22 June 2017
EMA/CHMP/431946/2017
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

SonoVue

International non-proprietary name: sulphur hexafluoride

Procedure No. EMEA/H/C/000303/X/0034/G

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

MCU : micturating cystourethrography

RNC : radionuclide cystography

UTI : urinary tract infection

VCUG : voiding cystourethrography

VUR : vesicoureteral reflux

VUS : voiding urosonography

UU: Pelvi-ureter units

CE-VUS: contrast enhanced void urosonography

1. Background information on the procedure

1.1. Submission of the dossier

Bracco International B.V. submitted on 29 August 2016 a group of variation(s) consisting of an extension of the marketing authorisation and the following variation(s):

Variation(s) requested		Type
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

Extension application to introduce a new route of administration (intravesical use in paediatric patients) grouped with a type II variation to add a new indication (to include use in ultrasonography of the excretory urinary tract in paediatric patients to detect or exclude vesicoureteral reflux). As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 6 of the SmPC are updated. The Package Leaflet is updated accordingly. In addition, the Marketing Authorisation Holder (MAH) took the opportunity to bring Annex IIIA in line with the latest QRD template version 10. Moreover, the updated RMP version 9.1 has been submitted as part of this application.

The legal basis for this application refers to:

Article 7.2 of Commission Regulation (EC) No 1234/2008 – Group of variations

Information on Paediatric requirements

Not applicable

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific Advice

The MAH received Scientific Advice from the CHMP on 19 November 2015. The Scientific Advice pertained to clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Alexandre Moreau Co-Rapporteur: N/A

- The application was received by the EMA on 29 August 2016.
- The procedure started on 29 September 2016.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 19 December 2016. The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on 19 December 2016.
- During the meeting on 12 January 2017, the PRAC agreed on the PRAC Assessment Overview and Advice to CHMP.
- During the meeting on 26 January 2017, the CHMP agreed on the consolidated List of Questions to be sent to the MAH.
- The MAH submitted the responses to the CHMP consolidated List of Questions on 19 April 2017.
- The Rapporteur circulated the Assessment Report on the responses to the List of Questions to all CHMP members on 25 May 2017.
- The PRAC Rapporteur circulated the Assessment Report on the responses to the List of Questions to all CHMP members on 25 May 2017.
- During the PRAC meeting on 9 June 2017, the PRAC agreed on the PRAC Assessment Overview and Advice to CHMP.
- During the meeting on 22 June 2017, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for an extension of the marketing authorisation for SonoVue on 22 June 2017.

2. Scientific discussion

2.1. Problem statement

SonoVue was not approved in the EU for use in **contrast enhanced void urosonography (CE-VUS)**. TThe MAH proposed to use the published literature about the use of the product in paediatric patients with medical need for assessment of vesicoureteral reflux (VUR), to support the new indication for use of SonoVue to assess VUR in paediatric patients. Diagnostic imaging plays a central role in diagnosis of VUR and decisions about therapeutic options.

2.1.1. Disease or condition

Urinary tract infection (UTI) is the most frequent serious bacterial infection during childhood, affecting approximately 2% of boys and 8% of girls by the age of 7 years. The prevalence of VUR in children with UTIs is 30% to 40% and increases in children with recurrent UTIs. Urinary tract infection (UTI) is the most frequent serious bacterial infection during childhood, affecting approximately 2% of boys and 8% of girls by the age of 7 years. The prevalence of VUR in children with UTIs is 30% to 40% and increases in children with **recurrent UTIs**. VUR is a common urinary tract abnormality in children characterized by retrograde flow of urine from the bladder into the ureter and toward the kidney, secondary to a dysfunctional vesicoureteral junction. This junction usually acts like a one-way valve which allows urine flow from the ureter into the bladder and closes during micturition, thus preventing back flow. Several pathologic conditions, either congenital or acquired, may be responsible for an ineffective

valve function of the vesicoureteral junction. VUR is detected most commonly during voiding, when intravesical pressure rises, but may occur at any time in the voiding cycle, particularly when bladder function is abnormal. VUR represents a common cause of non-obstructive chronic nephropathy in children. The presence of VUR is associated with an **increased risk of renal scarring** after UTI with **potential for nephrovascular hypertension and renal failure**.

2.1.2. Clinical presentation, diagnosis

The identification of VUR in patients with UTI is associated with increased risk of renal scarring. As reported in the guidelines of the European Association of Urology (EAU) and European Society for Paediatric Urology (ESPU)[1], imaging assessment is the basis for diagnosis and further management of VUR. The standard imaging tests include **voiding cysturoethrography (VCUG)**, and **radionuclide cystography (RNC)**. Both imaging modalities require exposure to ionizing radiation. Unenhanced ultrasonography cannot reliably detect VUR. **Voiding urosonography (VUS)** with SonoVue is a procedure similar to VCUG, with use of the SonoVue gas-filled microspheres instead of X-ray contrast agents, and it could be as accurate as VCUG; moreover, it does not involve any radiation exposure.

Voiding cysturoethrography (VCUG)

Currently, the standard test for VUR is VCUG, which provides precise anatomic details, optimal assessment of the urethra, and grading of the severity of VUR, for which the standardized, **International Reflux Study Committee grading system** was introduced in 1985 (Grade I to Grade V). The major disadvantage of VCUG is the associated exposure to ionizing radiation. The radiation exposure concern is particularly relevant in children because of their ongoing development, greater cell turnover, and increased lifetime risk of cancer based on a greater life expectancy when compared with an adult.

Radionuclide voiding cystography (RNC)

Radionuclide voiding cystography is also used for diagnosis of VUR. When compared to VCUG, radionuclide imaging is characterized by a lower radiation exposure and comparable sensitivity and specificity for detection of VUR. However, it is limited by poor anatomic resolution, inability to study the urethra, and less accurate grading of the severity of reflux.

Ultrasound (US)

Ultrasound (US) is a non-invasive imaging method that eliminates the risk of ionizing radiation and is readily available. It can detect urinary tract anomalies such as pyeloureteral dilatation, duplex renal system, and ureterocele which may raise the suspicion of VUR. However, the sensitivity of US for detecting VUR is low. In the **Appropriateness Criteria developed by the American College of Radiology (ACR)** for assessment of children with UTI, **US is recommended for screening** underlying congenital renal anomalies with exclusion of VUR.

Contrast-enhanced voiding urosonography (CE-VUS)

Contrast-enhanced voiding urosonography (CE-VUS) encompasses evaluation of the urinary tract after intravesical administration of an ultrasound contrast agent for diagnosis of VUR and assessment of the urethra. Furthermore, accurate grading of the severity of reflux may be possible with CE-VUS. Numerous studies have reported high sensitivity and specificity of CE-VUS in comparison with VCUG and radionuclide imaging. The clinical usefulness of **VUS with contrast** in paediatric patients is acknowledged by the Position Statement from the **European Federation of Societies for Ultrasound**

[1] European Association of Urology (EAU) and European Society for Paediatric Urology (ESPU) Guidelines on Paediatric Urology 2015, S. Tekgül (Chair), H.S. Dogan, E. Erdem (Guidelines Associate), P. Hoebeke, R. Koˇcvara, J.M. Nijman (Vice-chair), C. Radmayr, M.S. Silay (Guidelines Associate), R. Stein, S. Undre (Guidelines Associate).

in Medicine and Biology (EFSUMB) 2016[2] and in the update of guidelines and recommendations on the clinical practice of contrast-enhanced ultrasound and by the **European Society of Paediatric Radiology (ESPR) uroradiology task force 2012**[3]. Some of the clinical practice recommendations point to the change in the understanding of the standard of care with CE-VUS replacing in many centres the traditionally performed VCUG for detection of VUR (ie. European Federation of Societies for Ultrasound in Medicine and Biology [EFSUMB] 2016). Based on the published literature and the recommendations issued by the scientific societies, the applicant believes that the CE-VUS has the potential for replacing VCUG in the clinical assessment of paediatric patients with known or suspected VUR.

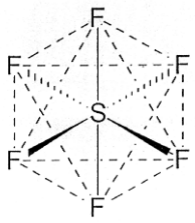
2.1.3. Management

According to the Guidelines of the EAU[4] there are two main treatment approaches: conservative (non-surgical) and surgical. The objective of conservative therapy is prevention of febrile UTI. Regular follow-up with imaging studies (e.g. VCUG, RNC) is part of the conservative management to monitor spontaneous resolution and kidney status. Conservative management should be dismissed in all cases of febrile breakthrough infections, despite prophylaxis, and intervention should be considered.

About the product

SonoVue (Sulphur Hexafluoride Microbubbles) is an ultrasound contrast agent (USCA) developed by Bracco International B.V., and is characterized by a microsphere structure, consisting of a low solubility gas, sulphur hexafluoride (SF6), stabilized by a phospholipid shell.

Bracco is the Marketing Authorisation Holder (MAH) for SonoVue, which belongs to the class of gas-filled microbubble contrast agents used as echo-enhancing agents in conjunction with medical ultrasound procedures. Sulphur hexafluoride (SF6) has the following chemical structure:



SonoVue has been commercialized in the European Union since March 2001 and is currently approved in 41 countries throughout the world. In the EU it is approved for intravenous use in adults for the following indications:

[2] **Role of Contrast-Enhanced Ultrasound (CEUS) in Paediatric Practice: An EFSUMB Position Statement 2016**; P. S. Sidhu1, V. Cantisani2, A. Deganello1, C. F. Dietrich3, C. Duran4, D. Franke5, Z. Harkanyi6,W. Kosiak7, V. Miele8, A. Ntoulia1, M. Piskunowicz9, M. E. Sellars1, O. H. Gilja; DOI http://dx.doi.org/10.1055/s-0042-110394

[3] **ESPR Uroradiology Task Force and ESUR Paediatric Working Group—Imaging recommendations in paediatric uroradiology, Part V: childhood cystic kidney disease, childhood renal transplantation and contrast-enhanced ultrasonography in children 2012**, Michael Riccabona & Fred Efraim Avni & Maria Beatrice Damasio & Lil-Sofie Ording-Müller & Johan G. Blickman & Kassa Darge & Maria Luisa Lobo & Frederica Papadopoulou & Pierre-Hugues Vivier & Ullrich Willi; Pediatr Radiol (2012) 42:1275–1283
DOI 10.1007/s00247-012-2436-9.

[4] **European Association of Urology (EAU) and European Society for Paediatric Urology (ESPU) Guidelines on Paediatric Urology** 2015, S. Tekgül (Chair), H.S. Dogan, E. Erdem (Guidelines Associate), P. Hoebeke, R. Ko˘cvara, J.M. Nijman (Vice-chair), C. Radmayr, M.S. Silay (Guidelines Associate), R. Stein, S. Undre (Guidelines Associate).

- **Echocardiography**, in patients with suspected or established cardiovascular disease to provide opacification of cardiac chambers and enhance left ventricular endocardial border delineation;

- **Doppler of macrovasculature** to increase the accuracy in detection or exclusion of abnormalities in cerebral arteries and extracranial carotid or peripheral arteries by improving the Doppler signal-to-noise ratio;

- **Doppler of macrovasculature** to increase the quality of the Doppler flow image and the duration of clinically useful signal enhancement in portal vein assessment

- **Doppler of microvasculature** to improve display of the vascularity of liver and breast lesions during Doppler sonography, leading to more specific lesion characterisation.

In addition, SonoVue is approved by the FDA under the trade name Lumason for intravenous use in ultrasound imaging:

- 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;
- and in ultrasonography of the liver for characterisation of focal liver lesions in adult and paediatric patients.

Type of Application and aspects on development

Bracco International B.V. submitted on 29 August 2016 an extension application to introduce a new route of administration (intravesical use) grouped with a type II variation (C.I.6.a) to add a new indication (to include use in ultrasonography of the excretory urinary tract in paediatric patients to detect or exclude vesicoureteral reflux). As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 6 of the SmPC were updated.

This ultrasound procedure is called voiding urosonography (VUS) and encompasses examination of the urinary tract, including bladder, ureters, and urethra after intravesical administration of an ultrasound contrast agent for detection or exclusion of VUR in paediatric patients. Considering that the imaging procedures most commonly performed for detection and follow-up of VUR are fluoroscopic voiding cystourethrography (VCUG) and direct radionuclide cystography (RNC) and that both modalities require exposure to ionizing radiation, the VUS indication for SonoVue answers an unmet medical need for a safe and effective procedure for the diagnosis of VUR in children.

The applicant proposed the following wording of the indication:

"SonoVue is indicated for use in ultrasonography of the excretory urinary tract in paediatric patients to detect or exclude vesicoureteral reflux".

The CHMP considered it is not possible to state that a negative result allows the practitioner to exclude a diagnosis of VUR. Therefore, the CHMP approved the following wording of the indication:

"SonoVue is indicated for use in ultrasonography of the excretory tract in paediatric patients from newborn to 18 years to detect vesicoureteral reflux. For the limitation in the interpretation of a negative urosonography, see section 4.4. and 5.1."

