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:	NDA203684/S0005
Drug Name:	Lumason® (sulfur hexafluoride lipid −type A microspheres) for Injectable Suspension
Indication(s):	For Use in Pediatric Patients (b) (4) with Suboptimal Echocardiograms to Opacify the Left Ventricular Chamber and to Improve the Delineation of the Left Ventricular Endocardial Border
Applicant:	Bracco Diagnostics Inc.
Date(s):	Receipt Date: January 30, 2019 PDUFA Due Date: November 30, 2019
Review Priority:	Standard
Biometrics Division:	Biometrics I, HFD-710
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1. EXECUTIVE SUMMARY

This NDA supplement is a post-marketing study to fulfill PREA requirement for Lumason. The study was a Phase III, multicenter, open-label study to evaluate the efficacy of Lumason enhanced transthoracic echocardiography (CEUS) compared to unenhanced transthoracic echocardiography (UEUS) in pediatric subjects with suboptimal Left Ventricular Endocardial Border Delineation (LV EBD). The study was prematurely terminated due to challenges of recruiting subjects. The efficacy of Lumason was assessed based on a small sample of 12 subjects who were recruited up to the time of study termination. Therefore, all the statistical analyses are considered exploratory.

2. INTRODUCTION

2.1 Overview

Echocardiography has become the primary imaging tool in the diagnosis and assessment of congenital and acquired heart disease in children and adolescents. This study was aimed to assess the safety and efficacy of Lumason (sulfur hexafluoride lipid-type A microspheres) for injectable suspension in children 9-17 years with suboptimal images undergoing resting transthoracic echocardiogram with harmonic imaging modality.

2.2 Data Sources

The sponsor's SAS datasets were stored in the directory of \\CDSESUB1\evsprod\NDA203684\0093\m5\datasets the Center's electronic document room.

3. STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The provided 'define file' was not clearly defined and the dataset(s) was not well structured.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

Primary Study Objective: The primary objective of the study was to assess the efficacy of Lumason (CEUS vs. UEUS) in pediatric subjects with suboptimal LV EBD.

Study Design: This was a Phase III multicenter, open-label study to evaluate the safety and efficacy of Lumason as a contrast agent for echocardiography in pediatric subjects with suboptimal LV EBD on non-contrast 2D transthoracic echocardiography with harmonic imaging. For both non-contrast and contrast-enhanced images, 4, 2, and 3 views with harmonic imaging were performed for each patient. Three off-site blinded (to patients' clinical history) readers evaluated LV EBD and Left Ventricular Opacification (LVO).

Primary Efficacy Endpoint: The co-primary efficacy endpoints were:

- Change from baseline in total LV EBD scores (CEUS vs. UEUS) calculated as the sum of the individual scores (0-inadequate, 1-sufficient, or 2-good) assigned to each of the 17 segment images with a total score range 0-34
- Proportion of subjects with adequate LVO. Adequate LVO was defined as LVO rating of +2 (nonhomogeneous) or +3 (complete and homogeneous)

3.2.2 Statistical Analysis Methodology

Determination of sample size: The originally planned sample size of 92 subjects (73 evaluable subjects) has 90% power to detect a difference of 3.2 (SD 8.3) on the total LV EBD scores between CEUS and UEUS. 13 subjects were finally enrolled to the study.

Primary efficacy analysis:

- Co-primary efficacy endpoints:
  - Change from baseline in total LV EBD scores: For each blinded reader assessment, paired t-test was used to compare total LV EBD scores between CEUS and UEUS. Inter-reader agreement of the assessment for each segment among 3 off-site readers was evaluated (for UEUS and CEUS separately) by kappa statistic.
  - Proportion of subjects with adequate LVO: The proportion and the 95% CI of subjects with adequate LVO scores at the CEUS was estimated using binomial proportion estimate method.

Multiplicity: No multiplicity adjustment was planned for the co-primary efficacy endpoints and assessments of multiple readers.

Handling missing data: Total EBD scores for a subject is calculated as the total of the EBD scores from the 17 segments. If any apical view of the 17 segment images is not available, the total EBD scores for the subject will be missing.

3.2.3 Patient Disposition

Thirteen subjects were enrolled. Of those, 12 subjects were dosed with Lumason. All the 12 subjects who received Lumason had off-site blinded assessment of LV EBD and LVO and were included in the intent-to-diagnose population (ITD) population for primary efficacy analysis.

3.2.4 Results and Conclusion

Applicant's Primary Efficacy Analysis Result:

1) Change from Baseline in total LV EBD scores: The mean of total LV EBD scores was 6.4, 10.6 and 7.3 from UEUS, and 33.5, 33.3, and 33.0 from CEUS for Reader 1, Reader 2 and Reader 3, respectively. The difference between CEUS and UEUS was statistically significant ($p<0.0001$) for all 3 readers, see the table below.

