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/BLA Serial Number:	NDA 203684/Supplement 2 SDN 93 Associated IND 46958 (first submitted December 1994)
Drug Name:	Lumason (sulfur hexafluoride microspheres for injectable suspension)
Indication(s):	Lumason is an ultrasound contrast agent indicated for use in ultrasonography of the (b) (4) urinary tract in pediatric patients (b) (4) vesicoureteral reflux (VUR).
Applicant:	Bracco Diagnostic Inc.
Date(s):	NDA Submission: June 29, 2016 PDUFA Date: December 29, 2016
Review Priority:	Priority
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Keywords: Sensitivity, Specificity, Meta-Analysis

Table of Contents

LIST OF TABLES

1. EXECUTIVE SUMMARY

Lumason® (sulfur hexafluoride-SF6 lipid-type A microspheres) was initially approved by the FDA in October 10, 2014 for use "in echocardiography to opacify the left ventricular chamber and to improve the delineation of the left ventricular endocardial border in adult patients with suboptimal echocardiograms". Subsequently, on March 31, 2016, Lumason received FDA approval for use "in ultrasonography of the liver for characterization of focal liver lesions in adult and pediatric patients."

In the current submission, the applicant is seeking an additional indication for use of Lumason during ultrasonography of the (b) (4) urinary tract in pediatric patients with known or suspected vesicoureteral reflux (VUR).The ultrasound procedure is called voiding urosonography (VUS) and encompasses examination of the urinary tract, including bladder, ureters, and urethra. The formulation used for VUS is the same formulation used for the approved indications.

This is a 505(b)(2) application based on literature reports. The four clinical studies reported used flat doses of 1 mL given intravesically, and the applicant proposes a flat dose of 1mL as the recommended dose for the package insert.

Four (4) clinical studies were identified during the literature search and presented in support of the indication for use of Lumason pediatric patients (b) (4) VUR during VUS. Efficacy endpoints were diagnostic performance endpoints, i.e. sensitivity and specificity for the detection/exclusion of VUR, measured against voiding cystourethrography (VCUG), used as the standard of truth. A meta-analysis of the 4 controlled studies comparing VUS with VCUG as the standard of truth was also performed.

In these 4 single-center prospective studies, 508 pediatric patients referred for assessment of vesicoureteral reflux (275 males, 233 female, age range: 2 days to 13 years) were evaluated after intravesical administration of 1.0 mL of Lumason. The findings of Lumason ultrasound (VUS) images were compared to voiding cystourethrography (VCUG) as the truth standard using one or two independent readers. The blinding of the readers to the patient's clinical information is questionable in all these studies. Sponsor's co-primary endpoints were sensitivity and specificity of consensus reading of Lumason images, with the unit of analysis reported in these papers being either pelvis-ureter unit or kidney-ureter unit (referred as ureter unit or UU thereafter). Sponsor couldn't present "by reader" analysis of sensitivity and specificity due to lack of the data.

Table 1: Diagnostic Performance of Lumason Ultrasound for the detection/exclusion of VUR, measured against VCUG at ureter level

Study		Age Range	N (Gender)		N (ureter units)*	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)
#	Authors		Males	Females			
1	Wong et al.	2-48 Months	23	8	62	100 (55-100)	84 (73-92)
2	Ključevšek et al.	5 days – 1 year	35	31	132	100 (79-100)	78 (69-85)
3	Kis et al.	2 days–44 months	94	89	366	86 (78-92)	86 (81, 90)
4	Papadopoulou et al.	6 days to 13 years	123	105	463	80 (69-89)	77 (73-81)

*There were two ureter units per patient in studies 1, 2 and 3 and in study 4 some patients had more than two ureter units.

The patient-level data were not provided in 3 out of 4 published studies for the FDA's assessment.

The sponsor presented the patient-level and by reader data only in one (Ključevšek et al.) study of 66 pediatric patients (35 males, 31 females, age range: 5 days to 1 year). There were no cases in which the two readers who assessed the VUS exams disagreed on the presence/absence of VUR; similarly, there were no cases in which the two readers who assessed the VCUG exams disagreed on the presence/absence of VUR. At the patient level, the following rules were applied for both VCUG and VUS: A patient was considered to have VUR (positive) if at least one of the patient's ureter units had VUR, and a patient was considered not to have VUR (negative) if none of the patient's ureter units had VUR. A summary of the diagnostic performance of VUS with Lumason at both the ureter level and the patient level using VCUG as the reference standard is presented below in Table 2.

Table 2: Diagnostic Performance Results at the Ureter and Patient Level in the Study By Ključevšek et al.

