Author's response to reviews

Title: Treatment adherence with the easypodTM growth hormone electronic auto-injector and patient acceptance: survey results from 824 children and their parents

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Author's response to reviews: see over
MS1843957958389409: Treatment adherence with the easypod™ growth hormone electronic auto-injector and patient acceptance: survey results from 824 children and their parents

Thank you for your continued interest in our article for publication in *BMC Endocrine Disorders*. We have amended the text further based on the reviewers’ comments and our responses to these comments are listed below. Changes in the text have been highlighted as requested. All the authors have seen and approved these changes.

**Responses to reviewers’ comments**

**Reviewer 1**

The authors overall addressed the comments from the previous review thoroughly. I remain concerned though about three issues that cannot be or were not addressed:

- **Comment 1.** Lack of details and psychometric properties of the adherence survey.
  
  *Response: The following text has been added to the Outcome measures section on page 7: “The survey was completed by the child or parent based on each family’s preference. This information was not collected during the survey; hence no psychometric properties of the survey were made available.”*

- **Comment 2.** The arbitrary nature of in some cases reporting statistics and in other cases describing the findings as “descriptive”.
  
  *Response: On page 8, the text has been clarified regarding the descriptive findings and now reads: “Analyses of parents and children’s device acceptance were descriptive. However, for the mean adherence values, 95% confidence intervals were calculated.”*
Comment 3. And finally, the novelty issue brought up by my colleague during the review. Although the N is considerably higher and the international sample is laudable, the follow-up period was short-term.

Response: As stated in our previous response to your colleague, compared with the current study, the two previous user trials studied fewer patients (61 vs 824 patients here – number of patients added to text), were carried out over a shorter term than in this study (60 days vs 3 months) and were only performed in a couple of countries.

Reviewer 2
I am happy with the answers of the author’s to my questions raised previously. However, I feel that this information should also be incorporated within the revised manuscript since the reader might have the same questions. Please do so.

Response: All answers to the questions raised previously are now incorporated in the manuscript (see answers in green highlight). All other comments were added in the previous round of review (in yellow highlight). Listed below are the previous comments and responses for your information.

Previous comments:
Reviewer 1
Comment 1. In the Introduction on page 4 (second paragraph), it would be helpful to briefly review the non-adherence rates for this population. This is done in the Discussion but I think that doing so here would better convey the scope of the problem.

Response: Data from Kapoor et al. 2008 have been added to the introduction to highlight the problem of non-adherence

Comment 2. It sounds like from page 7 that comparing treatment-naïve versus treatment-experienced patients is one of the study aims. This should be mentioned earlier with rationale in the Introduction for examining the difference. It’s a very interesting distinction that I think often is discussed under the rubric of patient age or developmental phase rather than potential “treatment fatigue”. Please also report secondary study aims. In the Results section, several analyses are mentioned without rationale (e.g., differences by treatment month, by country, etc).

Response: Some additional text has been included in the introduction to explain the rationale behind comparing adherence in treatment-naïve and treatment-experienced children. The secondary objective (to assess the acceptability of the electronic auto-injector) and outcome measures (rating of specific device features on 5-point scales or using multiple-choice responses in a questionnaire) are detailed on page 6.

Comment 3. In the Methods section, on page 6, much more detail is necessary about the study measures. Please discuss survey development in greater detail. Are there any psychometric properties available for any of the measures?
Response: The construction of this survey was based largely on the findings of the study by Dumas et al. 2006. No psychometric properties are available. This text was added on page 7.

Comment 4. Please also provide more details about the study procedure. For example, at what age did children start completing the survey versus parents? If age was not the criteria, how was it decided whether children or parents completed the survey? Did both do so? How many children versus parents completed the measures should be presented as well.

Response: The decision on whether the survey was completed by the child or parent was based on each family’s preference. Data were not collected with regard to whether the survey was completed by the parents or children, nor the age of the children according to who completed the survey. This text was added on page 7.

Comment 5. On page 7, the first paragraph is unclear. What do you mean by “the type of patient…was not a controlled factor?” Please explain in greater detail.

