Synopsis

Name and Address of Company:
Bracco Diagnostics Inc., 259 Prospect Plains Rd. Bldg. H, Monroe Twp., NJ 08831
Bracco Imaging S.p.A Via Folli 50 (*with offices at*: Via Caduti Di Marcinelle 13), 20134 Milan, Italy

Name of Finished Product: SonoVue®/Lumason®

Name of Active Ingredient: sulfur hexafluoride microbubbles/ sulfur hexafluoride lipid-type A microspheres

Protocol Number: BR1-145

Title of Study: An Observational Study of SonoVue®/Lumason®-enhanced Urosonography in Paediatric Patients with Known or Suspected Vesicoureteral Reflux. (BR1-145)

Investigators/Study Center(s): The study was conducted a 10 sites:

[redacted]

Publication: None

Study Period: First subject enrolled: 02 July 2020
Last subject completed: 08 July 2021

Phase of Development: IV

Objectives: The primary objective of this study was to assess patient management decision and changes during a follow-up period of 12 months among children undergoing SonoVue®/Lumason®-enhanced voiding urosonography (VUS group) in comparison with children undergoing voiding cystourethrography (VCUG group) for assessment of vesicoureteral reflux (VUR). Secondary objectives were: to estimate the proportion of technically inadequate imaging procedures for both VUS and VCUG groups among the population of patients screened for inclusion in the study; to describe the severity (grading) of VUR and the type of treatment (conservative or surgery) among patients in the VUS and the VCUG groups with positive findings; and to determine the incidence of recurrent urinary tract infections (UTIs) or breakthrough UTIs during the follow-up period among patients in the VUS and VCUG groups.

Study Design: This was a post-authorisation, observational, retrospective, multicentre, comparative study conducted in patients below 18 years of age who had undergone a VUS exam with intravesically administered SonoVue®/Lumason® or VCUG exam as part of their standard of care at least 12 months prior to their enrollment in the study and who had a documented follow-up during the 12 months after the baseline exam. No new evaluation of VUS or VCUG images was performed as part of this retrospective study. Instead, information from existing medical records was used to collect the data for the baseline/study-specific exam, for initial patient management decisions, and for the follow-up period through review of patients' medical records. Consecutive patients were screened from 12 months prior to the date of site initiation and moving earlier chronologically back up to 01 September 2017. The 01 September 2017 date was selected because the approval date of VUR indication for SonoVue® in EU was August 2017. This date provided an anchor date defining a consistent time period for enrollment and for data collection among the sites and among the two study groups (VUS and VCUG). Patients who met the prospectively defined inclusion/exclusion criteria were enrolled in the study and comprised the patient population for data collection. The detailed reason(s) for any exclusion of each patient screened was documented in the Patient Screening/Enrollment Log. In case of exclusion for technical inadequacy of the VUS/VCUG exam, the reason for exclusion was also documented (e.g. motion artifacts, equipment failure, etc.). Data from a documented follow-up at up to 12 ± 1 months after the baseline/study-specific VUS or VCUG exam were collected; if unavailable, an intermediate follow up (e.g. 9, 6, 3 months) closest to 12 months could be used. Patients with no documented follow-up were considered screen failures and to be documented in the screening log. At certain study sites in the European Union, a signed Privacy Disclaimer informed consent form was required from the patient or their parent or legal representative before the patient could be enrolled into the study. No signed informed consent form was required at study sites in France or North America. Enrollment was to continue in each study group until at least 100 patients with positive VUR imaging findings and at least 100 patients with negative VUR imaging findings were included.

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Subject Population: Number planned: 400; Number enrolled: 408; Number randomized: n/a; Number who received study agent: n/a; Number evaluated for efficacy: 408; Number evaluated for safety: 408

Diagnosis and Main Criteria for Inclusion: Patients <18 years of age at the time of the baseline/study-specific VUS or VCUG examination who had undergone a technically adequate SonoVue®/Lumason®-enhanced VUS or VCUG exam for known or suspected VUR not already surgically or endoscopically treated, as part of his/her standard of care, at least 12 months prior to enrollment and not before 01 September 2017 and who had clinical follow-up data available for the period of 12 months after baseline/study-specific VUS or VCUG based on medical records.