Unit of Analysis	Total Number	With VUR	Without VUR	Sensitivity	Specificity	True Positive	False Negative	True Negative	False Positive
Ureter	132	16	116	100.0	77.59	16	0	90	26
Patient	66	13	53	100.0	69.81	13	0	37	16

Sensitivity = TP/(TP+FN) Specificity =TN/(TN+FP)

The cumulative information provided and analyzed in this NDA submission provides support to the proposed indication for the pediatric patient population.

2. INTRODUCTION

Lumason® (sulfur hexafluoride lipid-type A microspheres) for injectable suspension is an ultrasound contrast agent developed by Bracco Diagnostics Inc. ("Bracco") and is characterized by a microsphere structure, consisting of a low solubility gas, sulfur hexafluoride (SF_6), stabilized by a phospholipid shell. Lumason has been commercialized under the brand name SonoVue® in Europe since 2001. SonoVue is currently approved for intravenous use in 41 countries throughout the world.

2.1 Overview

On October 10, 2014, Lumason was approved by the United States Food and Drug Administration (FDA) under NDA 203684 for use in adult patients with suboptimal echocardiograms to opacify the left ventricular chamber and to improve the delineation of the left ventricular endocardial border. Subsequently, on March 31, 2016, Lumason received approval from the FDA for use in ultrasonography of the liver for characterization of focal liver lesions in adult and pediatric patients.

Bracco is seeking an additional indication for use of Lumason during ultrasonography of the (b) (4) urinary tract in pediatric patients with known or suspected vesicoureteral reflux (VUR) and encompasses examination of the urinary tract, including bladder, ureters, and urethra. The formulation used for VUS is the same formulation used for the approved indications.

2.1.1 Regulatory History

Sponsor stated that Lumason is not approved for use in VUS in or outside the USA. However, the product is used off-label in pediatric patients with medical need for assessment of VUR, as documented in scientific studies reported in the peer-reviewed literature. Bracco conducted a broad literature search and identified a number of relevant published papers reporting efficacy and/or safety results from clinical trials with the use of Lumason during VUS in pediatric patients.

On July 27, 2015, Bracco requested a Type B meeting with FDA to present the available information supporting the efficacy and safety of Lumason use during VUS in pediatric patients and to obtain guidance regarding the format and content of a literature based submission 505(b)(2) sNDA under NDA 203684. The meeting was granted and a Briefing Package was submitted to the FDA on August 26, 2016. The FDA response on September 25, 2015 confirmed the acceptability of a literature based 505(b)(2) sNDA to support the proposed indication, provided that the submission meets the applicable requirements for filing.

On June 29, 2016, Bracco submitted a literature-based 505(b)(2) NDA in the Common Technical Document (CTD) format to support, seeking an additional indication for use of Lumason during VUS in pediatric patients with known or suspected VUR.

This was granted a priority review status on the basis of the demonstrated medical need in the pediatric patient population, the clinical benefit to pediatric patients of obtaining diagnostic

information without exposing them to potentially harmful radiation, and supporting the efficacy and safety of the use of Lumason.

2.1.2 Indication(s) and Doses

Proposed Indications:

- Lumason is an ultrasound contrast agent indicated for use in ultrasonography of the (b) (4) urinary tract (b) (4) vesicoureteral reflux in pediatric patients.

The proposed dose of Lumason is 1.0 mL. The route of administration for the approved indications is intravenous and for the new indication is intravesical. Lumason is for single use only.

2.1.3 Analysis Population

This is a 505(b)(2) submission. The data supporting the effectiveness of Lumason use during VUS for assessment of VUR in children were derived from the peer-reviewed literature. A literature search was performed utilizing PubMed, a service of the US National Library of Medicine®, using the following search terms (urosonography OR vesicoureteral reflux OR (voiding AND (ultrasonography OR ultrasound))) AND (contrast or enhanced or microbubbles). Limits for the literature search were: published up to December 31, 2015.

Publications that met all the following inclusion criteria were included in the Lumason efficacy and safety summaries for the pediatric population:

- Original publication of a clinical study in pediatric patients (birth to 18 years) with prospective or retrospective enrollment;
- Lumason was administered intravesically during VUS examination; and
- Information on efficacy and/or safety (e.g., adverse events, side effects, complications) of VUS with Lumason was reported.