There is no paediatric investigation plan (PIP) in place for SonoVue and article 8 of Regulation (EC) No 1901/2006 does not apply to this application, since the authorised medicinal product is not protected by a supplementary protection certificate under Regulation (EC) No 469/2009 or by a patent which qualifies for the granting of the supplementary protection.

2.2. Quality aspects

2.2.1. Introduction

There were no new quality data submitted in support of current application. The extension application is due to the new route of administration (intravesical route), but the product itself is unchanged (identical formulation and presentation). In this condition, no module 3 was provided. This was considered acceptable for the CHMP.

2.2.2. Conclusions on the chemical, pharmaceutical and biological aspects

There were no new quality data submitted in support of current application and this was considered acceptable for the CHMP.

2.3. Non-clinical aspects

2.3.1. Introduction

The non-clinical dossier was mainly based on the recall of previous studies **performed from intravenous route**. In addition to the standard non-clinical pharmacology, pharmacokinetic and toxicology studies required for the approval of the IMA application, several non-clinical studies were performed after marketing of SonoVue worldwide to contribute to an understanding of the mechanism of the rare cases of severe adverse events (SAR) observed with the product and similar ultrasound contrast agents. The majority of the non-clinical studies, with the exception of the reproduction toxicology studies, were performed using the first formulation of SonoVue studied clinically, which did not contain palmitic acid. The final marketed SonoVue formulation contains palmitic acid. The reproduction toxicology studies with this final formulation showed that SonoVue had no adverse effects on mating and fertility, and was not embryotoxic, fetotoxic or teratogenic.

In addition to the assessed previously study of venous and paravenous local tolerance, **a specific study using intravesical route of administration** was submitted and assessed within current application. This was a **local tolerance study for SonoVue after intravesical administration in the rat**. A single-dose study and a repeat-dose study, followed by a treatment-free period, were performed in female rats divided into 3 dose groups of 10 animals. Local toxicity was evaluated through macroscopic and histopathological examination of both kidneys, ureters, the urinary bladder and urethra. It did not reveal any test item-related lesions in any of the examined organs, in particular in the urinary bladder, in both the single-dose and the repeat-dose studies. It was therefore concluded that SonoVue is well tolerated in the urinary tract in the rat.

2.3.2. Pharmacology

Based on already authorised intravenous route of administration, the applicant reported numerous *in vitro* and *in vivo* data to demonstrate or elucidate:

- The acoustic properties of SonoVue and the resistance of the reconstituted preparation to pressure (*in vitro)*.
- The basic characteristics of SonoVue and early imaging results in dogs, minipigs, sheep and rabbits (*in vivo*), also reported in the literature (Schneider *et. al*., 1995).

- The possible mechanism of actions (*in vitro* and *in vivo)* for the serious adverse reactions (SAR) observed after administration of SonoVue in a low percentage of patients (overall current SAR-reporting rate of 0.012%) in countries where it is marketed.
- The safety pharmacology on vital organ functions including cardiovascular, respiratory and central nervous systems and potential pharmacodynamic drug interactions of SonoVue (*in vitro* and *in vivo*).

Based on the imaging studies in animals mentioned above, the **intended dose** of SonoVue for contrast enhancement of the cardiac cavities by 2-D mode was agreed to be **0.04 mL/kg (i.e. 2 mL for a 50 kg person).** The dose-effect relationship of ultrasound imaging in the clinical studies in humans was in line with the imaging studies in animal model. This showed that the results in the animal models were reasonably predictive for imaging in humans.

During development, palmitic acid was added to the SonoVue formulation to improve the long term stability of the lyophilized drug product by maintaining the performance characteristics of the lyophilizate after long term storage. The **addition of palmitic acid to the formulation** does not increase the duration of the microbubbles *in vivo*.

None of the non-clinical studies performed were able to provide a clear explanation on the mechanism(s) of the rare adverse reactions observed in humans after administration of SonoVue and other microbubble contrast agents.

2.3.3. Pharmacokinetics

The pharmacokinetics of SonoVue was examined *in vivo* and *in vitro*. A GLP study measuring the blood kinetics and elimination of the SF6 contained in SonoVue in rabbits was performed using the first formulation of SonoVue, which did not contain palmitic acid. A GLP study measuring the kinetics, biodistribution and elimination of 14C-DPPG (one of the main phospholipid of SonoVue) was performed in rats. Additionally, non-GLP *in vitro* studies were performed to verify that the phospholipids contained in SonoVue (DSPC and DPPG) were able to be hydrolysed by phospholipase A2 and that the microbubbles have a short half-life in plasma at 37 °C. Finally, a non-GLP study was performed in rats to measure the biodistribution and elimination of 14C-PEG-4000. The SF6 is administered to patients in a trace amount that is rapidly excreted via the pulmonary route.

2.3.4. Toxicology

The toxicology of SonoVue was examined in several *in vitro* and *in vivo* studies by intravenous route. Single dose studies were conducted in rats and monkeys. Repeated dose studies have been conducted in rats and monkeys for up to 28 days. Segment I, II and III reproduction studies were conducted in rats and Segment II reproduction studies were conducted in rabbits. *In vitro* and *in vivo* genotoxicity studies were also conducted. Special studies included local tolerance and blood compatibility studies. Regarding the extension application due to the new route of administration (intravesical route), intravesical local tolerance for SonoVue was assessed in a two part study. It was therefore concluded that SonoVue is well tolerated in the urinary tract in the rat. All the toxicology studies intended to support safety were conducted in compliance with Good Laboratory Practices (GLP).

2.3.5. Ecotoxicity/environmental risk assessment

It can be expected that following the authorisation of the line extension SonoVue will not pose a risk to the environment.

2.3.6. Discussion on the non-clinical aspects

The non-clinical pharmacology, pharmacokinetics, and toxicology of SonoVue have been evaluated in a number of *in vitro* and *in vivo* studies.

Imaging studies in animals showed that SonoVue is a compelling ultrasound contrast agent. The clinical ultrasound imaging studies showed that the imaging results in animal models had been predictive for imaging and dose-response in humans.

The core battery of safety pharmacology studies in animals showed that SonoVue had no adverse effects on cardiovascular or respiratory parameters, arterial blood gases, blood pressure, microcirculation, or brain circulation.

SonoVue did not interact with the actions of the main treatment generally administered in patients corresponding to the indication of SonoVue.

After intravenous administration of SonoVue to rabbits, the SF6 gas was eliminated rapidly and totally via the pulmonary route with an elimination half-life of less than 1 minute (about 4.5 min for a dose of 1 mL/kg).

A single intravenous dose of SonoVue had no adverse effects in rats and monkeys approximately a 69-fold and 140-fold of the human dose, based upon body surface area, respectively.

No drug-related adverse effects were observed after daily repeated dosing of 5 mL SonoVue /kg for 28 days in rats or in monkeys, (which represented 20 fold and 40 fold, respectively of the highest proposed human dose), with the exception of a species-specific caecum reversible lesion that was observed in the rats. These lesions, which were not reproducible in a second 28 day rat study, did not occur in rats after a single 20 mL/kg dose, which represented approximately 69 fold of the human dose based upon body surface area. Consequently, these caecum lesions, which were observed sporadically in rats only after 3-4 weeks of daily repeated treatment, are not relevant to possible effects in humans under the conditions of a single administration.

The study of venous and paravenous, intravesical local tolerance for SonoVue demonstrated the good well local tolerance.

However, in a local tolerance study with single or repeat intravesical administration to rats, minimal haemorrhage and minimal signs of inflammation were observed in the urethra in some animals. These effects, reversible in most of them after one or two weeks were considered to be due to the administration procedure (catheterization) and unrelated to the test item. No effects were observed in the urinary bladder, ureters and kidneys. A statement confirming that it was concluded that SonoVue is well tolerated in the urinary tract in the rat was added to section 5.3 of the SmPC.

Reproduction studies in rats and rabbits showed that SonoVue had no adverse effects on mating and fertility, and was not embryotoxic, fetotoxic or teratogenic.

Neither SonoVue nor the SF6 gas was mutagenic in the Ames assay. SonoVue was negative in the in vitro human peripheral blood lymphocyte assay, and in the in vivo mouse micronucleus assay.

Moreover, series of in vivo and in vitro studies were conducted to identify possible mechanisms of action involved in the rare hypersensitivity (anaphylactoid) reactions to SonoVue observed in humans with a reporting rate of about 1/10,000 patients.

Animal studies in pigs showed hemodynamic effects after the administration of SonoVue in relationship with the release of mediators, particularly of thromboxane, in the blood stream, and it was hypothesized that pulmonary intravascular macrophages could be involved in hypersensitivity reactions to SonoVue, results not confirmed in other rat models.

2.3.7. Conclusion on the non-clinical aspects

In line with the *ICH guideline M3(R2) Non-clinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals*, the characterization of the mechanism of action as well as the intended imaging properties of SonoVue for contrast enhancement of the cardiac cavities have been made. Appropriate models have been selected based on the target and mechanism of action.

An assessment of the impact of use of Sonovue on vital organ functions including cardiovascular, respiratory and central nervous systems was provided. Safety pharmacology studies did not raise safety concern related to these functions. The toxicology of SonoVue was examined in several *in vitro* and *in vivo* studies. Considering the safety margins established in the toxicology studies, SonoVue appeared to be a safe compound for administration to humans at the doses intended for ultrasound imaging after intravenous administrations, from 0.03 mL/kg for 2-D imaging to 0.2 mL/kg for Doppler or myocardial contrast enhancement.

The majority of the non-clinical studies, with the exception of the reproduction toxicology studies, were performed using the first formulation of SonoVue studied clinically, which did not contain palmitic acid. The potential effects of SonoVue on fertility and embryo-fetal toxicity were evaluated in rats and in rabbits. These studies used the SonoVue formulation intended for marketing, which contains palmitic acid: (1) Reproductive Toxicity Studies in Rats (Segments I, II, and III), (2) Reproductive Toxicity Studies in Rabbits (Segment II). Reproduction studies in rats and rabbits showed that SonoVue had no adverse effects on mating and fertility, and was not embryotoxic, fetotoxic or teratogenic.

Current application was considered acceptable by the CHMP from non-clinical point of view.

2.4. Clinical aspects

2.4.1. Introduction

No clinical studies were performed in support of the use of SonoVue for the evaluation of VUR in children. Instead, data supporting the efficacy and safety of SonoVue for this application was derived from the published literature. The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment.

Table A: Pivotal clinical studies assessing diagnostic performance of VUS with SonoVue

Reference	Patients M/F Age range	Study Design Truth Standard Image evaluation VUS imaging protocol	Sample size Endpoints	SonoVue dose Administration scheme	Results
Wong, Eur J Pediatr. 2014	31 pts with UTI and suspected VUR 23 M/8 F 2-48 months	Prospective, within-patient VCUG On-site, blinded, independent Low-MI (operated at 0.05-0.07) harmonic imaging	62 pelvi-ureter units (2 per patient) Sensitivity/ specificity for detection of VUR Agreement VUS/VCUG in grading VUR Assessment of urethral abnormalities Monitoring for adverse events	1.0 mL Pre-filling of bladder with saline (1/3 maximum bladder capacity), followed by SonoVue injection, followed by continuous instillation of saline until voiding	Sensitivity: 100% Specificity: 84% Agreement in grading of VUR severity: 100% No urethral abnormalities detected with either VUS or VCUG No adverse events or procedural complications
Kljucevsek, Acta Paediatr. 2012	66 pts with UTI or bacteriuria 35 M/ 31 F 5 days-1 year	Prospective, within-patient VCUG On-site, blinded, independent (2 readers) for detection of VUR Low-MI (operated at 0.06-0.1) harmonic imaging	132 renal units (2 per patient) Sensitivity/ specificity for detection of VUR Agreement in grading VUR Monitoring for adverse events	1.0 mL Pre-filling of bladder with saline (1/2 maximum bladder capacity), followed by SonoVue injection, followed by continuous instillation of saline until voiding	Sensitivity: 100% Specificity: 77.5% Agreement in grading of VUR severity: 68.8% No adverse events or procedural complications