Test Agent, Dose and Mode of Administration, Batch Number: Not applicable

Reference Agent, Dose and Mode of Administration, Batch Number: Not applicable

Duration of Treatment: Not applicable

Evaluations:

Efficacy:

Demographics, Urinary Medical History and Reason for the Baseline VUS or VCUG Examination: Patient's demographic information, urinary medical history prior to the baseline study-specific VUS or VCUG procedure and clinical reason for the VUS or VCUG examination was collected in the CRFs.

Initial VUR Diagnosis: The diagnosis of VUR, based on the baseline/study-specific VUS or VCUG exam, was collected in the CRF as follows: absence or presence of VUR; side (left, right) and grading of VUR, if present. The presence of any additional relevant findings observed in the kidneys, ureters, bladder, and urethra was also recorded.

Additional diagnostic procedures performed after the baseline/study-specific exam and before making a decision on patient treatment were also reported, together with the procedure results and the reason for the additional procedure.

Initial Patient Management and Treatment Decision: The patient management and treatment decision data as reported in the patient's medical records were recorded as follows: no treatment; antibiotic prophylaxis (type and planned duration); surgery (type); endoscopic treatment (type); continue/change ongoing treatment (type), for patients with known VUR already on a treatment scheme; other.

Follow Up Assessments: The following information was collected: surgery/endoscopic treatment performed (type, date, surgical/endoscopic findings confirm/do not confirm baseline VUS/VCUG findings); antibiotic prophylaxis or other non-surgical treatment (type and duration); compliance with antibiotic prophylaxis or other non-surgical treatment (yes/no); occurrence of febrile breakthrough UTI (date, treatment); occurrence of recurrent UTI (date, treatment); imaging procedures/tests performed during follow-up, i.e. after initial patient management decision (reason, type, date, results, specify whether additional imaging findings confirm/do not confirm baseline VUS/VCUG findings); any other new information about presence/absence and grading of VUR, if available.

Change in Patient Management/Treatment: The investigator at each site recorded any change in patient management/treatment that occurred during the follow-up period. For each patient the investigator was required to select one of the following pre-specified definitions to describe the change: no change; change from conservative to surgical or endoscopic treatment that was not initially planned; change from no treatment to treatment or change from treatment to no treatment that was not initially planned; results of additional diagnostic procedures during follow-up not confirming findings of baseline VUS or VCUG exam that are not justified by changes of VUR condition due to surgical/endoscopic correction or spontaneous improvement/resolution; surgical/endoscopic findings which did not confirm imaging findings of baseline/study-specific VUS or VCUG exam.

Safety:

All untoward medical occurrences that had occurred in a patient during the timeframe associated with the administration of SonoVue®/Lumason® in VUS group or with the iodinated contrast agent in the VCUG group were to be recorded in the Adverse Event section of the CRF.

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Statistical Methods:

All analyses were conducted by study group, i.e. VUS and VCUG group, and the statistical evaluations used were 2-sided tests at the 0.05 level of significance.

The Analysis Population (identical to Safety Population in this study) included all enrolled patients who underwent a technically adequate SonoVue®/Lumason®-enhanced VUS or a VCUG exam at least 12 months prior to enrollment and who had documented follow-up during the 12 months after the baseline exam.

Demographics, Baseline Characteristics, Urinary Medical History and Clinical Reason for Baseline/Study-Specific VUS or VCUG Exam: Summary statistics were provided for continuous variables including age, height and weight, and the number and percentage of each category were provided for categorical data, including sex and race. Urinary medical history and the clinical reason(s) for the baseline/study-specific VUS or VCUG exam were summarized. Initial patient management decisions and treatment status were summarized. For any patients in whom additional imaging procedures were performed after baseline/study-specific VUS/VCUG exam but before making the initial patient management decision, the date and type of exam, the reasons for the exam, and any comments regarding the findings of the exam were listed.

Efficacy: Data were summarized for the analysis population (N=408; same as safety population).

Primary Endpoint: The primary endpoint of change in patient management/treatment in the follow-up period included frequency count and percentage for each study group (VUS, VCUG). The point estimate of difference in proportions between the two groups with the 95% confidence interval (CI) was estimated using the Wilson score confidence interval method. Equivalence of the two groups could be concluded if the observed 2-sided 95% CI for the difference in the proportion of patients with change in patient management was within the pre-specified equivalence margin of 12.5%. Further, the difference in patient management change between the two groups was tested with chi-square analysis. An ad-hoc analysis for the primary endpoint was also conducted for the subgroups of patients with positive (VUR present) and negative (VUR absent) findings at the baseline/study-specific exam.