Publications that did not meet the inclusion criteria or met the following exclusion criteria were excluded from the Lumason efficacy and safety summary for the pediatric population:

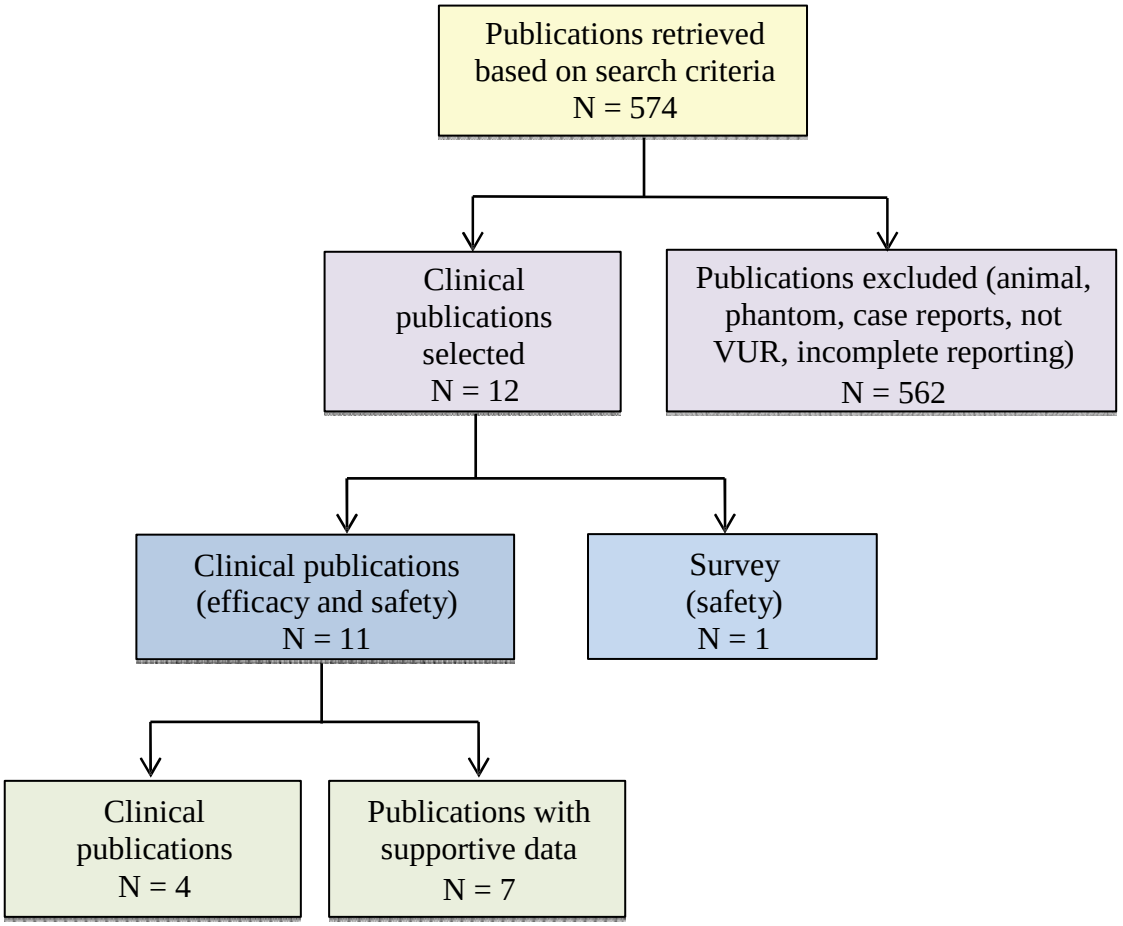
- Study was performed in non-human subjects (e.g., phantom, in vitro or animal studies);
- Lumason was not used or was not administered intravesically; or
- Publications were guidelines, reviews, letters-to-editor, commentary articles, case reports or
- Conference/ Scientific meeting abstracts that had no or insufficient data of study population, study methodology and results, or there was a lack of completeness in the reports.

In addition to publications identified directly in the search, Bracco reviewed the reference lists of the publications, as well as the reference lists of published professional guidelines and review

articles, to find other publications of potential relevance that may not have been identified in the primary search.

A total of 574 publications were retrieved and were analyzed in order to identify relevant publications describing efficacy and/or safety of VUS with Lumason in the diagnosis of VUR. Retrieved literature was reviewed by a physician who is a radiology specialist. A flow diagram showing the application of selection criteria during the review process is provided in Figure 1.

Figure 1: VUR Literature Review and Flow Chart (Sponsor)



Twelve (12) unique references met all inclusion criteria, as described below:

- Eleven (11) peer-reviewed clinical papers, each of which reported both efficacy and safety data on the use of Lumason during VUS.

- One large multicenter retrospective safety survey conducted by the Uroradiology Task Force of the European Society of Paediatric Radiology (ESPR) and the Paediatric Work Group of the European Society of Urogenital Radiology (ESUR).

