**Report on meeting of representatives of ESPR, ESUR, WFUMB / EFSUMB, GRP, ECR, AIUM and SPR with Bracco during the IPR in London, May 9th 2011 on paediatric approval for SonoVue®**

**Place:** Meeting Room 10, Hilton. London

**Time:** May 28th, 13:00 – 15:00

Attending: Riccabona M. (Chair, ESPR, ESUR, GPR), Avni F. (ESPR, ESR, ESUR), Claudon M. (WFUMB / EFSUMB, ESPR, ESUR), Coley B. (SPR, AIUM, ESUR), Darge K. (SPR), McCarville B. (SPR), Papadopoulou F. (ESPR, ESUR), Storto ML. (Bracco)

Aim, content: **The use and licensing of the ultrasound contrast media (US-CM) SonoVue® in children**

Objective:

- to define and analyse the present stage of paediatric use of US-CM
- to propose indications for off-license US-CM applications during childhood
- to summarize what we know about the use and safety of US-CM applications during childhood
- to present results from an ESPR survey on the use of US-CM in Europe, with its safety implications
- to discuss what can and needs to be done to promote paediatric registration of SonoVue®

**Order:**

Riccabona, Avni, Claudon

*Welcome and Introduction, with remarks on why US-CM are so important for paediatric imaging*

The recent worldwide efforts for reduction of radiation by diagnostic imaging particularly in children create an increased need for reliable and non-ionising imaging tools. The high profile hazards of "diagnostic radiation", especially during the two first decades of life, add further importance to the need for optimal exploitation of US diagnostic potential as provided by US-CM and support towards the interest of re-discussing and re-evaluating the use of contrast-enhanced ultrasound (CEUS) in children.

F. Avni "*How to promote and apply CEUS in children – considerations on the present state*: *The use of CEUS in children: Where do we stand? Where do we want to go?*

The use of sonographic contrast is approved for a limited number of indications in adults (cardiac analysis, large blood vessels, breast and liver indications). This approval is accompanied by a list of contraindications clearly identified. At this stage there is no approval for paediatric use. Potential effects in the fetus, gonads, brain or bowel are hypothetised but not demonstrated. So the aim of this session and the task force is to obtain approval for the use and to confirm its safety in children. This is the right time for achieving our goal: there are over 2500 published cases - mainly CE-VCUG- without any significant side effect but also without official industry approval or testing in children where as today the introduction of any new product is pending adult and paediatric testing. The list of indications of CEUS will surely widen in the future as illustrated by the many trials analyzing the clinical impact of CEUS in adult and paediatric oncology. So, the present session is aimed to define a new strategy and to convince Bracco company.

F. Papadopoulou, K. Darge: "*meta-analysis of ce-VUS applications based on a literature research"*

The systematic review of the data from 2550 children with 5080 pyelo-ureteric units provide a very strong diagnostic evidence for the accuracy of contrast-enhanced voiding urosonography (ce-VUS)

with a sensitivity of 90% and a specificity of 92% compared to VCUG and a sensitivity of 94% and a specificity of 95% compared to radionuclide cystography. The diagnostic performance of ce-VUS with SonoVue® did not differ significantly from Levovist® and, actually, SonoVue® performed slightly better. There was also excellent imaging of urethral anatomy in more than 97% of 880 patients in whom urethral assessment was reported feasible and reliable.

Furthermore, no significant side effects could be clearly attributed to SonoVue®. In one study only 2 minor symptoms were reported with Levovist®, probably attributed to the catheter itself.

K. Darge: "*present state on CEUS beyond Europe, particularly in the United States"*

Currently, 2 US contrast agents, Definity® and Optison®, are approved in the United States for use in echocardiography. There are none approved for non-cardiac use.

A phase III study is underway by Bracco to evaluate the use of SonoVue® for focal liver lesion characterization. This study is planned to be completed in December 2011.

Differences in practice pattern and regulatory requirements have hampered the introduction and widespread use of US contrast agents in the States. Increasing awareness of the negative effective of radiation may spur the search for alternatives and thus the use of US contrast agents. There are only few institutions conducting animal or clinical studies pertaining to paediatric applications.

The SPR has formed a "Contrast-enhanced Ultrasound (CEUS) Committee" with the objectives of raising the awareness among paediatric radiologist about the use of contrast-enhanced US in children and also to advice the FDA with regards to paediatric use of US contrast agent. In these undertakings the CEUS Committee will closely collaborate with the ESPR taskforce.