Secondary Endpoints: Among the population of patients screened for inclusion in the study, the proportion of technically inadequate imaging procedures in both VUS and VCUG groups, and the reasons for the inadequacy, were summarized.

Among patients with positive findings from the baseline/study-specific VUS or VCUG, the grading of VUR was summarized using descriptive statistics. In addition, In addition, any treatments performed during the follow-up period were summarized for each category with frequency and percentage for each study group.

The incidence rate of any UTIs or febrile or breakthrough UTIs as collected during the follow-up period are calculated together with 95% CIs for each study group.

Safety: Only those adverse events that occurred after VUS or VCUG were to be summarized. Adverse events were to be coded using MedDRA and summarized by system organ class and preferred term, by intensity and by causal relationship to SonoVue®/Lumason® administration for VUS or iodinated contrast agent administration for VCUG.

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Summary and Conclusions:

Disposition: The efficacy analysis/safety population consisted of 408 patients included in the study, 208 (51%) in the VUS group and 200 (49%) in the VCUG group; 286 (70.1%) patients were enrolled at 7 clinical sites in EU and 122 (29.9%) patients were enrolled at 3 clinical sites in the United States. No protocol violations occurred in the study.

Demographics and Baseline Characteristics: In the VUS group 62.0% of enrolled patients were female. Mean age was 1.8 ± 2.9 yrs (range: 0.0-15.0 yrs). The majority of patients were < 2 yrs (144 or 69.2%), with the remaining patients between the age of 2 to 5 yrs (40 pts or 19.2%), 6 to 11 yrs (22 pts or 10.6%), or 12 to 17 yrs (2 pts or 1.0%). Ethnic distribution was 87.0% Caucasian, 3.8% Black, 2.4% Asian, and 5.8% Other. In 2 (1.0%) patients, race was not reported.

In the VCUG group 38.0% of enrolled patients were female. Mean age was 2.8 ± 4.3 yrs (range: 0.0-17.0 yrs). The majority of patients were < 2 yrs (121 or 60.5%), with the remaining patients between the age of 2 to 5 yrs (46 pts or 23.0%), 6 to 11 yrs (17 pts or 8.5%), or 12 to 17 yrs (16 pts or 8.0%). Ethnic distribution was 35.5% Caucasian, 1.5% Black, 3.0% Asian, and 21.5% Other. In 38.5% of patients undergoing VCUG, race was not reported; most of these patients were enrolled at one clinical site in France where it is not permitted to collect data about race.

Urinary Medical History: The most commonly reported finding was UTI prior to the baseline VUS or VCUG procedure, present in 128 (61.5%) patients in the VUS group and 119 (59.5%) patients in the VCUG group. Prenatal hydronephrosis was reported in both groups: VUS group (61 or 29.3%) and VCUG group (78 or 39.0%).

Previous assessment of VUR was reported in a comparable number of patients in the VUS (38 or 18.3%) and the VCUG groups (44 or 22.0%) whereas previous assessment of genitourinary abnormalities or renal cortical abnormalities was more commonly reported among patients in the VCUG group than in patients in the VUS group.

Among those patients who underwent previous assessment of VUR, the presence of VUR was reported in 33 (86.8%) patients in the VUS group and 28 (63.6%) patients in the VCUG group.

Reason for the Baseline/Study-specific VUS or VCUG Exam: The most frequently reported reason for the baseline exam in both groups was UTI, either reported as initial episode or recurrent UTIs: 126 (60.6%) patients in the VUS group and 102 (51.0%) patients in the VCUG group. Other common reasons for performing the baseline/study-specific exam included renal pelvis dilatation (38.0%, VUS group and 45.0%, VCUG group), follow-up of known condition of VUR not already treated endoscopically or with surgery (15.9%, VUS group and 12.5%, VCUG group), or other reasons (7.7%, VUS group and 41.0%, VCUG group). In 3 (1.4%) patients the baseline/study-specific VUS exam was performed due to a diagnosis of VUR in one or more siblings.