Four (4) clinical trials were identified during the literature search and presented in support of the indication for use of Lumason pediatric patients (b) (4) VUR during VUS. A meta-analysis of the 4 controlled studies comparing VUS with VCUG as standard of truth was also performed. The selection of these studies was based on the following criteria:

- *Clinical settings*: Lumason was used in children referred for detection or exclusion of VUR following UTI, a diagnosis of pelvicalyceal dilatation, or for follow-up of a known VUR, i.e., in patients representative of the population in which VUS with Lumason is intended to be used. Only commercially available hardware and software was used for all studies;

- *Study design*: prospective, within-patient comparisons of VUS against VCUG, with blinded (limited to VCUG imaging and not to all other clinical information) evaluation of study images;

- *Efficacy endpoints*: diagnostic performance endpoints, i.e. sensitivity and specificity for the detection/exclusion of VUR, measured against VCUG, used as standard of truth;

- *Safety endpoints*: VUS and VCUG were performed in sequence during the same catheterization procedure. Patients were monitors for incidence of adverse events (or procedural complications) following administration of Lumason and iodinated contrast agents;

- *Lumason dose:* all 4 studies used the same dose of Lumason (1.0 mL).

Seven (7) supportive publications based on the following criteria:

- included a diagnostic performance endpoint with VCUG as truth standard, but using different doses of Lumason, or different dosing techniques; or

- presented a technical endpoint, such as quality of visualization

Safety information for intravesical administration of Lumason from the 12 publications was retrieved in the literature search.

2.2 Data Sources

This is a 505(b)(2) literature based submission. In support of this submission, the sponsor used literature review and statistical analysis for the summary data available in literature.

The NDA in EDR is located at: \\CDSESUB1\evsprod\NDA203684\203684.enx

3. STATISTICAL EVALUATION

The efficacy data from the clinical literature for the indication of VUS resulted in four (4) studies in the literature supporting the use of Lumason in the proposed indication. These available data from these 4 studies were analyzed. A meta-analysis of the study-level data from the 4 studies is also presented by using the essential diagnostic performance of the data and the study quality was evaluated by the Quality Assessment Tool for Diagnostic Accuracy (QUADAS) guidelines. Additionally, there were seven (7) supportive clinical studies in the literature that assessed the effectiveness of VUS with Lumason in the evaluation of VUR

3.1 Design, Patient Population, Data Assessment

This is a 505(b)(2) sNDA for Lumason (Sulfur Hexafluoride Lipid-Type A Microspheres). In support of this submission, the sponsor used literature review and information available in these applications. Since the data were captured from the published articles and reports, the quality of data, variables etc. were limited to the published information.

The statistical analysis methods included the use of available data, descriptive information related to estimates of sensitivity and specificity and meta-analysis supporting the indication.

The literature search resulted in four (4) clinical studies. They were all

- Prospective
- Within-patient comparisons of VUS against VCUG,
- Blinded evaluation of study images. In all 4 studies, the blinding seems to be limited to VCUG imaging. It does not seem to be applicable to all other clinical information.
- All 4 studies used the same dose of Lumason (1.0 mL).

Patient Population in four clinical studies:

- Pediatric patients (age range: 2 days-13 years)
- Referred for VCUG for suspected VUR, or follow-up of VUR,
- Overall, 508 pediatric patients were enrolled in four clinical studies

Patients were representative of the population in which VUS with Lumason is intended to be used.

3.2 Evaluation of Efficacy

3.2.1 Objective

The objective was to assess the clinical efficacy of vesicoureteral reflux (VUR) in pediatric patients during ultrasonography of the excretory urinary tract (also known as vesicourosonography or VUS) in support of the proposed indication that Lumason is an

ultrasound contrast agent indicated for use in ultrasonography of the (b) (4) urinary tract (b) (4) vesicoureteral reflux in pediatric patients.

3.2.2 Efficacy Endpoints

The efficacy endpoints were diagnostic performance endpoints, i.e. sensitivity and specificity for the detection/exclusion of VUR, measured against VCUG, used as the standard of truth.

3.2.3 Demographic and Baseline Characteristics

Due to the nature of data presented in the reported study publications in the analysis population, limited information on demographic and baseline characteristics was available.

3.2.4 Statistical Methodologies

Bracco is seeking approval of VUS indication for the product in the United States:

"Lumason is indicated for use in ultrasonography of the (b) (4) *urinary tract in pediatric patients* (b) (4) *vesicoureteral reflux".*

The sponsor's primary analysis was conducted by using sensitivity and specificity. The unit of analysis reported in the paper being either pelvis-ureter unit or kidney-ureter unit (referred as ureter unit or UU thereafter).

Total number of ureter units with disease, True Positive (TP), True Negative (TN), False Positive (FP), and False Negative (FN) were either extracted directly from each paper or derived basing on available information. The sensitivity and specificity of VUS for detecting VUR on a per-ureter basis were then calculated for each paper based on TP, TN, FP, and FN.