Reference	Patients M/F Age range	Study Design Truth Standard Image evaluation VUS imaging protocol	Sample size Endpoints	SonoVue dose Administration scheme	Results
Kis, Pediatr Nephrol. 2010	183 pts with UTI, pelvicalycea dilatation or follow-up of known VUR 94 M/89 F 2 days to 44 months	Prospective, within-patient VCUG On-site, blinded, independent (2 readers) for detection of VUR Harmonic imaging, MI: 0.4-0.6	366 kidney-ureter units (2 per patient) Sensitivity/ specificity for detection of VUR Agreement in grading VUR Monitoring for adverse events	1.0 mL With some urine left in the bladder, SonoVue injection, followed by continuous instillation of saline until voiding	Sensitivity: 86% Specificity: 86% Agreement in grading of VUR severity: 67.4% No adverse events or procedural complications
Papadopoulou, Pediatr Radiol. 2009[Error! Bookmark not defined.]	228 pts with UTI, follow-up of know VUR, antenatal urinary tract dilatation, or siblings of pts with VUR 123 M/105 F 6 days to 13 years	Prospective, within-patient VCUG On-site, blinded, independent (2 readers) for detection of VUR (discordant cases reassessed by consensus read) Low-MI (operated at 0.08-0.16) harmonic imaging	463 kidney-ureter units Sensitivity/ specificity for detection of VUR Monitoring for adverse events	1.0 mL Pre-filling of bladder with saline (1/3 maximum bladder capacity), followed by SonoVue injection, followed by continuous instillation of saline until voiding	Sensitivity: 80% Specificity: 77% Agreement in grading of VUR severity: 70.2% No adverse events or procedural complications

2.4.2. Pharmacokinetics

There were no new PK data submitted within current application. The dose of SonoVue to be used for new indication (1 mL) was initially not discussed in-depth. There was only limited justification provided for the proposed dose as the pivotal studies presented were not based on any dose research. The CHMP felt that there was a lot of variability in the indications where Sonovue was used, the dose of SonoVue used (0.5 -4.8 mL) and the final concentration of SonoVue (0.2 – 10 %) to draw reliable conclusions from the supportive studies. Therefore the SonoVue dose proposed in children was asked to be discussed in depth. Further justification was provided during the procedure. The safety and tolerability of a SonoVue dose of 1 mL, were excellent in all studies included in the dossier. The applicant provided several tables to justify this choice of dose. In particular, an estimate of the volume to be injected that would be based on a SonoVue dose equal to 1% of the theoretical bladder volume would lead to dose values between 0.75 and 2.4 mL for children between 6 months and 6 years. So although the choice of a 1 mL dose was not considered perfectly justified, the CHMP considered it reasonable to accept it because it is **a very well tolerated dose which gives satisfactory diagnostic performances**.

2.4.3. Pharmacodynamics

There we no new data submitted regarding pharmacodynamics and this was considered acceptable by the CHMP.

2.5. Clinical efficacy

The MAH provided:

- **A summary and discussion of four well-controlled studies** in the literature supporting the use of SonoVue in the proposed indication;
- **A meta-analysis of data** from the four well-controlled studies that presented essential diagnostic performance data and qualify based on the Quality Assessment Tool for Diagnostic Accuracy (QUADAS) guidelines;
- Presentation and discussion of data from **seven supportive clinical studies** in the literature that assessed the effectiveness of VUS with SonoVue in the evaluation of VUR.

2.5.1. Main studies

2.5.1.1. Main study 1: Wong et al. (European Journal of Paediatrics, 2014)

Study design and objectives

Wong and colleagues performed a prospective study of VUS with SonoVue using VCUG as the reference standard in children under the age of 5 years after a first episode of urinary tract infection.

The aim of this study was to assess the diagnostic performance of VUS with SonoVue versus VCUG (referred to in this paper as micturating cystourethrography or MCU) for the detection and grading of VUR and urethral abnormalities. Additional aims included the assessment of safety and duration of the VUS examinations, and the reliability of VUS in the diagnosis of VUR by means of inter-reader agreement.

Methods

Study population

All children below the age of five years referred for evaluation of VUR following their first episode of UTI between September 2010 and February 2012 were included. Those with active urinary tract infection or known contraindications to the ultrasound contrast agent were excluded.

Dose and mode of administration

Before VUS started, the urinary bladder was pre-filled with pre-warmed normal saline until one third of age-expected maximum bladder capacity [(age in years+2)×30 in milliliters] had been reached to prevent strong posterior acoustic shadowing caused by high intravesical concentration of contrast. Thereafter, 1.0 mL of SonoVue suspension was administered into the bladder and was followed by continuous instillation of normal saline until the child started to void. Immediately following the first voiding, the bladder was refilled with normal saline for a second voiding cycle, however no additional SonoVue was administered.

Image acquisition

The investigators performed sequential VUS with SonoVue and VCUG examinations in the same imaging session. For VUS, imaging was performed using low mechanichal index (MI) (operated at MI= 0.05-0.07) harmonic imaging. For urethral imaging, interscrotal or transperineal ultrasound scanning was performed with the child in the supine position, during the voiding phase.

VCUG was performed immediately following the VUS exam by an experienced operator. After the saline and SonoVue was drained from the bladder, the radiographic contrast agent was instilled using the same catheter.

Image evaluation

VUS and VCUG were acquired and assessed by two independent groups of operators:

- Three experienced paediatric radiologists and a senior sonographer, blinded to the VCUG results, performed and assessed VUS exams;
- Two senior radiologists, blinded to the results of the VUS exam, performed and assessed the VCUG exam.

The presence of VUR was identified and any urethral findings were assessed. VUR was defined at VUS as the presence of echogenic microbubbles in the ureters or renal pelvis, and at VCUG as the opacification of the upper urinary tract. The grading of VUR was determined according to the **International System of Reflux Grading in VCUG** and **the similar 5-tier system in VUS** established by Darge and Troeger. Each group of operators evaluated the presence and grading of reflux, and in case of discordance, the final decision was made after reviewing the recorded exam. Inter-observer reliability of VUS in the diagnosis of VUR was assessed by means of an independent review 6 months after study completion by a senior sonographer and a paediatric radiologist who were blinded to clinical data and prior assessments of VUR.

Safety assessments

Patients were monitored for adverse events (adverse reactions to contrast agents, procedural complications, or infection) by immediate observation after the procedure and by telephone follow-up at 2 days.

Data analysis and statistical methods

Pelvi-ureter units (UU) were used as the statistical unit for the analysis. The presence and grade of VUR was assessed and inter-observer agreement with the prior interpretation was tested with Cohen's kappa

statistic. Differences in procedural duration for the two examinations were assessed with the Wilcoxon signed-rank test.

Results

Demographics

In total, 31 patients (23 boys and 8 girls) with a median age of 6 months (range: 2-48 months) were included. A total of 62 UU were available for analysis.

Diagnostic performance

A summary of the diagnostic performance results of VUS from the study by Wong et al. is provided in **Table** C. VCUG detected reflux in 5 of 62 UU. VUS with SonoVue detected reflux in a total of 14 UU, including all five UU detected at VCUG (sensitivity of 100%; specificity of 84%). Concordance between the 2 imaging modalities for confirming or excluding the presence of VUR was 85.5% (53/62 UU). There was also good agreement between VCUG and VUS with SonoVue for grading VUR in the 5 diseased UU detected by both methods. All 5 reflux units (grade III [n=1], grade IV [n=4]) were graded concordantly. Grading of reflux for the 9 UU in 7 patients with VUR detected at VUS only was grade I (n=1), grade II (n=4), grade III (n=2) and grade IV (n=2). Among these 9 reflux units, 4 units occurred in 2 patients who had bilateral reflux, with grades II and III in 1 patient and grades III and IV in another.

Table C Wong et al., 2014: Summary of diagnostic performance results for detection of VUR in children on a per-UU basis

	VUS +	**VUS -**	**Total**
VCUG +	5	0	5
VCUG -	9*	48	57
Total	14	48	62

* 1 VUR Grade I, 4 VUR Grade II, 2 VUR Grade III, 2 VUR Grade IV

There was perfect inter-observer agreement in diagnosing VUR at VUS; Cohen's kappa statistics was 1.00 ($p<0.001$).

Imaging of the urethra at VUS was technically successful in all patients. No urethral abnormality was detected in the patients by either VCUG or VUS. The mean duration of the VCUG and VUS examinations was comparable (12.39 and 11.13 minutes, respectively; p=0.277). For VCUG, mean fluoroscopic screening time was 0.71 minutes, and for the ultrasound study the mean duration of preliminary (unenhanced) renal and bladder imaging was 6.35 minutes.

No adverse events or procedural complications following VUS and VCUG were observed.

Conclusion

In the study published by Wong et al, positive results (detection of reflux) were found in only 5 out of 62 statistical units with the reference diagnostic test (VCUG). The apparent agreement between VCUG and VUS with SonoVue was overall good but only based on the exclusion of VUR due to the low prevalence rate of patients in the sample. There were nine cases of disagreement between the two methods. It leads to a very low specificity for Sonovue VUS method when one considers VCUG as the standard of truth.

2.5.1.1.1. Main study 2: Kljucevsek et al. (Acta Paediatrica, 2012)

Study design and objectives

Kljucevsek and colleagues performed a prospective study comparing VUS with SonoVue versus VCUG as the reference standard for the detection of VUR in infants during the first year of life.

Methods

Study population

All children up to one year of age referred for evaluation of VUR were eligible for this study; children were prospectively enrolled between February and July 2010. Urinary tract US and VUS were performed in accordance with the accepted indications for VCUG in the author's center, followed immediate by VCUG using the same urinary catheter. Sixty-six children were enrolled in the study; 39 of the children were referred for examination after a febrile UTI, 8 because of bacteriuria, and 19 because of an isolated urinary tract abnormality seen at US.

Dose and mode of administration

For the VUS exam, the urinary bladder was first drained using a 6F or 8F catheter, then filled with pre-warmed normal saline to half of predicted bladder capacity [capacity = 10 mL/kg body weight]. At this point, 1.0 mL of SonoVue® was administered intravesically through the catheter, after which the remaining saline was administered under hydrostatic pressure to predicted bladder capacity.

Image acquisition

All children enrolled in the study underwent examinations by unenhanced US, VUS and VCUG in the same imaging session. Urinary tract US was performed prior to VUS and VCUG to assess the location and morphology of the kidneys and bladder, and to evaluate the degree of ureteropelvicalyceal dilitation.

For VUS, each kidney was scanned with the child in the prone position. US imaging was performed using low-MI (operated at MI=0.06-0.10) harmonic imaging. The exam was continued until the child had voided completely or until the presence or absence of VUR had been assessed.

VCUG was performed in the same imaging session using the same catheter. A radiographic contrast agent was diluted with normal saline heated to body temperature to an iodine concentration of approximately 85 to 105 mgI/mL (contrast media to saline ratio of approximately 1:3) and instilled into the bladder at the same hydrostatic pressure as the saline with ultrasound contrast agent. A pulsed fluoroscopy technique was used to evaluate children for possible VUR.

Image evaluation

All examinations were recorded and thereafter evaluated and interpreted independently by two radiologists. Discordant cases were jointly reassessed by both radiologists, and the VUR grade was determined by consensus. VUR grading at VUS was assessed by using the modified Kenda's 3-point scale. VUR identified at VCUG was graded using the standard 5-point international scale.

Safety assessments

Monitoring of patients for adverse events or procedural complications by the referring nephrologist for 48 hours following VUS and VCUG.

Data analysis and statistical methods

Pelvi-ureter units (UU) were used as the statistical unit for the analysis. The sensitivity and specificity of VUS for the detection of VUR were calculated based on findings at VCUG.

Results

Demographics

The 66 infants examined included 35 boys and 31 girls between 5 days and 1 year of age (mean age of 5.06 months and median of 4 months). A total of 132 UU were available for analysis.

Diagnostic performance

VCUG identified VUR in 16/132 (12%) of UU examined, while VUS detected VUR in 42/132 (32%) UU, including all the UU with reflux identified at VCUG. Using VCUG as the reference standard, the sensitivity of VUS with SonoVue for detection of VUR was 100%, with a specificity of 77.5%.

A summary of the diagnostic performance results VUS from the study by Kljucevsek et al. is provided in **Table D**.

Table D: Kljucevsek et al., 2012: Summary of diagnostic performance results for detection of VUR in children on a per-UU basis

	VUS +	**VUS -**	**Total**
VCUG +	16	0	16
VCUG -	26*	90	116
Total	42	90	132

* 19 VUR Grade II and 7 Grade III, based on the 3 point scale of Kenda.

VUS and VCUG agreed for grading of VUR in 11 of the 16 abnormal UU, including six graded as II-III at VCUG (i.e., VUS Grade II), and five graded as IV-V at VCUG (i.e., VUS Grade III). All VUR detected by VUS but missed by VCUG were either Grade II (N=19) or III (N=7) on the 3 point scale of Kenda, corresponding with Grades II-III and Grades IV-V, respectively, on the standard international grading scale for VCUG. Ureteropelvicalyceal dilatation was observed in 40/132 UU; in the remaining 92 UU, results were normal. VUR was detected by VUS in 15 of 40 (37.5%) UU with ureteropelvicalyceal dilatation and in 27 of 92 UU (29.3%) without dilatation. The length of each exam depended on the time from the application of the contrast agent into the bladder until the child voided, which was similar on the VUS and VCUG exams. On average, this took 15 minutes. Actual fluoroscopic time for VCUG was less than one minute.

