Author’s response to reviews

Title: Efficacy and Safety of Oral Sildenafil in Children with Down Syndrome and Pulmonary Hypertension

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Marijana Tadic, PhD
BMC Cardiovascular Disorders

Dear Dr. Tadic,

We would like to thank your reviewers for their thoughtful consideration of our manuscript titled “Efficacy and Safety of Oral Sildenafil in Children with Down Syndrome and Pulmonary Hypertension” for publication in BMC Cardiovascular Disorders.

We have amended the manuscript as stated below in our point-by-point response. We believe the revised manuscript addresses the concerns and questions posed by the reviewers, and that these revisions have strengthened the manuscript. We hope you find the revised manuscript suitable for publication and look forward to your decision regarding final acceptance and publication of our work.
Reviewer 1:

The study of Beghetti and co-workers shows the result that in pediatric patients with Down Syndrome medication with sildenafil did not lead to an improve in hemodynamics in comparison to pediatric patients with a non Down Syndrome related type.

Comment 1. The authors explain pathomechanisms that might be responsible for the ineffective treatment success of the sidenafil medication in Down Syndrome patients presenting with pulmonary arterial hypertension. However an important result is that there are no major safety concerns related to sildenafil treatment in pediatric patients.

Author response: Thank you for pointing out this important consideration. On page 12 line13, we have stated that sildenafil is well tolerated in our pediatric DS patients as well as the STARTS-1 study population as a whole.
Reviewer 2:

In this post-hoc analysis from the STARTS-1 trial, the authors compared the effect of po sildenafil on PVRI, mPAP and CI, in children with PH, with and without DS.

They concluded that children with DS do not experience the benefit of sildenafil, compared to non-DS patients. They also offer useful pathophysiological explanations for the lack of this effect.

Comment 1. As stated in the results there are significant differences in baseline characteristics between the 2 groups. This should be added in the limitations of this analysis.

Author response: We have added the following text to page 12, line 17. The new text reads ”Another potential limitations is the difference in the baseline characteristics between the DS and non DS groups. An imbalance in etiology was observed with approximately 60% of the non-DS patients had non-IPAH/HPAH, whereas approximately 90% of the DS patients had non-IPAH/HPAH.”

Comment 2. In reference to the above, it will be useful to the have in Tables 1 and 2, the p-values, if statistical differences have been identified.

Author Response: While we did not run a formal statistical comparison, these data could be generated but will require time and we do not feel it will add substantially to the manuscript.

Comment 3. Is there dosing information available from the STARTS-1 study to better guide the reader, besides the sildenafil plasma concentrations (ex. mg/kg dose)-

Author Response: We have added the following dosing information to the Methods section on page 6, line 10;”Patients with body weight between 8– 20 kg were randomly assigned to receive medium (10mg TID) or high dose (20mg TID) sildenafil ; patients between 20–45 kg were
randomly assigned to receive low (10mg TID), medium (20mg TID) or high dose (40mg TID) sildenafil, and patients >45 kg were randomly assigned to receive low (10mg TID) medium, (40mg TID) or high dose (80mg TID) sildenafil.”

Comment 4. 2. in p.7, para 1, l. 5, "further analysis...", please clarify this sentence.

Author response: Treatment comparisons of each of sildenafil dose vs. placebo, and pooled sildenafil doses vs. placebo were conducted by etiology (primary PH, secondary PH) for non-Downs Syndrome subjects, and for Downs Syndrome subjects with secondary PH. Results from non-Downs Syndrome subjects with primary PH (IPAH/HPAH) are presented in Table 3.

Comment 5. In p. 12, para 1, l. 1, what do you mean by "secondary PH in DS patients…"?

Author response: We agree that this sentence is confusing and does not add anything to the understanding or explanation of the results and we have removed it.