Four (4) clinical studies were identified during the literature search and presented in support of the indication for use of Lumason pediatric patients (b) (4) VUR during VUS. Efficacy endpoints were diagnostic performance endpoints, i.e. sensitivity and specificity for the detection/exclusion of VUR, measured against VCUG, used as the standard of truth. A meta-analysis of the 4 controlled studies comparing VUS with VCUG as the standard of truth was also performed.

3.3 Results and Conclusions

The efficacy of LUMASON for the evaluation of pediatric patients with suspected or known vesicoureteral reflux was established in four published prospective studies. Patients received 1 mL of Lumason intravesicularly and underwent voiding urosonography (VUS). Patients were then evaluated with voiding cystourethrography (VCUG) as the reference standard. The presence or absence of urinary reflux with Lumason ultrasound was compared to the radiographic reference standard.

In these selected 4 studies, 508 pediatric patients referred for assessment of vesicoureteral reflux (275 males, 233 female, age range: 2 days to 13 years) were evaluated after intravesical administration of 1.0 mL of Lumason. The findings of Lumason ultrasound images were compared to voiding cystourethrography as the truth standard. The patient-level detailed data were provided in only 1 out of these 4 published studies.

3.3.1 Results at the Ureter Level

In these studies, at the ureter level, the sensitivity of Lumason enhanced ultrasonography for detecting vesicoureteral reflux ranged from 80% to 100%, while the specificity ranged from 77% to 86%.

Study 1 (Wong et al., Eur J. Peditr., 2014) evaluated 31 patients (23 male, 8 female; age 2 days - 48 months) with a total of 62 pelvic-ureter units (2/patient). The images were interpreted by blinded independent reads of VUS (3 radiologist) and 2 VCUG (2 radiologist). Out of 5 pelvic-ureter units (2/patient) reference standard-positive images, Lumason ultasonography was positive in 5 units and falsely negative in 0 units. In 57 units with negative reference standard, the Lumason ultrasonography was negative in 48 and falsely positive in 9.

Study 2 (Ključevšek et al., Acta Paediatr. 2012) evaluated 66 patients (35 male, 31 female; age 5 days – 1 year) with a total of 132 pelviv-ureter units (2/patient). The images were interpreted by on-site blinded independent (2 readers) for detection of VUR. Out of 16 l units (2/patient) reference standard-positive images, Lumason ultasonography was positive in 16 units and falsely negative in 0 units. In 116 units with negative reference standard, the Lumason ultrasonography was negative in 90 and falsely positive in 16.

Study 3 (Kis et al., Pediattr Nephrol. 2010) evaluated 183 patients (94 male, 89 female; age 2 days - 44 months) with a total of 366 kidney-ureter units. The images were interpreted by one on-site reader, blinded to the reference standard. Out of 103 reference standard-positive images, Lumason ultasonography was positive in 89 units and falsely negative in 14 units. In 263 units with negative reference standard, the Lumason ultrasonography was negative in 226 and falsely positive in 37.

Study 4 (Papadopoulou et al., Pediatr Radiol. 2009) evaluated 228 patients (123 male, 105 female; age 6 days - 14 years) with a total of 463 kidney-ureter units (some patients had more than 2 units). The images were interpreted independently by two on-site readers, blinded to the reference standard. Five discordant cases were adjudicated by consensus read by the same two readers. Out of 71 reference standard positive images, Lumason ultrasonography was positive in 57 and falsely negative in 14. In 392 units with negative reference standard, Lumason ultrasonography was negative in 302 and falsely positive in 90.

A tabulated summary of the four clinical studies is presented in Table 4.

Table 3: Sensitivity and Specificity Estimates by Studies and Meta-Analysis

Trial ID	Patients (# Males) Age Range	Image Evaluation	Sample Size	Sens. (%) 95% CI	Spec. (%) 95% CI	
Wong et al., Eur J Pediatr. 2014	31 pts (23M) with UTI and suspected VUR 2 days -48 Months	On-site blinded, independent reads of VUS (3 radiologist) and 2 VCUG (2 radiologist)	62 pelvi-ureter units (2/patient)	5/5 = 100% (55-100%)	48/57 = 84% (73-92%)	
Ključevšek et al., Acta Paediatr. 2012	66 pts (35M) with UTI or bacteriuria 5 days – 1 year	On-site blinded, independent (2 readers) for detection of VUR	132 renal units (2/patient)	16/16= 100% (79-100%)	90/116= 77.5% (69-85%)	
Kis et al., Pediatr Nephrol. 2010	183 pts (94M) with UTI, pelvicalyceal dilatation or follow-up of known VUR 2 days–44 months	On-site blinded, independent (1 reader) for detection of VUR	366 kidney-ureter units (2/patient)	89/103= 86% (78-92%)	226/263= 86% (81, 90%)	
Papadopoulou et al., Pediatr Radiol. 2009	228 pts (123M) with UTI, follow-up of know VUR 6 days to 13 years	On-site blinded, independent (2 readers) for detection of VUR (discordant cases reassessed by consensus read)	463 kidney-ureter units (2+ /patient)	57/71= 80% (69-89%)	302/392= 77% (73-81%)	
Meta-Analysis						
Fixed Effect Model Estimate 95% CI				84% (78-89%)	80% (77–83%)	
Random Effect Model Estimate 95% CI				84% (78-89%)	81% (75-86%)	