No adverse events or complications were observed in the 48 hours after the imaging procedures.

Conclusions

The 66 infants examined comprised 35 boys and 31 girls between 5 days and 1 year of age (mean age of 5.06 months and median of 4 months). A total of 132 UU were available for analysis. VCUG identified VUR in 16/132 (12%) of UU examined, while VUS detected VUR in 42/132 (32%) UU, including all the UU with reflux identified at VCUG. The study did not provide data confirming that “positive VUS + negative VCUG” cases were true positive cases (confirmed reflux). This raised a question of a high rate of false positive results with VUS.

2.5.1.2. Main study 3: Kis (Paediatric Nephrology, 2010)

Study design and objectives

Kis and colleagues performed a prospective comparative study of VUS with SonoVue versus standard fluoroscopic VCUG in children four years of age or less. The objective of this study was to assess the diagnostic performance of VUS with SonoVue using VCUG as the standard of truth.

Methods

Study population

Children under the age of two, referred for evaluation of VUR at the authors' institution were prospectively enrolled. One hundred eighty-three (183) children were enrolled in the study. Indications for evaluation of VUR included: UTI (N=112), pelvicalyceal and ureter dilatation (N=47), and follow up of known VUR (N=24). Children with duplex kidneys were excluded from the study.

Dose and mode of administration

A 6F-8F catheter was introduced via the urethra under aseptic conditions. With some residual urine left in the bladder, 1.0 mL of SonoVue was administered under ultrasound monitoring, then the bladder was filled slowly with room-temperature saline solution from a plastic bottle placed 100 cm above the examination table.

Bladder volume was calculated according to the maximum bladder capacity [volume in milliliters = (age in years + 2) x 30]. Filling was continued until slight back pressure to the infusion occurred or the child needed to void.

Image acquisition

All children underwent examinations by unenhanced US, VUS and VCUG in the same imaging session. VUS was performed using harmonic imaging and MI comprised between 0.4 and 0.6.

Preliminary US was performed to assess renal size and structure and to identify the presence of pelvicalyceal or ureter dilatation. After catheterization, ultrasound monitoring of the bladder and kidneys was performed during the filling phase and voiding in the supine, prone or lateral position. The right and left kidneys and the bladder, lower ureter and retrovesical space were scanned alternatively.

VCUG was performed in the same imaging session using the same catheter. A radiographic contrast agent (300 mgIode/mL) was diluted 1:5 with room temperature normal saline and was instilled into the bladder by drop infusion. Fluoroscopic VCUG was performed using standard techniques.

Image evaluation

The US and X-ray procedures were performed and evaluated independently by 2 expert paediatric radiologists, blinded to the result of the other voiding examination. For both the US and X-ray examination, VUR was defined by the presence of contrast medium in the ureters or the pelvicalcyceal system.

The five point grading scale of Darge and Troeger was used for VUR identified at the VUS exam while the standard 5-point international grading scale was used for VUR identified at the VCUG exam.

Safety assessments

Patients were directly monitored for adverse events in the 6 hours following the imaging procedures. Phone follow-up with parents was extended to the following 24 hours.

Data analysis and statistical methods

Ureter units were used as the statistical unit for analysis. The sensitivity and specificity of VUS for the detection of VUR was calculated based on findings at VCUG. Non-parametric analysis was used for all categorical data. Inter-rater agreement between the two methods for detection of VUR was assessed by the kappa statistic.

Results

Demographics

In total, 183 children (94 boys and 89 girls) with a mean age of 7.6 months (range: 2 days - 44 months) were enrolled. A total of 366 UU were available for analysis.

Diagnostic performance

VCUG identified VUR in 103/366 UU (28.1%), while VUS identified VUR in 126/366 UU (34.4%). VUR was identified by both methods in 89 UU, by VCUG alone in 14 UU and by VUS alone in 37 UU. Using the results of VCUG as the reference standard, the sensitivity of VUS with SonoVue® for detection of VUR was 86% and the specificity was 86%.

A summary of the diagnostic performance results of VUS from the study by Kis et al. is provided in Table E

Of the 14 reflux UU detected only on VCUG, 4 were Grade 1 and 10 were Grade II reflux. Of the 37 reflux

Table E: Kis et al., 2010: Summary of diagnostic performance results for detection of VUR in children on a per-UU basis

	VUS +	**VUS -**	**Total**
VCUG +	89	14#	103
VCUG -	37*	226	263
Total	126	240	366

4 VUR Grade I, 10 VUR Grade II

* 2 VUR Grade I, 26 VUR Grade II, 2 VUR Grade III, 7 VUR Grade IV

UU identified only at VUS, 2 were Grade I, 26 were Grade II, 2 were Grade III, and 7 were Grade IV. Inter-rater agreement between VUS and VCUG for the presence of VUR was considered good (κ= 0.68); agreement for VUR grading was moderate (κ=0.54). The mean duration of the VUS exam was 11 min (range: 8-15 minutes). Overall exam time for VCUG was not reported; mean fluoroscopic imaging time during VCUG was 62 seconds (range: 21-120 seconds).

No adverse events or complications were observed during the 24 hours following the imaging procedures.

Conclusions

A total of 183 children (94 boys and 89 girls) with a mean age of 7.6 months (range: 2 days - 44 months) were enrolled. Data from 366 UU were available for analysis. VCUG identified VUR in 103/366 UU (28.1%), while VUS identified VUR in 126/366 UU (34.4%). VUR was identified by both methods in 89 UU, by VCUG alone in 14 UU and by VUS alone in 37 UU. Using the results of VCUG as the comparator, the sensitivity of VUS with SonoVue for detection of VUR was 86% and the specificity was 86%. This sensitivity was still considered good but lower than in the previous articles while there were greater number of patients included in the current study (366 UU here versus 132 and 62 UU in Main study 1 and Main study 2, accordingly). In the observed cases of discrepancies, it was surprising that the reference method VCUG could have missed 7 cases of grade IV (37 reflux UU identified only at VUS : 2 were classified as grade I, 26 as grade II, 2 as grade III, and 7 as grade IV). The 14 reflux UU detected only on VCUG were classified as grade I (n=4) and grade II reflux (n=10). The kappa values for the CE-VUS and VCUG between-readers agreement were not very good, in particular for the VUR grade (Inter-rater agreement between VUS and VCUG for the presence of VUR was considered good (κ= 0.68); agreement for VUR grading was moderate (κ=0.54)).

2.5.1.3. Main study 4: Papadopoulou et al. (Paediatric Radiology, 2009)

Study design and objectives

Papadopoulou and colleagues performed a prospective study comparing VUS with SonoVue versus VCUG for the identification and evaluation of VUR.

The specific aim of this study was to assess the diagnostic performance of VUS with SonoVue, using VCUG as the reference standard.

Methods

Study population

Children referred for evaluation of VUR were enrolled in this study in a consecutive manner. Indications for evaluation of VUR included: UTI (164 children), follow-up of VUR (40 children), antenatal urinary tract dilatation (15 children), sibling of child with confirmed VUR (9 children).

Dose and mode of administration

A 6F-8F catheter was introduced into the bladder under sterile conditions. The bladder was emptied of urine, after which it was filled to approximately one third of predicted total volume [(age in years + 2) x 30] with body temperature saline. Immediately afterward, 1.0 mL of SonoVue was administered intravesically through the catheter, after which the bladder was filled with normal saline until the child had the urge to micturate. Immediately following the first voiding, the bladder was refilled with normal saline for a second voiding cycle, however no additional SonoVue was administered.

Image acquisition

The investigators performed sequential VUS with SonoVue and VCUG examinations in the same imaging session.

Preliminary unenhanced US was performed to evaluate renal size and structure and to identify the presence of pelvicalyceal or ureter dilatation. VUS included alternate imaging of the bladder and kidneys with the patient in the supine and prone position during bladder filling and voiding. VUS was performed using low-MI (operated at MI=0.08-0.16) harmonic imaging.

VCUG was performed using intermittent pulsed digital fluoroscopy immediately following the VUS exam. Using the same catheter, the empty bladder was filled with a 1:3 solution of iodinated contrast medium (300 mgI/mL) in body temperature normal saline. As with VUS, two cycles of filling and voiding were recorded.

Image evaluation

All examinations were recorded digitally and interpreted independently at the end of the session by two expert radiologists without knowledge of the results of previous reflux examinations. Discordant cases were assessed together to achieve consensus. At VUS, the presence of VUR was defined as the presence of microbubbles in the ureter or pelvicalyceal system. The standard 5-point scale was used to grade any VUR detected. At VCUG, the presence of contrast medium in the ureter or pelvicalyceal system was considered diagnostic of VUR, which was graded according to the five-point international scale.

Safety assessments

Patients were directly monitored for adverse events in the 6 hours following the imaging procedures. Phone follow-up with parents was extended to the following 24 hours.

Data analysis and statistical methods

Pelvi-ureter units (UU) were used as the unit of analysis. Differences in categorical variables were tested using the chi-squared test while differences between continuous variables were tested with the students *t*-test. Concordance in findings for the presence or absence of VUR was determined using the kappa coefficient.

Results

Demographics

A total of 228 children (123 boys, 105 girls) enrolled in consecutive fashion. The mean age was 17.6± 23.1 months, with a range of 6 days to 13 years. A total of 463 kidney-ureter units (UU) evaluated; 222 children had 2 kidneys and ureters, 3 children had a unilateral duplex kidney, 2 had bilateral complete duplex kidneys, and 1 child had a single solitary kidney. The mean bladder volume determined for the total population was 99.65±72.41 mL and the estimated dose of SonoVue administered per child was 1.03±0.3 mL.

Diagnostic performance

The VCUG exam identified VUR in 71/463 UU (15.3%) UU, while the VUS exam identified reflux in 147/463 UU (31.7%). Reflux was identified by both methods in 57 UU (12.3%). Using results from the VCUG procedure as the reference standard, the sensitivity and specificity of VUS with SonoVue® in detecting VUR were 80% and 77%, respectively.

A summary of the diagnostic performance results of VUS from the study by Papadopoulou et al. is provided in **F**.

Concordance between the two exams for the presence or absence of VUR was 77.5% (359/463 UU; κ=0.40). Overall of the 161 UU with reflux identified on either or both exams, 90 (56%) were detected only at VUS. Reflux that was missed by VCUG tended to be of higher grades [Grade I (2), Grade II (65), Grade III (19), Grade IV (4)] than reflux missed by VUS [Grade I (8), Grade II (5), Grade III (1)].

Table F: Papadopoulou et al., 2009: Summary of diagnostic performance results for detection of VUR in children on a per-ureter basis

Table F: Papadopoulou et al., 2009: Summary of diagnostic performance results for detection of VUR in children on a per-ureter basis

	VUS +	VUS -	Total
VCUG +	57	14#	71
VCUG -	90*	302	392
Total	147	316	463

8 VUR Grade I, 5 VUR Grade II, 1 VUR Grade III

* 2 VUR Grade I, 65 VUR Grade II, 19 VUR Grade III, 4 VUR Grades IV or V

The duration of VUS, including pre-contrast US and catheterization time was approximately 15-20 minutes.

No adverse events or complications were observed during the 24 hours following the imaging procedures.

Conclusions

A total of 228 children (123 boys, 105 girls) were enrolled in a consecutive way. The mean age was 17.6 ± 23.1 months, with a range of 6 days to 13 years. A total of 463 UU was evaluated (222 children had 2 kidneys and ureters, 3 children had a unilateral duplex kidney, 2 had bilateral complete duplex kidneys, and 1 child had a single solitary kidney). The VCUG examination identified VUR in 71/463 UU (15.3%) UU, while the VUS examination identified reflux in 147/463 UU (31.7%). Reflux was identified by both methods in 57 UU (12.3%). Using results from the VCUG procedure as the reference standard, the sensitivity and specificity of VUS with SonoVue in detecting VUR were 80% and 77%, respectively. The results obtained with both techniques disagree in a lot of cases (22.5 %) in grading the reflux. It was not understood why the reference method did not identify reflux of higher grade: reflux that were missed by VCUG tended to be of higher grades [Grade I (2), Grade II (65), Grade III (19), Grade IV (4)] than reflux missed by VUS [Grade I (8), Grade II (5), Grade III (1)].

2.5.1.4. Summary of main efficacy results

All four studies selected by the MAH as pivotal to support current application were performed in paediatric patients (age range: 2 days-13 years) referred for VCUG for suspected VUR, or follow-up of VUR, i.e., involved patients representative of **the population in which VUS with SonoVue is intended to be used**:

- The first peak of UTI is in the **first year of life**, and VUR is more prevalent in younger children. All studies included patients in their first year of life, even after their first episode of febrile UTI;
- The second peak of UTI occurs between the **ages of 2 to 4 years old** during toilet training, and three studies focused on children below 5 years of age, including patients with UTI, patients with imaging ultrasound findings suspected for VUR, and patients on follow-up for known VUR;
- The prevalence of VUR in children with UTIs decreases with age, and **after the age of 6 years** UTIs are infrequent; however, UTIs are often associated with dysfunctional elimination in older children. One study included patients older than 6 years of age.