The committee will also seek collaboration with the newly established "International Contrast Ultrasound Society (ICUS)

M. Claudon: "*general consideration concerning indications for and applications of SonoVue® and US-CM applications in children – present state"*

Based on the WFUMB recommendation on the use of CEUS (Ultraschall in Med 2008) the proposed indications were listed for both intravenous and intravcesical use, with respect to the respective evidence level. Caution should be used with application in sensitive or particularly endangered organs (cavitation effects etc …) such as the brain, gonads, lung, and intestines. Further studies on safety in the bladder & ureter / kidney might be necessary, as we don't know any details for SonoVue® on these applications (allergising potential, how is the gas eliminated, what happens in terms of cavitation in intrarenal reflux etc …).

M. Riccabona: *"safety aspects of SonoVue® and US-CM in childhood - data and results form an Europe-wide ESPR survey and questionnaire"*

Forty-four reports on paediatric applications of SonoVue® have been filed from all over Europe documenting over 4000 cases (i.e. 2000 per year) with no evident or severe side effect in all intravesical applications (i.e., ce-VUS, performed for VUR assessment, making about 85% of all reported applications).

Five patients were reported to have suffered six minor side effects in the group of intravenous SonoVue® applications (mostly performed for lesion detection and/or characterisation in abdominal parenchymal organs) such as minor skin reaction / rush, strange taste and hyperventilation.

The data suggest safety of the contrast media and additionally demonstrate that there is not only a medical need, but also a market for paediatric US-CM applications.

Ninety answers to the questionnaire stated that no ce-US was performed in children because of regulatory issues; but many (from all over the world) claimed that they would appreciate the paediatric approval and would use ce-US in children.

ML. Storto: *"Possible regulatory paths for SonoVue® use in paediatric subjects"*

The new aspects, regulations and objectives for European drug approval (according to Paediatric Regulation EC1902/2006) were presented, ie., submission of a paediatric investigation plan (PIP), with the possibility of submission of a waiver, and the option of extending approval for drugs already marketed for adults to children for the SAME INDICATIONS such as applicable to SonoVue® (i.e., paediatric use marketing authorisation = PUMA) based on data from new clinical studies, from paediatric studies in the literature or from studies in dossiers of other approved products. Possible scenarios and "PIPs" were suggested and discussed.

- Extension of existing indications to paediatric patients = PK study, phase 3 studies, use of published studies - with an expected duration of the entire procedure of 4 – 5 years, but Bracco has been granted a waiver for these applications
- New indications requiring intravenous administration = PK study, phase 2 and 3 studies, use of published studies - with an expected duration of the entire procedure of 6 – 7 years
- New indications requiring a different route of administration (i.e., ce-VUS = intravesical use) = toxicological & pharmacologic non-clinical studies, phase 1 to 3 studies, use of published studies - with an expected duration of the entire procedure of 8 – 9 years

In the discussion, eventually – as a first promising and happily welcomed result of the joint efforts of many major societies (e.g., ESPR, ESUR, GPR, ESR Ultrasound Group, EFSUMB / WFUMB, now also supported by the SPR and the AIUM) – we became more optimistic as Bracco agreed on starting thorough internal assessments on the possible development of new indications (e.g., the paediatric licensing for SonoVue®) and on providing a response to us soon. Dr. Storto reported what would be needed to extend the current indication to pediatric patients, but also stated that it seems there is restricted medical need for that. She also shared with us what would be needed to develop new indication using the same route of administration or a different one - a major investment and several years of work. And Mrs. Storto offered to present her statement to the public task force session attendees, which was warmly welcomed.
It is not yet decided whether trying to get rid of the waiver thus extending the existing adult approvals for intravenous application to children - as a first step, which might be achievable in about 4 years – or primary a completely new approval is the best way to go; the second objective, however, is the final goal. We discussed a step by step procedure, i.e., after extending adult indications to children (as no approval for intra-luminal or intra-vesical use exists for SonoVue® neither in adults nor in children), this other urgently needed and broadly accepted ce-VUS application will have to be validated and explored in depth, even if the need for new laboratory and animal studies as well as phase 1 to 3 trials unfortunately suggest it might be a long term project.

All these presented data and the result of these (partially ongoing) discussions and communications will be brought forward to the official bodies (i.e., the EMEA) by the scientific community (i.e., the societies mentioned above) as soon as considered appropriate asking to help with registering US-CM for paediatric applications based on the already gathered experience as expressed by the meta-analysis and the survey. Bracco agreed to be present at these meetings. These data and experiences will also be shared with SPR and AIUM, trying to collaborate in these important projects. The meta-analysis as well as the survey will be published, and Bracco may use these data for supporting paediatric SonoVue® licensing. The SPR (as well as all other scientific societies involved) and Bracco will receive a protocol of this meeting, too; the protocol of the public task force session will be published and distributed via the ESPR website.

July 2011, Riccabona Michael (chair)