Notes: (1) All trials were prospective, within-patient comparison with VCUG as truth standard

(2) Sens-Sensitivity for detection of VUR, Spec- Specificity for detection of VUR, CI – Confidence Interval – Exact- based on Clopper-Pearson MLE for individual studies

(3) Study quality and applicability were assessed by using a modified checklist based on the Quality Assessment (QA) for Diagnostic Accuracy Studies (QUADAS) guidelines. Scale 0-10

(4) Used Meta-Analysis software developed by Dr. Michael Borenstein and his group at Biostat and funded by NIH (www.Meta-Analysis.com)

(5) QA Score: Study quality and applicability were assessed (independently) by using a modified checklist based on the Quality Assessment for Diagnostic Accuracy Studies (QUADAS) guidelines.

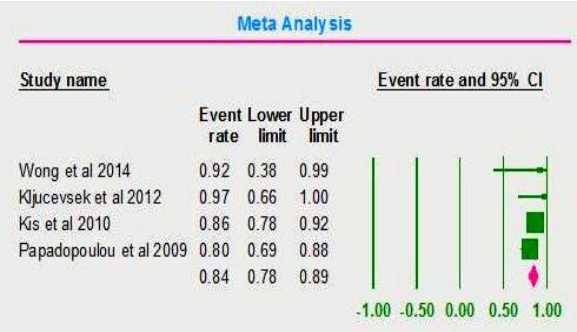
(6) Tau squared for sensitivity (a measure of variability between studies) = 0.0003 resulting in approximatively same sensitivity for fixed and random effect model in meta-analysis.

3.3.2 Meta-Analysis Results (Ureter Level)

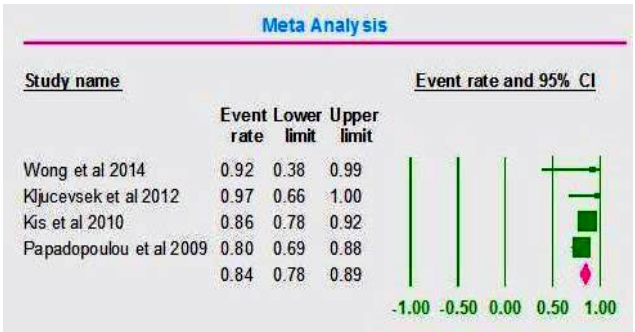
Forest plots for sensitivity/specificity were created and given below for both fixed effects and random effects model to graphically display sensitivity/specificity and their 95% confidence intervals from the individual studies and the overall pooled results. A meta-analysis resulted in a pooled sensitivity of 84% (95% CI: 78% to 89%) and pooled specificity of 80% (95% CI: 77% to 83%) for fixed effect model.

Figure 2: Forest Plot for Sensitivity-Lumason Pediatric

Fixed-Effect model



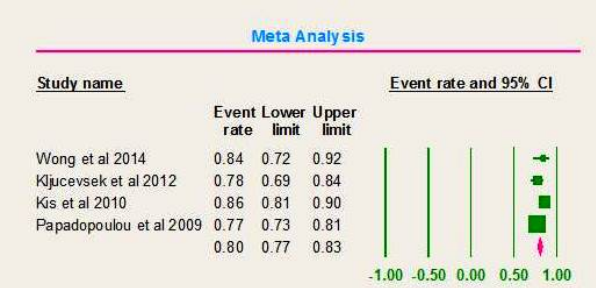
Random-Effect model



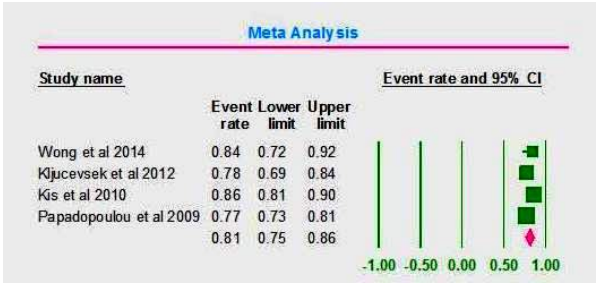
Reference: Meta-Analysis software developed by Dr. Michael Borenstein and his group at Biostat and funded by NIH (www.Meta-Analysis.com)