Overall, 508 paediatric patients were enrolled in the pivotal studies.

In all studies, VUS was followed by VCUG during the same session. Both imaging procedures were well tolerated, and no adverse events or complications were reported after patient monitoring for 24-48 hours. All studies used administration of both saline and SonoVue. SonoVue was always injected at the dose of 1.0 mL into a bladder that was partially filled with urine or saline. This is usually done in VUS imaging in order to have better visualization of the microbubbles and avoid a strong dorsal acoustic shadow. At the same time, filling the bladder to the maximum prior to injecting SonoVue would have the disadvantage that low-pressure reflux could be obscured. Moreover, in neonates and infants due to repeated voiding at small bladder filling volume, there would be insufficient time to administer SonoVue and scan the urinary tract. In all studies, the administration of saline followed the administration of contrast, and was continued until the child had the urge to micturate or there was the first slight sign of back pressure to the infusion, so that imaging during voiding could be started.

The following administration scheme of SonoVue and saline is therefore recommended:

- Following bladder emptying of urine, pre- filling of bladder to approximately one third or one half of predicted total volume in mL [(age in years + 2) x 30] with body temperature saline;
- Immediately afterward, administration of 1.0 mL of SonoVue;
- After administration of SonoVue, filling of the bladder with normal saline until the child has the urge to micturate or there is the first slight sign of back pressure to the infusion.
- Immediately following the first voiding, the bladder may be refilled with normal saline for a second cycle of voiding and imaging.

The SonoVue dose was not adjusted based on age, body weight, or body size of the patients. No reports of ineffective imaging or technical artefacts were reported in any of the studies, **even if the same 1.0 mL dose was used in new born, infants and older children**.

Harmonic imaging increases contrast and spatial resolution and also results in a reduction of artifacts. The highest contrast difference between tissue and the SonoVue microbubbles is achieved with low-MI harmonic imaging, in which the tissue is suppressed and the microbubbles become more conspicuous. Three of the four studies used low-MI harmonic imaging (MI comprised between 0.05 and 0.16, according to the different systems used) and reported VUS sensitivities between 80% and 100%, and specificities between 77% and 84%. One study used harmonic imaging and higher MI (0.4-0.6), and VUS sensitivity and specificity were 86%.

VUR Detection

When compared to VCUG, which is the imaging reference standard for assessment of VUR, VUS with SonoVue at 1.0 mL dose provided high sensitivity (80-100%) and specificity (77-86%) for detection of VUR in children.

Most studies emphasize that CE-VUS was able to detect VUR in a higher number of UU than VCUG. Since the radiographic procedure was chosen as the “standard of truth”, all additional VUR cases detected by CE-VUS only decreased the specificity of the procedure. Possible explanations for the apparently higher detection rate of VUR with CE- VUS include the continuous real-time assessment of the urinary tract, which is possible with contrast-enhanced ultrasound but not with VCUG (where an intermittent imaging technique is recommended in order to limit radiation exposure to the patient), and the ability of contrast-enhanced ultrasound to diagnose VUR via the presence of even a small number of microbubbles in the ureter or the renal pelvis.

VUR Grading

When considering the 3 clinical studies in which the same grading system was applied for assessing the severity of VUR, agreement between VUS with SonoVue (1.0 mL) and VCUG for VUR grading was observed in 105 out of 151 (69.5%) diseased UU detected by both methods (**Table** G). Agreement for VUR grading was highest for Grade II (73.6%), Grade III (71.9%), and Grade IV (80.9%).

Discordant finding were more prevalent at lower VUR grades (Grades I and II, 26/67 UU disagreed, or 38.8%) than at more clinically significant grades (Grades III-V, 20/84 disagreed, or 23.8%).

Table G: Agreement between VCUG and VUS with SonoVue for grading of VUR on a per-UU Basis* in the pivotal clinical studies using a 5 point grading scale

		VUS with SonoVue®					
		Grade I	**Grade II**	**Grade III**	**Grade IV#**	**Grade V**	**Total**
VCUG	**Grade I**	2	6	4	2	0	14
	Grade II	1	39	11	1	1	53
	Grade III	0	5	23	4	0	32
	Grade IV#	1	2	2	39	3	47
	Grade V	0	0	0	3	2	5
	Total	4	52	40	49	6	151

* For all UU with VUR detected by both methods.

Papadopoulou et al. used 5-point grading scales but reported agreement combining Grades IV and V together. For this presentation of the data, all Grades IV/V from the Papadopoulou study were assigned to Grade IV.

Conclusions

The VUR detection rate with SonoVue VUS was reported to be almost twice as high as that of the standard method (VCUG). The choice of VCUG as the "standard of truth" was therefore questioned. No data provided within current application supported this fundamental assumption used for analyses. VCUG is a well-established and long used method but in the opinion of the CHMP that does not make it a "standard of truth" as "**standard of truth" is believed to give the true state of a patient or the true value of a measurement** as per *EMA Guideline on clinical evaluation of diagnostic agents (CPMP/EWP/1119/98/Rev.1)*. Consequently, all the results concerning the diagnostic performances (sensitivity, specificity) of the new method (VUS with Sonovue) were questioned. If the "reference" test was not "a standard of truth", it was only possible **to give values of agreement between the results obtained by the two methods**. Agreement results were not very good for the evaluation of the grade of VUR: discrepancies between lower grade (I and II) and higher grades (III, IV and V) were observed in 27 out of 151 (18 %). Therefore **follow-up data** would have been very **useful in obtaining a true classification of subjects in all cases of discrepant results** between both diagnostic modalities. However, the explanations provided by the applicant strongly suggest that the VUS with SonoVue would detect more cases of VUR than the comparator (VCUG).

Meta-analysis of the pivotal studies

To further evaluate and support the efficacy of SonoVue for VUS, a meta-analysis of the four pivotal studies was performed for sensitivity and specificity versus the reference standard, VCUG. Population

composition, study design, analysis methods, quality of data, and reference standards were key elements considered across the studies. All included studies were evaluated based on the **Quality Assessment Tool for Diagnostic Accuracy (QUADAS)** and the relevant study data were extracted and summarized.

The selection process used to confirm the adequacy of the studies for inclusion in the meta-analysis was included in the detailed meta-analysis report containing statistical methodology and results. In brief, a study was included in the meta-analysis if:

- It was a controlled study with prospective enrollment;
- Paediatric patients were referred for VUS for the diagnosis of VUR;
- VCUG was used as the reference standard;
- Cases were reported in absolute numbers of True Positive (TP), True Negative (TN), False Positive (FP), False Negative (FN) results, or stated data adequate to derive this information was available;
- A similar volume of SonoVue was administered for VUS, with similar administration scheme of SonoVue and saline.

A study was excluded from the meta-analysis if it was performed in fewer than 10 patients. Data extraction was performed by one physician and one statistician. Inconsistencies were resolved by discussion and consensus. The following information was extracted from each study:

- First author
- Year of publication
- Journal
- Study population
- Gender
- Mean or median or range of age, whichever available.

In addition, diagnostic performance results were extracted from the included studies.

Study quality and applicability were assessed by using a modified checklist based on the Quality Assessment for Diagnostic Accuracy Studies (QUADAS) guidelines. The modified checklist of questions used to assess study quality and applicability is shown in **Table B**. The total scores (total number of items checked Yes) ranged from 8 to 10 across the studies. After all relevant data from the identified studies were extracted, a **random effect model** was employed to estimate combined sensitivity and specificity, with their 2-sided 95% Confidence Intervals. The analysis end point was sensitivity and specificity, with the unit of analysis reported in the study being either pelvis-ureter unit or kidney-ureter unit (referred as ureter unit or UU thereafter). The overall likelihood ratios were estimated based on the overall sensitivity and specificity derived from meta-analysis. Meta-analysis results were calculated based on the random effect model which formally takes into consideration heterogeneity among the trial results. A Q statistic, asymptotically distributed as a chi-square random variable with n-1 degrees of freedom, was used to test heterogeneity among studies.

Table B: Quality assessment (QUADAS guidelines)

First Author	QUADAS Item										Total Score
	1	2	3	4	5	6	7	8	9	10	
Wong et al.	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	9
Kljucevsek et al.	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9
Kis et al.	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	8
Papadopoulou et al.	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	10

Item 1 = Was the population clinically relevant, defined as a group of patients covering the spectrum of disease that is likely to be encountered in the current or future use of the test?
Item 2 = Was there complete verification by the reference standard?
Item 3 = Was there blinded interpretation of the test results?
Item 4 = Was there consecutive patient selection?
Item 5 = Was there prospective enrollment of patients?
Item 6 = Was there adequate description and quality of the imaging procedure?
Item 7 = Was the quality of the reference test technically adequate?
Item 8 = Was there adequate clinical description of the patient population?
Item 9 = Was the sample size >=35 patients?
Item 10 = Was there adequate reporting of results, including summary and subgroup indices of accuracy?"

Total number of ureter units with disease, TP, TN, FP, and 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. Forest plots for sensitivity/specificity were created to graphically display sensitivity/specificity and their 95% confidence intervals from the individual studies and the overall pooled results, along with the relative weight of each study.

Population characteristics

Overall, 508 paediatric patients, with a total of 1,023 ureter units, were included in the four studies. Patients in the studies ranged in age from 2 days to 13 years, and slightly more than half of the patients were male (N=275, 54.1%). The ultrasound Mechanical Index settings used in these studies were all <0.6, ranging from 0.05 to 0.6. Key study and population characteristics of the four studies are displayed in **Table C**.

Table C: Key study and population characteristics from the individual studies

Study	Patients (N) M (%) / F (%) Ureter Units	Age Range / Mean	Population	SonoVue Volume (mL)
Wong et al., Eur J Pediatr. 2014	31 pts M: 23 (74%) / F: 8 (26%) 62 units	2 to 48 months / mean not reported	Children <5 years of age, after their 1st episode of urinary tract infection	1.0
Kljucevsek et al., Acta Paediatr. 2012	66 pts M: 35 (53%) / F: 31 (47%) 132 units	5 days to 1 year / 5.06 months	Children with proven febrile urinary tract infection (39), bacteriuria (8), isolated abnormal urinary tract ultrasound (19)	1.0
Kis et al., Pediatr Nephrol. 2010	183 pts M: 94 (51%) / F: 89 (49%) 366 units	2 days to 44 months / 7.6 months	Children with urinary tract infection (112), dilatation of the uretero-pelvicalyceal system (47), follow-up of VUR (24)	1.0

Table C: Key study and population characteristics from the individual studies

Papadopoulou et al., Pediatr Radiol. 2009	228 pts M: 123 (54%) / F: 105 (46%) 463 units	6 days to 13 years / 17.6±23.1 months	Children with urinary tract infection (164), follow-up of VUR (40), antenatal urinary tract dilatation (15), sibling of a child with VUR (9)	1.0

M = male; F = female

Individual study results

Using VCUG as the reference standard, in the 4 studies the sensitivity of VUS with SonoVue for detecting VUR ranged from 80% to 100%, while the specificity ranged from 77% to 86%. Diagnostic performance results from the four studies, with ureter unit as the analysis unit, are provided in **Table D**.

Table D: Diagnostic performance results from the individual studies

Study	Total Ureter Units (N)	Ureter Units with Disease (N)	TP (n)	TN (n)	FP (n)	FN (n)	Sensitivity (%)	Specificity (%)
Wong et al., Eur J Pediatr. 2014	62	5	5	48	9	0	100	84
Kljucevsek et al., Acta Paediatr. 2012	132	16	16	90	26	0	100	78
Kis et al., Pediatr Nephrol. 2010	366	103	89	226	37	14	86	86
Papadopoulou et al., Pediatr Radiol. 2009	463	71	57	302	90	14	80	77

Results from meta-analysis

Based on the combined data, VUS with SonoVue displayed a **pooled sensitivity of 89%** (95% CI: 80% to 97%), and a **pooled specificity of 81%** (95% CI: 76% to 86%). Assessments of heterogeneity by Cochran's Q indicated no significant heterogeneity among studies in sensitivity (p=0.0828) and significant heterogeneity in specificity (p=0.0196). However, due to the small number of studies included in the meta-analysis, no subgroup analysis was performed to explore the heterogeneity in specificity.

Meta-analysis conclusion

The findings of the MAH-conducted meta-analysis of the performance of VUS with SonoVue versus the VCUG considered as the reference test demonstrated a pooled sensitivity of 89% and a pooled specificity of 81% for the detection of VUR.

