Author’s response to reviews

Title: In-vitro and In-vivo Evaluation of a Novel Bioprosthetic Pulmonary Valve for Use in Congenital Heart Surgery

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Author’s response to reviews:

Dear Editor, dear Reviewers

Thank you very much for your time and interest concerning our study and manuscript submitted to the Journal of Cardiothoracic Surgery.

We have with great interest read your comments and thoughts about our work. We believe that the changes based on your comments have improved the manuscript.

Overall, two major changes have been included in the new revised manuscript. Firstly, as this is an acute study, we have tried to include more of our knowledge about the SIS-ECM material regarding the long term potential in cardiac surgery. Please see the response to reviewer 1's comment for further regarding this.

Secondly, the manuscript has been shortened a lot. With the new shortened manuscript we tried to keep focus on describing our ideas and thoughts behind this valve concept and how it showed
a promising performance in our single animal setup. In-depth detail about procedures and setup has been left out. The manuscript has been shortened from 2772 to 1998 words.

Among the issues raised by the reviewers was a change of the manuscript from a full article to a brief report format. We certainly agree that such a format could be a potential solution for this manuscript. The revised version is submitted as a "research article" rather than a "case report" as this seems still to be the most fitting category based on the authors submission guide for the Journal of Cardiothoracic Surgery. If the editor sees it more fit that it is changed into a case report this will of course be accepted.

Below you will find a detailed response to each reviewer’s comments. Submitted is a clean version of the revised manuscript along with some changed made by request regarding the title page, order of content and so on.

Attached as a supplementary documents is a version of the original manuscript with "track changes" and deleted sections are marked in red with strikethrough.

Should any further details or material be needed we will promptly submit so.

Once again, thank you for your contributions, and we hope that our revised manuscript will be well received and considered of interest for the journal and its readers.

On behalf of the authors,

Sincerely

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Reviewer #1:

Thank you very much for the opportunity to review the manuscript entitled "In vitro and in-vivo evaluation of a novel bioprosthetic pulmonary valve for use in congenital heart surgery" by Rasmussen et al. In this very well written manuscript, the authors design the design and the very initial experience in a (single) animal model of a novel bioprosthetic made from SIS-ECM with a basal non closed ring of LactoSorb for stabilization, which according the authors "does not promote foreign body reactions" and absorbs 12-18 months after the implantation.

The authors describe in detail the making of the valve and its testing in-vitro and in a single porcine in-vivo model. The acute hemodynamic outcomes showed a peak gradient of 10 mm Hg and mild regurgitation.

Although these initial results are promising and appear to be well-substantiated, I do not think that they are sufficient to warrant a publication in a clinically-oriented journal as of yet. The results are limited to hyper-acute hemodynamics in a single animal whereas the potential advantages of this specific valve, which include longer term longevity and growth, as well longer term favorable hemodynamics, are not reported here and are of greater interest to the readers of this and other clinically-oriented journals. I therefore think that at this point, reporting these results in a bioengineering journal will better suit this manuscript.

Response

We would like to thank the reviewer for the interest in our study and manuscript.

The long-term durability of the valve is definitely very interesting and without longevity the valve will have no potential for clinical use. Within our research group we already have performed quite extensive research regarding the long-term performance of SIS-ECM in cardiac surgery. We have published data on both acute and long/mid-term use in both a tricuspid and mitral position. This and more references to our earlier work have been added to the revised manuscript.

Of special interest for this study we recently published a paper about the SIS-ECM material in a tricuspid position after 6 month in a similar porcine model as used in the present pulmonary study. Here it was found that after 6 month the SIS-ECM tissue was stronger than the native leaflet tissue. Histological examinations of the SIS-ECM tissue showed evidence tissue remodeling and endothelialization.

In the revised version of the manuscript these findings have been included as part of the introduction and discussion concerning the potential of this new pulmonary valve.
As well, as further discussed in response to Reviewer #2, the manuscript has been shortened to make this a more brief report on the concept of this valve. This is done with the aim of making the manuscript more interesting for a clinical setting in terms of new developing ideas and concepts that might one day ultimately be used in human patients.

Reviewer #2:

This is an exciting paper that will be interesting for the readers once revised. The construction of a bio-absorbable valve is described and tested in vitro and in a single animal experiment.

The authors show that the valve has acceptable function both in a pulse duplicator and in a single acute pig experiment. The animal experiment was preceded by another animal procedure which was performed to study pulmonary artery pressures and the normal pulmonary valve and its diameter.

Obviously a single animal case is not that much to report on, but this could potentially be an important device for use in growing children. However, I think the paper should be shortened a lot. There are too long descriptions of procedures, pressure measurements etc for reporting on only one experiment. It would be interesting to see some more pictures and illustrations of the valve itself, unless the authors are concerned about their potential IPR interests.

It would be interesting to see a bit more about the potential use of this valve. Maybe the use of interventional valve implantation (Melody) should be mentioned and also the possibility that this valve could be used in an interventional setting?

In conclusion I think that this contribution should be published as a brief report rather than a full paper, this could be done at a later date when there are more animals to report on.

Response

Thank you for the positive response and constructive feedback regarding our study.

Concerning the length of the manuscript, it was in the original form indeed quite extensive and therefore in the revised version it has been shortened a lot. It has been done with the aim of keeping focus on the idea and concept of the valve and its performance in our acute in-vitro and in-vivo setup, but leaving out details and longs descriptions regarding technical aspects of the procedures and the setup.
We believe that this shortening have improved the manuscript in terms of readability while still maintaining accurate descriptions and relevant discussion on the topic.

In the development of new heart valves interventional opportunities should definitely always be kept in mind. The potential of SIS-ECM valves and particularly our valve in an interventional setting is interesting. Based on the aim and setup of our study it will only be speculative though on the potential use in an interventional setup. Nonetheless, as the SIS-ECM is very pliable it could have some potential. As described in the manuscript, the Lactosorb ring is made as a complete but non-closed ring. This was done to allow gradual separation of the two ends during the initial growth prior to reabsorption of the material. Using the same principle in reverse, it should be possible crimp the valve allowing for catheter-based delivery. Using echocardiography or MRI scans prior to the procedure the valve could be pre-manufactured for optimal sizing using the simple valve design.

Although this is very interesting, only a short comment regarding this discussion has been added to the revised manuscript in an effort to keep it on-point and focused.