In the VUS group, the most common "other" reasons for performing the baseline/study-specific exam was congenital anomalies of the kidney-ureter system (n=7). In the VCUG group, the most common "other" reasons for performing the baseline/study-specific exam included neurogenic bladder (n=26), hydronephrosis or ureteral dilatation (n=13), congenital anomalies of the kidney-ureter system (n=12), voiding dysfunction (n=4), or dysuria (n=3).

Additional diagnostic procedures after the baseline/study-specific exam and before making a decision on patient treatment were performed more frequently in patients in the VCUG group (75 additional exams in 68 patients, including 41 US without contrast medium, 33 nuclear medicine exams, and 1 other exam) than in the VUS group (39 additional exams in 35 patients, including 28 nuclear medicine exams, 7 US without contrast medium, 3 other exams, and 1 VCUG study).

VUR on the Baseline/Study-specific VUS or VCUG Exam: VUR was present at the baseline exam in 99 (47.6%) patients in the VUS group and 99 patients (49.5%) patients in the VCUG group; the side distribution of VUR between the 2 group was comparable.

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Efficacy:

Initial Patient Management Decision: In 137 patients (33.6%) no treatment was planned (35.6% in the VUS group and 31.5% in the VCUG group). Antibiotic prophylaxis was the most common treatment decision in both groups (55.3% in the VUS group and 37.0% in the VCUG group); in most cases in both groups this involved continuation of ongoing antibiotic treatment. Surgery was recommended in 13 (6.3%) patients in the VUS group and 26 (13.0%) patients in the VCUG group; an endoscopic procedure in 11 (5.3%) patients in the VUS group and 8 (4.0%) patients in the VCUG group; and non-surgical treatment in 8 (3.8%) patients in the VUS group and 30 (15.0%) patients in the VCUG group. Other treatment was recommended in 30 (14.4%) patients in the VUS group and 43 (21.5%) patients in the VCUG group; in the majority of cases, "other" treatment was reported for patients in whom antibiotic prophylaxis was recommended and could include medications for constipation relief, intermittent bladder catheterization, behavioral management of voiding, or recommendation for a follow-up visit ≤ 12 months after the baseline procedure.

Primary Efficacy Endpoint:

- No changes were made in patient management during the follow-up period in 169 (81.3%) patients in the VUS group and 155 (77.5%) patients in the VCUG group.
- A total of 39 (18.8%) patients in the VUS group and 45 (22.5%) patients in the VCUG group had a change in patient management or treatment during the study follow-up period. The estimated difference in the proportion of patients with a change in patient management or treatment (VCUG -VUS) was 3.75. The observed 2-sided 95% CI (-4.10, 11.60; p=0.349) for this difference was small and within the pre-specified equivalence margin of ±12.5%. Therefore the primary endpoint of the study was met.
- The types of patient management/treatment changes were similar in the two groups: a change from no treatment to treatment, or a change from treatment to no treatment that was not initially planned was reported in 24 (11.5%) patients in the VUS group and 30 (15.0%) patients in the VCUG group. A change from conservative to surgical or endoscopic treatment that was not initially planned was made in 15 (7.2%) patients in the VUS group and 14 (7.0%) patients in the VCUG group.
- In the ad-hoc analysis in the subgroup of patients with presence of VUR at the baseline/study-specific exam:
  - No change in management during the follow-up period was reported for the majority of patients in the VUS and VCUG groups (73.7% and 69.7% patients, respectively). A change in management/treatment was reported for 26 (26.3%) patients in the VUS group and 30 (30.3%) patients in the VCUG group. The estimated difference in the proportion of patients with a change in management or treatment (VCUG - VUS) was 4.04 (p=0.528).
- In the ad-hoc analysis in the subgroup of patients with absence of VUR at the baseline/study-specific exam:
  - No change in management during the follow-up period was reported for the majority of patients in the VUS and VCUG groups (88.1% and 85.1% patients, respectively). A change in management/treatment was reported for 13 (11.9%) patients in the VUS group and 15 (14.9%) patients in the VCUG group. The estimated difference in the proportion of patients with a change in management or treatment (VCUG - VUS) was 2.92 (p=0.533).