Figure 1. Forest plot of sensitivity

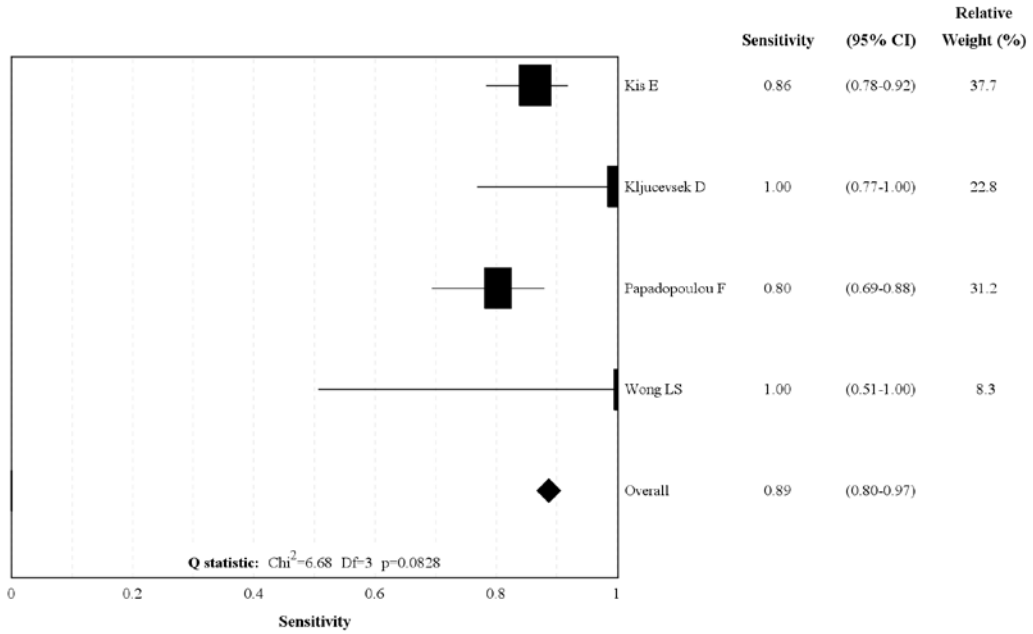
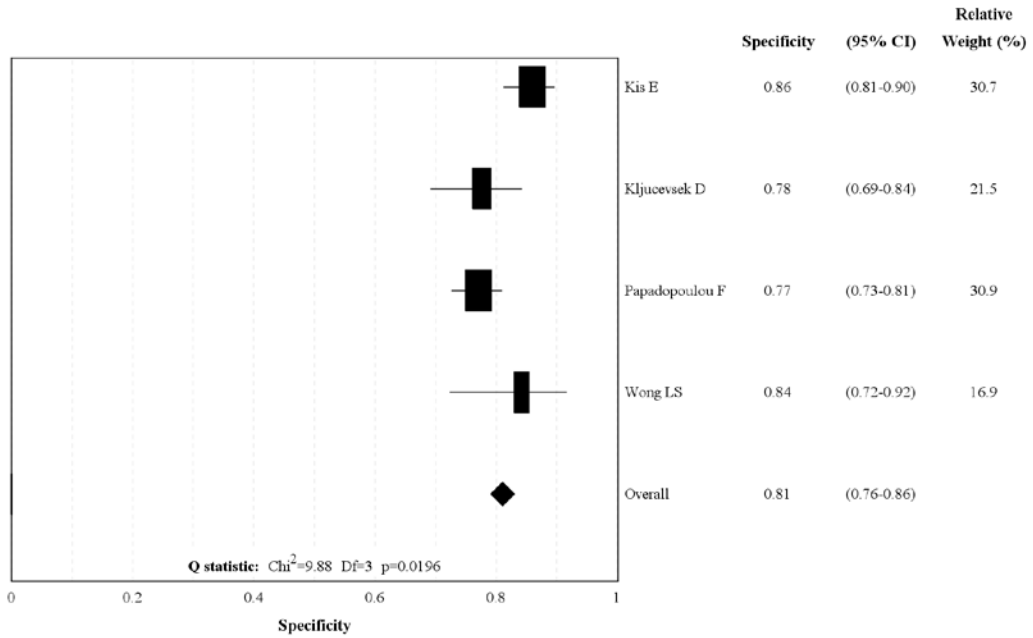


Figure 2. Forest plot of specificity



The meta-analysis provided by the applicant consolidated the individual results but did not give any arguments in favor of the classification of VCUG test as a standard of truth.

Supportive studies

Seven additional published studies reporting on the use of SonoVue and confirming the utility of SonoVue for the evaluation of VUR in children were retrieved in the literature search performed by the Applicant.

Although they did not meet the tough criteria (controlled study of SonoVue in VUS, VCUG truth standard, sensitivity/specificity endpoints, consistent SonoVue dose and administration scheme) required for pivotal publications, they nevertheless directly supported the use of SonoVue in VUS.

These supportive clinical studies are summarized in Table B, below.

Table B: Supportive clinical studies evaluating efficacy of SonoVue for evaluation of VUR in children

Study	**Patients M / F Ureter units (ureter units with VUR[a])**	**age range**	**SonoVue Volume (mL)**	**Diagnostic performance of VUS vs. VCUG (if available) or other efficacy findings**	
				Sensitivity %	**Specificity %**
Ascenti et al., Pediatr Radiol. 2004**Error! Bookmark not defined.**	80 pts (36 M / 44 F) 160 (49)	3 months to 5 yrs	0.5 in 4.5 mL of saline; 2 cycles if needed	100	97.3
Duran et al., Pediatr Radiol. 2012	295 pts (154 M / 141 F) 591 units	13 days- 18 yrs (mean: 27±42 months)	1.0 in 500 mL of saline	High-quality images of the bladder were obtained with SonoVue; the male urethra was well visualized. 137 UU with VUR by VUS.	
Wozniak et al., J Ultrasonog. 2013	*Stage 1*: 80 pts (18 M / 62 F) 161 units (60)	*Stage 1*: 3 months to 17.25 yrs	2.4 in 250 mL saline (babies and infants); 4.8 in 500 mL of saline (older children)[#]	*Stage 1*: 84.5	*Stage 1*: 90.0

Table B: Supportive clinical studies evaluating efficacy of SonoVue for evaluation of VUR in children

Study	Patients M / F Ureter units (ureter units with VUR[a])	age range	SonoVue Volume (mL)	Diagnostic performance of VUS vs. VCUG (if available) or other efficacy findings	
				Sensitivity %	Specificity %
Wozniak et al., J Ultrasonog. 2013	*Stage 2*: 58 pts (14 M / 44 F) 116 units	*Stage 2*: 4 months to 10.17 yrs	2.4 in 250 mL saline (babies and infants); 4.8 in 500 mL of saline (older children)[#]	*Stage 2*: VUR was detected by VUS in 23 children (39.5%) and 31 UU (26.7%). Morphologic assessment of the urethra was possible in all patients.	
Deng et al., J South Med Univ. 2013	36 pts (23 M/ 13 F) 72 units (21)	21 days - 10 yrs	0.2 in every 30.0 mL of saline[##]	100	90.2
Wozniak et al., Pediatr Radiol. 2014	17 pts (1 M / 16 F) 25 units	4 months - 15.7 yrs	2.4	Intraoperative VUS with SonoVue improved overall treatment success and identified UU that would benefit from re-treatment in the same session	

Information obtained through direct contact with the lead author

Incorrectly reported as 0.2 mL in 3 mL saline in the published study. Correct dosing information obtained through direct contact with the lead author.

Following the analysis of data provided in the dossier, VCUG did not detect high grade VUR forms. VCUG test requires the use of a media contrast agent. A dilution effect of the contrast media agent can occur in case of largely dilated pyelic or-ureteral cavities. The dilution effect was considered a satisfactory hypothesis to explain the occurrence of such discordant cases. This effect does not intervene with SonoVue microbubbles which amplify the ultrasound signal at very low concentrations.

2.5.2. Discussion on clinical efficacy

Diagnostic imaging plays an important role in the diagnosis of VUR and the therapeutic management of young patients. The applicant chose **VCUG as the reference standard test for diagnosis of VUR** in line with recommendations from the clinical practice guidelines. VCUG requires x-ray imaging of the

bladder and ureters. VCUG remains the most appropriate, approved and commonly used test to detect or exclude the presence of VUR, for which there is no current alternative. CE-VUS with SonoVue is a procedure similar to VCUG, with use of SonoVue gas-filled microspheres instead of X-ray contrast agents. The requested initially indication was for use in ultrasonography of the excretory urinary tract in paediatric patients **to detect or exclude vesicoureteral reflux.**

Major objection was raised during the procedure as the CHMP considered that based on the available data in the dossier, the interpretation of negative or positive results for identified VUR was quite difficult. It would have a major impact on the clinical therapeutic management of young patients. It was unclear whether **VCUG (the comparator test) lacks sensitivity or if specificity of VUS** was the real issue given that in main studies VUR was detected in more patients with CE-VUS with Sonovue method as compared to reference standard test VCUG. To answer this uncertainty about the sensitivity and specificity values, the MAH was asked **to provide clinical follow-up of the patients** with VUR identified either with VUS or with VCUG. By this way, significance of grading VUR from VCUG and of CE-VUS could be compared. It was considered **not possible to obtain follow-up data from four main studies as this was a literature-based submission** and no follow-up information was available.

The MAH gave plausible reasons for **discordant results between VCUG and VUS**. These reasons were, on the one hand, that VUS allows a continuous acquisition of the urinary tree, unlike VCUG where the acquisition is discontinuous to reduce the burden of exposure to ionizing radiation in young patients, on the other hand that the VCUG can miss of high grade reflux due to a marked dilution effect of the contrast medium in a highly dilated urinary tree. These reasons make it possible to consider that patients with VUS positive results and VCUG negative results are true reflux cases and not false positives. Nevertheless, this did not allow explaining on the dissociations for cases that were VUS negative but VCUG positive. This confirmed that the **VCUG should not to be considered as the "standard of true"** as per *EMA Guideline on clinical evaluation of diagnostic agents (CPMP/EWP/1119/98/Rev.1)* but as the best available comparator method recognized by medical and scientific societies. It was also noted that VCUG was used as reference method in a large number of clinical trials. Nevertheless, the question of the **sensitivity of VUS** with Sonovue was not considered solved and it was not possible to state that a negative result for VUR following the VUS with Sonovue allows the practitioner to exclude a diagnosis of VUR. Therefore, the CHMP agreed that the proposed indication should be restricted for use in ultrasonography of the excretory tract in paediatric patients from newborn to 18 years **to detect vesicoureteral reflux (but not "to exclude VUR")**. In addition, a statement regarding the limitation in the interpretation of a negative results of VUS with Sonovue, was added to the indications (and also described in sections 4.4. and 5.1 of the SmPC).

The CHMP acknowledged that some of the clinical practice recommendations[5] point to the change in the understanding of the standard of care in paediatric patients with known or suspected VUR with CE-VUS replacing in some centres the traditionally performed VCUG (European Federation of Societies for Ultrasound in Medicine and Biology [EFSUMB] 2016). Given that in the opinion of the CHMP the VCUG cannot be considered as the "standard of true", it was concluded that **the use of Sonovue in VUS require additional investigation, in order** to further evaluate the sensitivity and specificity of Sonovue to detect VUR through its impact on patient's management; therefore, in view of a possible change in the understanding of the current standard of care for diagnosing of the VUR and the consequent management of patients, the MAH was requested to conduct and submit the results of a post-authorisation efficacy study (**prospective observational cohort study)** where one year of clinical follow-up data should be provided. The protocol of the study should be submitted to CHMP for agreement.

[5] **Role of Contrast-Enhanced Ultrasound (CEUS) in Paediatric Practice: An EFSUMB Position Statement 2016**; P. S. Sidhu1, V. Cantisani2, A. Deganello1, C. F. Dietrich3, C. Duran4, D. Franke5, Z. Harkanyi6,W. Kosiak7, V. Miele8, A. Ntoulia1, M. Piskunowicz9, M. E. Sellars1, O. H. Gilja; DOI http://dx.doi.org/10.1055/s-0042-110394

2.5.3. Conclusions on the clinical efficacy

Based on the delivered documentation such as:

- A summary and discussion of four well-controlled studies in the literature supporting the use of SonoVue in the proposed indication;
- A meta-analysis of data from the four well-controlled studies that presented essential diagnostic performance data and qualify based on the Quality Assessment Tool for Diagnostic Accuracy (QUADAS) guidelines;
- Presentation and discussion of data from seven supportive clinical studies in the literature that assessed the efficacy of VUS with SonoVue in the evaluation of VUR

and taking into account the arguments provided by the applicant, the CHMP agreed that:

- The studies provided in the dossier were carried out with the most widely used comparator test (VCUG);
- Although the methodology of the four pivotal studies was not optimal, the analyses of data provide sufficient results to support the use of SonoVue in VUS to detect VUR in young patients;
- The results of the 4 pivotal studies were not sufficient to support the recommendation to use the VUS with Sonovue to exclude vesicoureteral reflux;
- Additional evidence of efficacy, in particular the sensitivity and specificity of Sonovue, was needed; the applicant agreed to conduct a post-authorisation efficacy study (PAES) to generate a 1-year follow-up data;
- The radiation exposure concern when using VCUG method is particularly relevant in children because of their ongoing development. There is no radiation exposure when performing VUS with SonoVue.
- The dose of SonoVue proposed for VUS diagnosis is 1 mL. This dose has good diagnostic performances and is very well tolerated.

