware of differences in safety profile based on this.
- Stress testing was a common confounding event, and some of the reported adverse events may have been due to stress rather than Definity.
- Infants and young children have limited ability to report adverse experiences, likely resulting in underreporting.
- Kutty 2016 relied on retrospective chart assessment for adverse event assessment, likely resulting in underreporting.
- Follow up for adverse events was generally short. However, it should be noted that this is congruent with the short half-life of Definity.

Conclusion:

While suboptimal echocardiograms occur in infants and young children, they are uncommon. Because of this rarity, evidence of effectiveness in pediatric patients was extrapolated from adults. The extrapolation was adequately supported by mechanistic justification and by pharmacodynamic data obtained in pediatric patients without suboptimal echocardiograms.

No new safety signals were observed among pediatric patients who received Definity.

From a clinical perspective, the benefit-risk balance of Definity for use in pediatric patients with suboptimal echocardiograms to opacify the left ventricular chamber and to improve the delineation of the left ventricular endocardial border is favorable. Approval of this efficacy supplement is recommended for pediatric patients of all ages.

Appendix:

References

Fine, N. M., S. C. Greenway, S. L. Mulvagh, R. Huang, S. A. Maxon, M. J. Hepinstall, J. H. Anderson and J. N. Johnson (2021). "Feasibility of Real-Time Myocardial Contrast Echocardiography to Detect Cardiac Allograft Vasculopathy in Pediatric Heart Transplant Recipients." J Am Soc Echocardiogr 34(5): 503-510.

Kutty, S., Y. Xiao, J. Olson, F. Xie, D. A. Danford, C. C. Erickson and T. R. Porter (2016). "Safety and Efficacy of Cardiac Ultrasound Contrast in Children and Adolescents for Resting and Stress Echocardiography." J Am Soc Echocardiogr 29(7): 655-662.

Financial disclosures

DMP 115-419 was conducted by investigators who were not employees of the Applicant. The Applicant provided (b) (4) to the investigators to conduct the study. The measures taken to prevent bias were stated by the Applicant as:

> During the implementation of the protocol and conduct of the pediatric clinical trial (DMP115-419), Dr. Fraser Golding was assisted by three co-investigator physicians, as described in the final study report. Having more than one site investigator contribute to clinical trial conduct lessens the potential for the conduct to be impacted by financial arrangements between the company and clinical site investigators and assistants. None of the clinical site investigators were employees (i.e., neither full nor part-time) of Lantheus.
>
> Compliance with Good Clinical Practice (GCP) for Study DMP115-419 aligns with oversight by the Research Ethics Board of the Hospital for Sick Children, which further attests to the inability of financial arrangements to impact the conduct of the study, including the study results.
>
> Lantheus further verifies that no financial arrangements were planned or implemented in a manner that might impact the study results, i.e., the financial arrangements did not include plans for results-contingent reimbursement and/or proprietary equity.
>
> The design and conduct of Study DMP115-419 also helped to minimize the potential for bias in image interpretation, particularly due to the use of two independent image readers (who were masked to each other's results); hence, the study design ensured that study results were not determined by a single individual.
>
> Lantheus further verifies that conduct of Study DMP115-419 was monitored in real-time by the performance (i.e., by Lantheus staff) of on-site visits to the Hospital for Sick Children to ensure recorded clinical trial data aligned with medical records, the clinical protocol, and Research Ethics Board expectations.

These measures are acceptable.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

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