Author’s response to reviews

Title: Animal study assessing safety of an acoustic coupling fluid that holds the potential to avoid surgically induced artifacts in 3D ultrasound guided operations

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Author’s response to reviews: see over
Dear Editor

BMC Medical Imaging

Concerning the manuscript MS: 2099559579114798: “Animal study assessing safety of an acoustic coupling fluid that holds the potential to avoid surgically induced artifacts in 3D ultrasound guided operations”

Thank you for the review. The reviewer wants further animal experiments. Although we can understand the concern we have now addressed it in the discussion. Since we already are doing a phase 1 safety study in selected patients further testing on animals now is not an option for us. This phase 1 study was approved after very thorough ethical review and also a thorough process in the Norwegian Medicines Agency. We thank you for your understanding.

You will find the specific comments to the reviewer in the section below. We think these changes have made potential limitations clearer for the readers and also the rationale for performing a phase 1 study at this time point is discussed.

Yours sincerely,

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Response to reviewers

Reviewer # 1 comments:

One methodological issue:
In the rat group the fluid was injected intraparenchymally into the brain, but in the pig group it was injected into the subarachnoid space. That means the effect was local in one group and systematic in the second?

Answer:

Thank you for finding the concept interesting.

We now mention that the effect in one group is strictly local (rats) and in the other is more regional (CSF).

Reviewer # 2 comments:

Dr. Jakola and colleagues describe an animal safety study concerning a new acoustic coupling fluid for ultrasound-guided neurosurgical operations. According to previous studies the new acoustic coupling fluid holds the potential of improving image quality for resection control in neurosurgical image-guided operations. Thus, this is an important study as the problem of artefact formation in the resection cavity is unsolved up to date. The study is well written and methodology and results are easy to follow. However, as the authors already point out in their discussion, toxicity may be dose related. Only a rather low dose was administered in the animals corresponding to only 7.5 ml in humans. In large glioma resections, one might need double the amount of fluid to fill the resection cavity. Moreover, the fluid might be administered several times during the operation. Even if the fluid can be rinsed away easily, there is no guarantee that it might not accumulate in some place. In the clinical example, they give in the article, the neurosurgeon might have to open the ventricle to remove the entire tumour. During resection control, acoustic coupling fluid might get into the ventricle and might be difficult to get washed out again. In my point of view, further experiments with higher dosage of intraparenchymal, subarachnoid and intraventricular acoustic coupling fluid in animals are needed before starting a phase I trial in humans. I suggest resubmitting the paper with the new results. The discussion and conclusion should be changed accordingly.

Answer:
Thank you for finding the study important.

We have tried to address your concerns with respect to safety. We have tried to discuss this in more detail in the discussion where we also describe the situation when entering the ventricles. However, at this stage when we are already recruiting patients, doing more research on the animals is not an option. We have been through a very detailed process with the Norwegian Medicines Agency and the ethical committee and they have both, independently, approved the phase 1 trial. Even though we fully respect your advice, we ask for your understanding and we hope you feel that the safety aspect is more thoroughly discussed now. We agree that there remains an uncertainty concerning safety (as with all animal studies being translated to humans), but we felt these uncertainties could not be answered by more animal research and this is why we already have started the recruitment for our phase 1 study which is ongoing.