Clinical follow-up data in patients with VUR identified at either VUS or VCUG could not be provided because this was a literature based submission and no follow-up information was available (nor could be retrieved) in the four pivotal studies selected in support of the application. Therefore applicant committed to carry out a post-authorisation efficacy study (Prospective Observational Cohort Study of SonoVue-Enhanced Ultrasonography in Paediatric Patients with Known or Suspected Vesico-Ureteral Reflux) to provide additional evidence of efficacy in view of a change in the understanding of the standard of care for diagnosing of the VUR and growing role of the CE-VUS in diagnosing VUR as suggested in statements from learned societies in this clinical field. The CHMP agreed that this study should be a condition to the MA. The study will be conducted according to agreed protocol.

In conclusion, the CHMP considered Sonovue to be efficacious for contrast enhanced ultrasonography of the excretory tract in paediatric patients from newborn to 18 years to detect vesicoureteral reflux following intravesical administration.

2.6. Clinical safety

This section presents a summary of the methods and available clinical safety data on the intravesical administration of SonoVue for the indication of VUS.

In addition, the Bracco pharmacovigilance database was reviewed to provide information about any spontaneous reports of adverse events that occurred following intravesical administration of SonoVue in paediatric patients.

Patient exposure

Key safety findings from these 12 studies are summarized below in table K.

Table K - Summary of safety findings from Use of SonoVue for VUS in children

Study	Patients (N) M / F	Age Range	Safety	
			Assessment	Result
Ascenti, Pediatr Radiol. 2004	80 44 / 36	3 months to 5 yrs	- All patients hospitalized for 12 hr after the procedure and monitored for signs of adverse events. - Parents instructed to report any symptom occurring within 24 hr of the procedure	- No adverse effects during the examination - No complications reported during the 24 hr follow-up
Papadopoulou, Pediatr Radiol. 2009	228 123 / 105	6 days to 13 yrs	- Adverse event during the 6 hr clinic period - 24 hour follow-up	- All examinations were well tolerated - No adverse events related to SonoVue administration up to 24 hr after the procedure
Kis, Pediatr Nephrol. 2010	183 94 / 89	2 days to 44 months	- Adverse event during the 6 hr clinic period or at 24 hr follow-up	- No adverse reactions were reported up to 24 hr after the procedure
Duran, Pediatr Radiol. 2012	295 pts 154 / 141	13 days to 18 yrs (mean age: 27.1 ± 42.5 months)	- Patients observed during and after the procedure. - Parents or guardians asked to report any symptoms occurring within 48 hrs of the procedure	- No adverse effects during the examination - No complications or adverse effects during the 48 hr follow-up
Kljucevsek, Acta Paediatr. 2012	66 pts 35 / 31	5 days to 1 yr;	- Adverse events related to SonoVue administration up to 48 hrs	- No adverse events related to SonoVue administration were reported
Woźniak, J Ultrasonog. 2013	*Stage 1:* 80 pts 18 / 62 *Stage 2:* 58 pts 14 / 44	*Stage 1:* 3 months to 17.25 yrs *Stage 2:* 4 months to 10.17 yrs	- Not Specified	- No adverse effects related to the contrast agent were observed *
Deng, J South Med Univ. 2013	36 pts 23 / 13	21 days to 10 yrs	- Monitoring of children during study for acute reactions - 24 hr follow-up to observe late adverse reactions	- No adverse reactions observed during immediate or delayed follow-up

Table K - Summary of safety findings from Use of SonoVue for VUS in children

Study	Patients (N) M / F	Age Range	Safety	
			Assessment	Result
Woźniak, Pediatr Radiol. 2014	17 pts 1 / 16	4 months to 15.66 yrs	- All patients were monitored for adverse reactions to the contrast agent.	- No adverse effects related to the contrast agent were observed
Wong, Eur J Pediatr. 2014	31 pts 23 / 8	2 to 48 months	- Adverse reactions to contrast immediately after the procedure - Delayed monitoring for up to 2 days after the procedure	- No immediate or delayed complications observed - no incidents related to contrast allergy, infection or catheterization
Papadopoulou, Pediatr Radiol. 2014	1,010 pts 447 / 563	Males: Mean age: 1.6 yrs (15 days to 15.5 yrs) Females: Mean age: 2.6 yrs (15 days to 17.6 yrs)	- Vital signs assessed during and for 1 hr after the study - Observation of local effects to skin or tissue - Monitoring for adverse reactions, including allergic reactions - Observation by parents with 7 day telephone follow-up	- No serious adverse events (AEs) - No AEs during or at 1 hour after the exam - Minor AEs in 37 children, most considered related to catheterization - None of the AEs could be directly related to SonoVue administration
Riccabona, Pediatr Radiol. 2012	4,131 intracavitary exams # Gender distribution: 1 male to 3 females	Infant - 18 yrs	- Not Specified	- No adverse effects attributable to the contrast agent; a few complaints reported were considered to be the result of catheterization
Woźniak, Eur J Radiol. 2015	69 pts 21 / 48	1 yr to 13.7 yrs	- Not Specified	- No adverse effects related to the contrast agent were observed *

* Information obtained through direct contact with the lead author

\# Reported for all intracavitary administration of SonoVue (most were intravesical administration)

Adverse events

Overall, among the 12 publications, non-serious minor adverse events were reported in 37 patients. None of the reported adverse events were considered related to SonoVue, but instead were considered related to the catheterization procedure during VUS. All events were reported in one study of 1,010 children. In this single study, adverse events were reported in 19 males (mean age: 2.8 years, range: 1 month - 8.6 years) and 18 females (mean age: 3.4 years, range: 1 month - 8.9 years), or 3.7% of the study population. Dysuria was the most frequently reported symptom, in 26 children. Other reported adverse events included abdominal pain (n=2), anxiety (n=1) and crying (n=1) during micturition, blood and mucous discharge (n=1), increased frequency of micturition (n=1), vomiting (n=1), perineal irritation (n=1), and urinary tract infection 10 days after VUS (n=1). Of the 37 adverse events, 91.9% occurred between 2 and 24 hours after the ultrasound procedure. All reported events were self-limiting and none required hospitalization.

Serious adverse event / deaths / other significant events

None reported in the studies listed above.

Safety in special populations

Not applicable.

Discontinuation due to adverse events

None reported in the studies listed above.

2.6.1. Discussion on clinical safety

Based on data submitted, which included published data, Sonovue was considered to be safe in intravesical administration. No other ultrasound contrast agent is approved in the EU for intravesical administration. Among the 12 publications which reported safety information in over 6200 children exposed to SonoVue after intravesical administration, no adverse effects were attributable to the contrast agent. Non-serious adverse events were reported in 37 patients. None of the reported adverse events were considered related to SonoVue, but instead they were considered related to the catheterization procedure during VUS.

2.6.2. Conclusions on the clinical safety

The CHMP considered Sonovue to be safe in contrast enhanced ultrasonography of the excretory tract in paediatric patients from newborn to 18 years to detect vesicoureteral reflux for intravesical administration.

2.7. Risk Management Plan

The updated RMP version 9.1 was submitted as part of this application. Subsequent revised RMP versions, i.e. versions 9.2, 9.3 and 9.4 were then submitted and assessed throughout this procedure. The below information regarding safety concerns, pharmacovigilance plan and risk minimisation measures relates to RMP version 9.4 which was the latest version of the RMP submitted and assessed.

Safety concerns

Summary of Safety Concerns

Important identified risks	• Anaphylactic/anaphylactoid reactions
Important potential risks	• Potential for off-label use in paediatrics
Missing information	• Pregnant or lactating women • Paediatric patients (intravenous administration and use in echocardiography and vascular Doppler imaging)

Pharmacovigilance plan

No additional pharmacovigilance activities are foreseen. Only routine pharmacovigilance activities apply for all safety concerns.

Risk minimisation measures

Summary Table of Risk Minimisation Measures

Safety Concern	Routine risk minimisation measures	Additional risk minimisation measures
Important identified risk		
Anaphylactic/anaphylactoid reactions	SmPC language (Sections 4.3, 4.4, and 4.8)	None required.
Important potential risk		
Potential for off-label use in paediatrics	SmPC language (Section 4.1)	None required.
Missing information		
Pregnant or lactating women	SmPC language (Section 4.6)	None required.
Paediatric patients (intravenous administration and use in echocardiography and vascular Doppler imaging)	SmPC language (Section 4.2)	None required.

Conclusion

The CHMP and PRAC considered that the risk management plan version 9.4 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the MAH fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

VUR is a common urinary tract abnormality in children characterized by retrograde flow of urine from the bladder into the ureter and toward the kidney, secondary to a dysfunctional vesicoureteral junction. This junction usually acts like a one-way valve which allows urine flow from the ureter into the bladder and closes during micturition, thus preventing back flow. Several pathologic conditions, either congenital or acquired, may be responsible for an ineffective valve function of the vesicoureteral junction. VUR is detected most commonly during voiding, when intravesical pressure rises, but may occur at any time in the voiding cycle, particularly when bladder function is abnormal.

VUR represents a common cause of non-obstructive chronic nephropathy in children. The presence of VUR is associated with **an increased risk of renal scarring after urinary tract infection (UTI)** with potential for nephrovascular hypertension and renal failure. **UTI is the most frequent serious bacterial infection during childhood**, affecting approximately 2% of boys and 8% of girls by the age of 7 years, and represents a frequent indication for diagnostic imaging in children. The prevalence of VUR in children with UTIs is 30% to 40% and increases in children with recurrent UTIs.

3.1.2. Available therapies and unmet medical need

Diagnostic imaging plays a central role in the diagnosis of VUR and decisions about therapeutic options. **The most commonly used, recommended standard test for diagnosing VUR is voiding cystourethrography (VCUG)**, in which x-ray imaging of the bladder and urethra is performed while the bladder fills and empties. To help distinguish the contents of the urinary bladder, a radiopaque iodinated contrast agent is instilled into the bladder via a transurethral catheter. Opacification of the upper urinary tract by the radiographic contrast agent during bladder filling and voiding phases is diagnostic of VUR. VCUG also provides precise anatomic details and optimal assessment of the urethra. The major **disadvantage of VCUG is the associated exposure to ionizing radiation**, which remains substantial even when using a digital technique or intermittent fluoroscopic imaging. The standard mean effective dose of VCUG is approximately 0.4 to 0.9 mSv. **The radiation exposure concern is particularly relevant in children** because of their ongoing development, greater cell turnover, and increased lifetime risk of cancer based on a greater life expectancy when compared with an adult.

Radionuclide cystography (RNC) is also used for diagnosis of VUR. The RNC procedure is similar to VCUG except that rather than a radiopaque contrast material a radiopharmaceutical is instilled into the bladder. When compared to VCUG, radionuclide imaging is characterized by comparable sensitivity and specificity for detection of VUR. RNC carries the advantage of lower gonadal radiation dose. The estimated dose to the ovary is 0.005 to 0.01 mGy, and dose to the testis is even smaller. However, RNC is limited by **poor anatomic resolution** and inability to study the urethra.

Ultrasonography (US) is a non-invasive imaging method that eliminates the risk of ionizing radiation and is widely available. It can detect urinary tract anomalies such as pyeloureteral dilatation, duplex renal system, and ureterocele which may raise the suspicion of VUR; however, **the sensitivity of US for detecting VUR is low**. In a retrospective analysis of 493 infants and children, renal US was compared to VCUG for assessing the presence of VUR. Among the 272 kidneys with VUR, 201 (74%) showed normal findings at US; 28% of the missed refluxing kidneys had grade III or higher reflux.

In **contrast enhanced void urosonography (CE-VUS)**, a microbubble ultrasound contrast agent is administered intravesically for examination of the urinary tract for the purpose of detecting or excluding VUR in paediatric patients. As in VCUG and RNC, the contrast material is administered through a catheter into the bladder and imaging is acquired during filling of the bladder and voiding. The diagnosis of VUR using VUS is done in the following way: when the microbubbles are administered intravesically, any detection of microbubbles in the upper urinary tract (ureter, renal pelvis) indicates the presence and severity of reflux. Results of *in vitro* testing suggest that microbubbles in the ureter do not ascend passively and that reflux pressure is necessary for propagation. This is even more relevant *in vivo* because of a constant counter-flow of urine from the renal pelvis to the bladder. CE-**VUS does not require exposure to ionizing radiation** and has been reported to have diagnostic performance (sensitivity and specificity for the detection/exclusion of VUR) similar to that of VCUG and RNC. In a meta-analysis encompassing 26 studies of VUS using VCUG as a reference method (including a total of 2,341 children with 4,664 pelvi-ureteral units), VUS showed a sensitivity of 90% and a specificity of 92%.