Figure 2: Forest Plot for Specificity-Lumason Pediatric

Fixed-Effect model



Random-Effect model



Reference: Meta-Analysis software developed by Dr. Michael Borenstein and his group at Biostat and funded by NIH (www.Meta-Analysis.com)

3.3.3 Results at the Patient Level

The sponsor had provided the efficacy data at the ureter level as reported in four clinical studies considered for the primary evidence in support the proposed indication. The agency requested the sponsor to provide efficacy data for these four trials both at ureter level and patient level**.**

The efficacy data at the ureter level from the clinical study by Ključevšek et al. were retrieved from the author of the study, whereas patient level efficacy data were derived from the ureter level data. The data were submitted to FDA on November 16, 2016 together with the algorithm used to classify a patient as TP, FP, FN or TN (patient level analysis). The data for other 3 studies at patient level were not provided.

The sponsor presented the patient-level and by reader data only in one (Ključevšek et al.) study of 66 pediatric patients (35 males, 31 females, age range: 5 days to 1 year). There were no cases in which the two readers who assessed the VUS exams disagreed on the presence/absence of VUR; similarly, there were no cases in which the two readers who assessed the VCUG exams disagreed on the presence/absence of VUR.

At the patient level, the following rules were applied for both VCUG and VUS:

- A patient was considered to have VUR (positive) if at least one of the patient's ureter units had VUR, and
- A patient was considered not to have VUR (negative) if none of the patient's ureter units had VUR.

The following definitions were utilized for the computation of diagnostic performance of VUS at both the ureter and patient level:

- True Negative (TN) – diagnosed with no VUR (negative) according to both VUS and VCUG
- True Positive (TP) – diagnosed with VUR (positive) according to both VUS and VCUG
- False Negative (FN) – diagnosed with no VUR (negative) according to VUS, but diagnosed with VUR (positive) according to VCUG
- False Positive (FP) – diagnosed with VUR (positive) according to VUS, but diagnosed with no VUR (negative) according to VCUG.

Sensitivity was calculated as TP/(TP+FN) while specificity was calculated as TN/(TN+FP). A summary of the diagnostic performance of VUS with Lumason at both the ureter level and the patient level using VCUG as the reference standard is presented in Table 5 below.

Table 4: Diagnostic Performance Results at the Ureter and Patient Level in the Study By Ključevšek et al.

Unit of Analysis	Total Number	With VUR	Without VUR	Sensitivity	Specificity	True Positive	False Negative	True Negative	False Positive
Ureter	132	16	116	100.0	77.59	16	0	90	26
Patient	66	13	53	100.0	69.81	13	0	37	16

Sensitivity = TP/(TP+FN) Specificity =TN/(TN+FP)

3.3.4 Supportive Studies

Seven (7) additional published studies provided supportive evidence. This included 1,645 patients. A summary of supportive evidence is given below:

Patients enrolled were representative of intended pediatric VUS population. Age range of patients enrolled in the supportive studies was 13 days to 17.6 years. Dose of Lumason used during VUS varied from 0.5 mL to 4.8 mL

Results suggest that Lumason dose and administration scheme does not seem to affect diagnostic performance of CE-VUS with Lumason

When VCUG was used as reference standard, despite variable Lumason doses and administration schemes, the sensitivity ranged from 85% to 100%; and specificity ranged from 87% - 97%

Results of these studies support the feasibility of urethral imaging with CE-VUS and Lumason in terms of imaging quality and concordance with VCUG for assessment of urethra for anatomic malformation or posterior valves (performed in one clinical study and 6 supportive studies)

3.4 Evaluation of Safety

The sponsor reported that there were no SAEs reported in more than 6,000 children with age ranging from 2 Days to 18 years from the use of Lumason for CE-VUS. Non-serious AEs reported were considered related to catheterization procedure rather than Lumason [dysuria, crying, anxiety, abdominal pain, frequency, UTI, hematuria]. Most non-serious AEs occurred between 2-24 hours post procedure. All AEs were self-limited and none required hospitalization. No reports of ineffective imaging or technical artifacts were reported in any of the studies, even though the same 1.0 mL dose was used in newborns, infants and older children. The details are covered in the clinical report.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

Due to the nature of data collection based on published papers and 505(b)(2) submission, the information on race, and age was limited.