Secondary Efficacy Endpoints:

A total of 1,489 patients were screened across the 10 sites involved in the study, including 1,097 patients in the VUS group and 392 in the VCUG group. The majority of patients in the VUS group were enrolled at sites that required a signed informed consent whereas the majority of patients in VCUG group were enrolled at sites that did not require the signed informed consent; this explains the difference in the number of patients screened in the two study groups.

- Among patients screened for inclusion in the study, technically inadequate imaging procedures were reported in 4 cases (0.4%) in the VUS group and in 5 cases (1.3%) in the VCUG group.
- Among the 99 patients with VUR identified on the baseline/study-specific in the VUS group, 87.9% had VUR Grade II, III, or IV. In the VCUG group, among 99 patients with VUR identified 86.9% had VUR Grade II, III, IV, or V. Five (5/99, 5.1%) patients in the VUS group and 7 (7/99, 7.1%) patients in the VCUG group had VUR Grade reported as "other"; these were mostly patients in whom grading was reported as a combined score of two contiguous grades, such as Grade II/III or Grade III/IV.

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Secondary Efficacy Endpoints (continued):

- Additional findings at the baseline exam were reported commonly in the kidney (55, 26.4% of all exams) and the ureter (29, 13.9% of all exams) in the VUS group, and in the urethra (40, 20.0% of all exams) and the ureter (24, 12% of all exams) in the VCUG group.
- No treatment was provided during the follow up period in 86 (41.3%) patients in the VUS group and in 53 (26.5%) patients in the VCUG group.
- Antibiotic prophylaxis was provided in 98 (47.1%) patients in the VUS group and 90 (45.0%) patients in the VCUG group; surgical treatment in 16 (7.7%) patients in the VUS group and 35 (17.5%) patients in the VCUG group; endoscopic procedure in 14 (6.7%) patients in the VUS group and 8 (4.0%) patients in the VCUG group; and non-surgical treatment in 6 (2.9%) patients in the VUS group and 28 (14.0%) patients in the VCUG group. Other treatment was provided in 9 (4.3%) patients in the VUS group and 36 (18.0%) patients in the VCUG group; other treatment could include medications for constipation relief, intermittent bladder catheterization, behavioral management of voiding.
- Data on the incidence of recurrent or breakthrough UTIs during the follow-up period were available in a subset of patients: in the VUS group 122 patients with a combined 100.8 years of follow up, and in the VCUG group 147 patients with a combined 126.2 years of follow up. In the VUS group, a total of 26/122 (21.3%) patients experienced 38 UTIs (incidence rate of 0.377, 95% CI: 0.274, 0.518), of which 27 were reported as febrile/breakthrough UTIs (incidence rate of 0.268, 95% CI: 0.184, 0.390). In the VCUG group, a total of 53/147 (36.1%) patients experienced 114 UTIs (incidence rate of 0.903, 95% CI: 0.752, 1.085), of which 91 were reported as febrile/breakthrough UTIs (incidence rate of 0.721, 95% CI: 0.587, 0.885). Differences between the 2 groups were statistically significant since there was no overlapping of the 95% CIs.

Safety: There were no AEs reported for any patient in this retrospective study.

Conclusions:

Study BR1-145 was a retrospective observational study conducted in children with known or suspected VUR who were evaluated with SonoVue®/Lumason®-enhanced VUS or with VCUG. The primary endpoint of the study was the need for changes in patient management/treatment during a follow-up period after the baseline VUS or VCUG exam.

Study results show that the clinical impact of patient management/treatment decision based on SonoVue®/Lumason®-enhanced VUS findings is not different from management/treatment decision based on VCUG findings. Indeed, the majority of patients in the VUS and VCUG groups did not need any change in management/treatment of their VUR condition during follow-up, and the estimated difference in the proportion of patients with a change in management/treatment was small and within the pre-defined equivalence margin. Furthermore, the number of patients in whom a change from no treatment to treatment or vice versa was reported and the number of patients with a change from conservative to surgical or endoscopic treatment was similar between the VUS and the VCUG groups. Similar results were observed in the subgroup analysis by VUR status (VUR present or absent) at patients' baseline exam.

There were no AEs with SonoVue®/Lumason® reported for any patient in this retrospective study.

Date of Report: 11 March 2022