The American Urology Association postulated the need to find "less traumatic methods of determining whether reflux is present" as well as techniques of voiding cystourethrography (VCUG) that results in less radiation exposure[6]. The clinical usefulness of VUS in paediatric patients is acknowledged by the **European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB)** in the 2011 update of guidelines and recommendations on the clinical practice of contrast-enhanced ultrasound[7] and by the **European Society of Paediatric Radiology (ESPR) Uroradiology Task Force**[8]. The **EFSUMB** recently released a dedicated position statement on the use of CE-US in children (2016)[9], in which it is concluded that CE-VUS has proven to be a safe and reliable imaging technique for detecting VUR and urethral abnormalities in children of both genders. Similarly, the American College of Radiology (ACR) recognized that contrast enhanced voiding ultrasonography is a non-ionizing, safe, and reliable method to evaluate for VUR[10]. Based on published literature and the recommendations issued by the scientific societies, **VUS has been increasingly used instead of VCUG** in the clinical assessment of paediatric patients with known or suspected VUR.

3.1.3. Main clinical studies

All **four clinical studies selected from published literature** by the MAH as pivotal to support this application were performed in paediatric patients (age range: 2 days-13 years) referred for VCUG for suspected VUR, or follow-up of VUR, i.e., involved **patients representative of the population in which VUS with SonoVue is intended**. Overall, 508 paediatric patients were enrolled in the pivotal studies. In all studies, VUS was followed by VCUG during the same session. SonoVue was always used intravesically in the dose of 1.0 mL. **No reports of ineffective imaging or technical artefacts** were reported in any of the studies, even if the same 1.0 mL dose was used in new born, infants and older children. This dose was also not adjusted based on body weight, or body size of the patients.

[6] Elder, J.S., Peters, C.A., Arant Jr., B.S., et al. (1997) Pediatric Vesicoureteral Reflux Guidelines Panel Summary Report on the Management of Primary Vesicoureteral Reflux in Children. The Journal of Urology, 157, 1846-1851. http://dx.doi.org/10.1016/S0022-5347(01) 64882-1.

[7] **The EFSUMB Guidelines and Recommendations on the Clinical Practice of Contrast Enhanced Ultrasound (CEUS):** Update 2011 on non-hepatic applications.

[8] **ESPR Uroradiology Task Force and ESUR Paediatric Working Group—Imaging recommendations in paediatric uroradiology**, Part V: childhood cystic kidney disease, childhood renal transplantation and contrast-enhanced ultrasonography in children. Pediatr Radiol (2012) 42:1275–1283; DOI 10.1007/s00247-012-2436-9.

[9] **Role of Contrast-Enhanced Ultrasound (CEUS) in Paediatric Practice: An EFSUMB Position Statement 2016**; P. S. Sidhu1, V. Cantisani2, A. Deganello1, C. F. Dietrich3, C. Duran4, D. Franke5, Z. Harkanyi6,W. Kosiak7, V. Miele8, A. Ntoulia1, M. Piskunowicz9, M. E. Sellars1, O. H. Gilja; DOI http://dx.doi.org/10.1055/s-0042-110394

[10] ACR Appropriateness Criteria urinary Tract Infection- Child; J Am Coll Radiol 2017; 14: S362-S371.

A MAH conducted also **a meta-analysis of data from the four main studies** that presented essential diagnostic performance data and qualify based on the Quality Assessment Tool for Diagnostic Accuracy (QUADAS) guidelines.

3.2. Favourable effects

When compared to VCUG, which is the imaging standard for assessment of VUR, VUS with SonoVue at 1.0 mL dose provided high **sensitivity (80-100%) and specificity (77-86%) for detection of VUR in children** in four pivotal clinical studies as reported by the applicant.

When considering the three of these clinical studies in which the same grading system was applied for assessing the severity of VUR, **agreement between VUS with SonoVue (1.0 mL) and VCUG for VUR grading was observed in 105 out of 151 (69.5%) pelvi-ureter units (UU)** detected by both methods. Agreement for VUR grading was highest for Grade II (73.6%), Grade III (71.9%), and Grade IV (80.9%).

The findings of the meta-analysis of the performance of VUS with SonoVue versus the VCUG considered as the reference test **demonstrated a pooled sensitivity of 89% and a pooled specificity of 81% for the detection of VUR**.

CE-VUS with SOnovue has been reported to have diagnostic performance (sensitivity and specificity for the detection of VUR) similar to that of VCUG and RNC.

Contrary to standard diagnostic methods used for detection of VUR, VCUG and RNC, **CE- VUS does not require exposure to ionizing radiation** which is of particular importance in paediatric patients.

3.3. Uncertainties and limitations about favourable effects

The SonoVue dose was not adjusted based on age, body weight, or body size of the patients. However **no reports of ineffective imaging** or technical artefacts were reported in any of the studies, even if the same 1.0 mL dose was used in new born, infants and older children.

VCUG was considered a well-established and long-used method but questioned being **a "standard of truth"**. Therefore **the results concerning the diagnostic performances (sensitivity, specificity) of the new method might be impacted and should be interpreted with caution**. If the "reference" test was not "a standard of truth", it was **only possible** to give **values of agreement between the results obtained by the two methods**. Agreement results were not very good for the evaluation of the grade of VUR: discrepancies between lower grade (I and II) and higher grades (III, IV and V) were observed in 27 out of 151 (18 %). Therefore follow-up data would have been very useful in obtaining a true classification of subjects in all cases of discrepant results between both diagnostic modalities.

The VUS **detection rate with SonoVue VUS was almost twice as high** as that of the standard method: VCUG. Since the radiographic procedure was chosen as the "standard of truth", all additional VUR cases detected by CE-VUS **only decreased the specificity of the procedure**. Possible explanations for the apparently higher detection rate of VUR with VUS include the continuous real-time assessment of the urinary tract, which is possible with contrast-enhanced ultrasound but not with VCUG (where an intermittent imaging technique is recommended in order to limit radiation exposure to the patient), and the ability of contrast-enhanced ultrasound to diagnose VUR via the presence of even a small number of microbubbles in the ureter or the renal pelvis.

It was **unclear whether VCUG (the comparator test) lacks sensitivity or if specificity of VUS was the real issue** given that in main studies VUR was detected in more patients with CE-VUS with Sonovue method as compared to reference standard test VCUG.

It was also not possible to state that a negative result of VUS allows the practitioner **to exclude a diagnosis of VUR** given that sensitivity of VUS with Sonovue to detect VUR was questioned as **VCUG could not be considered as "standard of truth" and no clinical follow-up data in patients with VUR identified at either VUS or VCUG was available**. Therefore, the indication was adapted to take into consideration these limitations as follows: "*SonoVue is indicated for use in ultrasonography of the excretory tract in paediatric patients from newborn to 18 years **to detect** vesicoureteral reflux. For the limitation in the interpretation of a negative urosonography, see section 4.4. and 5.1.*"

3.4. Unfavourable effects

The safety of SonoVue after intravesical administration was based on evaluation of published literature involving use of SonoVue in over 6000 paediatric patients (age range 2 days to 18 years), as reported in the published literature. VUS with Sonovue was well tolerated, and no adverse events or complications were reported after patient monitoring for 24-48 hours. Non-serious minor adverse events were reported in 37 patients.

3.5. Uncertainties and limitations about unfavourable effects

None of the reported adverse events were considered related to SonoVue, but instead they were considered to be related to the catheterization procedure during VUS.

3.6. Benefit-risk assessment and discussion

The studies provided in the dossier were carried out with the most widely used comparator test (VCUG). **The "standard of true" for diagnosing VUR is currently not clear**. The VCUG is currently considered as the best reference method for detection/exclusion of VUR. However its use is associated with radiation exposure. The radiation exposure concern when using VCUG method is particularly relevant in children because of their ongoing development. VUS method has advantage of **no such radiation exposure**.

CE-VUS with Sonovue has been reported to have diagnostic performance (sensitivity and specificity for the detection of VUR) similar to that of VCUG and RNC. Comparisons have been made against VCUG, and in these comparisons **the concordance between SonoVue-enhanced US and VCUG was considered to be low**, and lower even when grading of the reflux is studied.

Although the methodology of the four pivotal studies was not optimal, the analyses of data provide sufficient reassurance to support the use of SonoVue in VUS to detect VUR in young patients. The results of the four pivotal studies were however not sufficient to support the recommendation to use the VUS with Sonovue and **to exclude VUR** as it was not possible to state that the negative result with VUS allows the practitioner to exclude the diagnosis of VUR.

It appears that the radiation exposure associated with the use of VUCG and a positive diagnostic result from a SonoVue-enhanced US are sufficient to both justify an invasive procedure for the detection of VUR and to omit further investigations when reflux is detected.

The fact that Sonovue in CE-VUS is used "off-label" in the EU was acknowledged as well as the fact that some of the clinical practice recommendations[11] point to the change in the understanding of the standard

[11] **Role of Contrast-Enhanced Ultrasound (CEUS) in Paediatric Practice: An EFSUMB Position Statement 2016**; P. S. Sidhu1, V. Cantisani2, A. Deganello1, C. F. Dietrich3, C. Duran4, D. Franke5, Z. Harkanyi6,W. Kosiak7, V. Miele8, A. Ntoulia1, M. Piskunowicz9, M. E. Sellars1, O. H. Gilja; DOI http://dx.doi.org/10.1055/s-0042-110394

of care in paediatric patients with known or suspected VUR with CE-VUS replacing in some centres the traditionally performed VCUG (European Federation of Societies for Ultrasound in Medicine and Biology [EFSUMB] 2016).

Given the VCUG in the opinion of the CHMP cannot be considered as the "standard of true", and no clinical follow-up data in patients with VUR identified at either VUS or VCUG could be provided because this was a literature based submission, it was considered that **the use of Sonovue in VUS require additional evidence of efficacy**. Therefore, in view of a possible change in the understanding of the current standard of care for diagnosing of the VUR and the consequent management of patients, the MAH was requested to conduct and submit the results of a post-authorisation efficacy study (prospective observational cohort study) where one year of clinical follow-up data should be provided. An accurate assessment of the impact on patient management should be done by using appropriate questionnaires. The protocol of the study should be submitted to CHMP for agreement. It was agreed that this post-authorisation efficacy study (PAES) is a condition to the marketing authorisation and is reflected therefore in the Annex II. The clinical study report should be provided by 2Q 2020.

The dose of SonoVue proposed for VUS diagnosis is 1 mL. This dose has good diagnostic performances and is very well tolerated.

3.7. Conclusions

The overall B/R balance of SonoVue was considered positive in the proposed revised indication associated with a new route of administration for intravesical use:

Ultrasonography of excretory urinary tract

SonoVue is indicated for use in ultrasonography of the excretory tract in paediatric patients from newborn to 18 years to detect vesicoureteral reflux. For the limitation in the interpretation of a negative urosonography, see section 4.4. and 5.1.

4. Recommendations

Outcome

Based on the CHMP review of data on safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of, SonoVue 8 microlitres/mL powder and solvent for dispersion for injection to introduce a new route of administration (intravesical use in paediatric patients) is favourable in the following new indication:

Ultrasonography of excretory urinary tract
SonoVue is indicated for use in ultrasonography of the excretory tract in paediatric patients from newborn to 18 years to detect vesicoureteral reflux. For the limitation in the interpretation of a negative urosonography, see section 4.4. and 5.1.

The CHMP therefore recommends the extension of the marketing authorisation for SonoVue subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Obligation to conduct post-authorisation measures

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
Post-authorisation efficacy study (PAES): In order to further evaluate the sensitivity and specificity of Sonovue to detect vesicoureteral reflux through its impact on patient's management, the MAH should conduct and submit the results of a prospective observational cohort study (according to an agreed protocol).	Final study report to be submitted by 2Q 2020

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

In addition, CHMP recommended the variation to the terms of the marketing authorisation, concerning the following change:

Variation(s) requested		Type
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

Extension of indication to include use in ultrasonography of the excretory tract in paediatric patients from newborn to 18 years to detect vesicoureteral reflux; as a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.3 and 6.6 of the SmPC were updated. The Package Leaflet was updated accordingly. Furthermore, Annex II has been updated upon request by the CHMP to include a new obligation to conduct a post-authorisation efficacy study (PAES). In addition, the Marketing Authorisation Holder (MAH) took the opportunity to bring Annexes I, IIIA and IIIB in line with the latest QRD template version 10. Moreover, the updated RMP version 9.4 has been agreed during the procedure.