4.2 Other Special/Subgroup Populations

There were 11 studies in pediatric patients that met pre-defined inclusion/exclusion criteria and were used by the sponsor for efficacy analysis. There were 4 studies that met the efficacy criteria. No special or subgroup patient population was identified.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

Four (4) clinical studies were identified during the literature search and presented in support of the indication for use of Lumason pediatric patients (b) (4) VUR during VUS. Efficacy endpoints were diagnostic performance endpoints, i.e. sensitivity and specificity for the detection/exclusion of VUR, measured against VCUG, used as the standard of truth. A meta-analysis of the 4 controlled studies comparing VUS with VCUG as the standard of truth was also performed.

There were only 4 publications identified for the primary efficacy analysis. This sample size for a meta-analysis is small. There is a possibility of publication bias in meta-analysis.

This reviewer independently analyzed the data and all the graphs and tables were generated by this reviewer. This reviewer independent analysis is supportive of the efficacy and safety of the use of Lumason for VUS in pediatric patients.

5.2 Conclusions and Recommendations

Lumason® (sulfur hexafluoride-SF6 lipid-type A microspheres) was initially approved by the FDA in October 10, 2014 for use "in echocardiography to opacify the left ventricular chamber and to improve the delineation of the left ventricular endocardial border in adult patients with suboptimal echocardiograms". Subsequently, on March 31, 2016, Lumason received FDA approval for use "in ultrasonography of the liver for characterization of focal liver lesions in adult and pediatric patients."

In the current submission, the applicant is seeking an additional indication for use of Lumason during ultrasonography of the (b) (4) urinary tract in pediatric patients with known or suspected vesicoureteral reflux (VUR).The ultrasound procedure is called voiding urosonography (VUS) and encompasses examination of the urinary tract, including bladder, ureters, and urethra. The formulation used for VUS is the same formulation used for the approved indications.

This is a 505(b)(2) application based on literature reports. The four clinical studies reported used flat doses of 1 mL given intravesically, and the applicant proposes a flat dose of 1mL as the recommended dose for the package insert.

In these 4 single-center prospective studies, 508 pediatric patients referred for assessment of vesicoureteral reflux (275 males, 233 female, age range: 2 days to 13 years) were evaluated after intravesical administration of 1.0 mL of Lumason. The findings of Lumason ultrasound (VUS) images were compared to voiding cystourethrography (VCUG) as the truth standard using one or two independent readers. The blinding of the readers to the patient's clinical information is questionable in all these studies. Sponsor's co-primary endpoints were sensitivity and specificity of consensus reading of Lumason images, with the unit of analysis reported in these papers being

either pelvis-ureter unit or kidney-ureter unit (referred as ureter unit or UU thereafter). Sponsor couldn't present "by reader" analysis of sensitivity and specificity due to lack of the data.

Table 5: Diagnostic Performance of Lumason Ultrasound for the detection/exclusion of VUR, measured against VCUG at ureter level

Study		Age Range	N (Gender)		N (ureter units)*	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)
#	Authors		Males	Females			
1	Wong et al.	2-48 Months	23	8	62	100 (55-100)	84 (73-92)
2	Ključevšek et al.	5 days – 1 year	35	31	132	100 (79-100)	78 (69-85)
3	Kis et al.	2 days–44 months	94	89	366	86 (78-92)	86 (81, 90)
4	Papadopoulou et al.	6 days to 13 years	123	105	463	80 (69-89)	77 (73-81)

*There were two ureter units per patient in studies 1, 2 and 3 and in study 4 some patients had more than two ureter units.

The patient-level data were not provided in 3 out of 4 published studies for the FDA's assessment.

The sponsor presented the patient-level and by reader data only in one (Ključevšek et al.) study of 66 pediatric patients (35 males, 31 females, age range: 5 days to 1 year). There were no cases in which the two readers who assessed the VUS exams disagreed on the presence/absence of VUR; similarly, there were no cases in which the two readers who assessed the VCUG exams disagreed on the presence/absence of VUR. At the patient level, the following rules were applied for both VCUG and VUS: A patient was considered to have VUR (positive) if at least one of the patient's ureter units had VUR, and a patient was considered not to have VUR (negative) if none of the patient's ureter units had VUR. A summary of the diagnostic performance of VUS with Lumason at both the ureter level and the patient level using VCUG as the reference standard is presented below in Table 7.

Table 6: Diagnostic Performance Results at the Ureter and Patient Level in the Study By Ključevšek et al.

Unit of Analysis	Total Number	With VUR	Without VUR	Sensitivity	Specificity	True Positive	False Negative	True Negative	False Positive
Ureter	132	16	116	100.0	77.59	16	0	90	26
Patient	66	13	53	100.0	69.81	13	0	37	16

Sensitivity = TP/(TP+FN) Specificity =TN/(TN+FP)

The cumulative information provided and analyzed in this NDA submission provides support to the proposed indication for the pediatric patient population.

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I concur with this review and conclusions written by the primary statistical reviewer.

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12/10/2016