Off-site Readers	UEUS	CEUS	Difference (CEUS - UEUS)
Reader 1			
N	12	11	11
Mean (SD)	6.4 (5.57)	33.5 (1.29)	27.5 (5.73)
Median	5.5	34.0	29.0
Range (min, max)	(0, 20)	(30, 34)	(14, 34)
95% CI	(2.9, 10.0)	(32.6, 34.3)	(23.7, 31.4)
p-value (95% CI)[a]			<0.0001
Reader 2			
N	11	9	9
Mean (SD)	10.6 (5.66)	33.3 (2.00)	23.0 (5.77)
Median	8.0	34.0	26.0
Range (min, max)	(3, 21)	(28, 34)	(11, 29)
95% CI	(6.8, 14.4)	(31.8, 34.9)	(18.6, 27.4)
p-value (95% CI)[a]			<0.0001
Reader 3			
N	12	11	11
Mean (SD)	7.3 (5.17)	33.0 (1.79)	26.0 (6.48)
Median	8.0	34.0	25.0
Range (min, max)	(0, 14)	(29, 34)	(17, 34)
95% CI	(4.0, 10.5)	(31.8, 34.2)	(21.6, 30.4)
p-value (95% CI)[a]			<0.0001

(Source: Applicant's Table G, confirmed by the reviewer's analysis)

2) Proportion of subjects with adequate LVO: For all 3 readers, the degree of LVO at CEUS was evaluated as complete (score=+3) for all 12 subjects, the proportion of adequate was 100% (95% CI: 73.5%, 100.0%), see the table below.

Characteristics	Reader 1	Reader 2	Reader 3
Total[a]	12	12	12
None n(%) (95% CI)[b]	0 (0, 26.5)	0 (0, 26.5)	0 (0, 26.5)
Faint n(%) (95% CI)[b]	0 (0, 26.5)	0 (0, 26.5)	0 (0, 26.5)
Non-Homogenous n(%) (95% CI)[b]	0 (0, 26.5)	0 (0, 26.5)	0 (0, 26.5)
Complete n(%) (95% CI)[b]	12 (100) (73.5, 100)	12 (100) (73.5, 100)	12 (100) (73.5, 100)
Adequate n(%) (95% CI)[b]	12 (100) (73.5, 100)	12 (100) (73.5, 100)	12 (100) (73.5, 100)

(Source: Applicant's Table H, confirmed by the reviewer's analysis)

Reviewer's Result: A sensitivity analysis was conducted to assess the impact of missing data on the primary efficacy. There were 5 (13.9%, 5/36) missing measures from either CEUS (n=4, Readers 1-3) or UEUS (n=1, Reader 2). A worse case strategy was applied to the missing measures: a zero value was assigned to the missing measure from CEUS and the true value or a maximum score of 34 assigned to the missing measure from UEUS. The results showed that the differences on change from baseline in total LV EBD scores between CEUS and UEUS were smaller for all 3 readers. Specially, the difference was substantially smaller for Reader 2, see the table below.

Reader	N	Mean Difference (CEUS-UEUS)	95% CI Mean Difference
Reader 1	12	24.3	16.2, 32.3
Reader 2	12	9.8	-5.8, 25.4
Reader 3	12	23.0	15.3, 30.7

(Source: The reviewer's analysis)

4. SUMMARY AND CONCLUSIONS

4.1 Statistical Issues

The study was originally planned to enroll 92 subjects (73 evaluable subjects) for providing a 90% power. The study was prematurely terminated due to challenge of recruiting subjects to the study. A total of 13 subjects was finally enrolled and 12 subjects were included in the primary efficacy analysis.

From a statistical point of view, this study is exploratory in nature. The statistical analysis based on this small sample of 12 subjects should be considered exploratory, no formal statistical inference should be drawn from the analysis.

Furthermore, the primary efficacy result appeas to be impacted by:

- missing data. A sensitivity analysis showed that the differences on change from baseline in total LV EBD scores (CEUS vs. UEUS) were smaller for all three readers, especially for Reader 2 (27.5, 23 and 26 for readers 1, 2 and 3, respectively in the primary efficacy analysis, compared to 24.3, 9.8 and 23 for readers 1, 2 and 3, respectively in a sensitivity analysis).
- potential presence of ascertainment bias due to an open-label, unbinded and non-randomized study design.

4.2 Collective Evidence

We view the statistical analysis based on this small sample of 12 subjects as exploratory.

Missing data appears to impact the primary efficacy result.

The primary efficacy result based on LV EBD scores is preliminary in an exploratory study.

4.3 Conclusions and Recommendations

The study is exploratory in nature. Regarding reviewer's recommendation, see Section 4.4.

4.4 Labeling Recommendations

This reviewer recommends that if this study is to be mentioned in Section 14, it should be descriptive without any statistical results and without any changes in the indication.

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