Response: The ‘type’ of patient refers to whether they were treatment-naïve or -experienced. This is not something that could be controlled for during study recruitment; therefore, there were unequal numbers of each. This text has been amended to explain this.

Comment 6. Also on page 7, please justify the definition of adherence used. This I think would fit better when describing the other study measures.

Response: As adherence is expected to be high during the first three months of treatment (in the order of 80–95%; Haverkamp et al. 2008) the figure of 92% was selected (i.e. a maximum of two daily injections missed per month or six daily injections for the 3-month period). This text was added on page 7.

Comment 7. Similarly, the third paragraph on page 7 beginning with “Three different imputations were used” is unclear. What “tick boxes” are referred to? I think if the study measures are explained in greater detail, this will become clear.

Response: The text describing the imputations used has been clarified. Tick boxes refer to the boxes on the questionnaire from which the subject could make their selection in order to indicate their answer. This has been added to the description of outcome measures on page 7.

Comment 8. On page 8, please discuss the reasons for incomplete data.

Response: As with many questionnaire-based surveys, information is often incomplete. We have added that children had incomplete data sets if they had incomplete information for the numbers of reported and recorded injections.

Comment 9. In the Results section, there are many instances where differences are referred to without corresponding statistics. Please report the analyses conducted (e.g., for increased non-adherence by month, differences between countries, etc). If any differences are non-significant, this should be stated.

Response: Statistics were not performed for all observed differences as the analyses were intended to be descriptive only. Hence, any differences should be treated with caution. Analyses of parents and children’s device acceptance were descriptive. However, for the mean adherence values, 95% confidence intervals were calculated. This text has been added on page 8.

Comment 10. Please report test statistic values, not just p values, throughout.

Response: The test statistic value corresponding to the p value has been added.
Comment 11. The authors have a great opportunity to share even more about the findings. I think it is essential to break down adherence by whether or not the child versus the parent is administering the injections.
Response: Overall for the 3 month survey period, there was a slight difference in favour of greater adherence in children whose parents administered their injections compared with children administering their own injections (84.8% vs 82.7%). These data have been added to the manuscript on page 9.

Comment 12. Please also report whether children versus parents report different adherence levels.
Response: Please see the previous response.

Comment 13. On page 14, the “key factors” paragraph is unclear. The present study did not analyze correlates of adherence. Please clarify how this review relates to the present findings or delete to avoid suggesting associations that cannot be made in the context of the present study.
Response: We feel that it is within the context of this paper to include some discussion on factors influencing patient adherence to growth hormone therapy. We have amended the text to emphasize that reasons influencing adherence were not explored in our study, but we present some of the reasons reported by others.

Reviewer 2
Comment 1. It is unclear if the patients were informed that adherence was prospectively checked by the easypod-device. This information will potentially create some bias with respect to patient compliance. If so, this issue should be addressed in the discussion section.
Response: It became apparent during the course of the survey that some questionnaires were being administered prospectively and some retrospectively. We acknowledge that this could introduce a potential bias, but the numbers of questionnaires administered prospectively and retrospectively were approximately equal and a limited exploratory analysis showed no apparent differences between the two approaches. This text was added on page 11.

Comment 2. The data are clearly presented but appear to be of poor novelty. Two analyses on this topic were published previously. The observation period was rather short to thoroughly assess compliance to rhGH treatment, which is usually given for many years.
Response: As mentioned in the introduction and discussion, compared with the current study, two previous user trials studied fewer patients (61 vs 824 patients here) and over a shorter term (60 days vs 3 months here). Furthermore, our manuscript includes an analysis of the adherence data collected using the device (and reported by patients), which was not done in the previous publications. These novel aspects of our manuscript have been further highlighted in the discussion.

Editorial comments
Comment 1. In the methods section of your manuscript, you state that "each child or participating family member consented to the survey."
In your revised manuscript we require you to revise this statement to specifically state that the guardians of the children consented to the study.
Response: The text in the methods section has been extended accordingly.
I hope that these changes have suitably addressed the reviewers’ comments and that this article is now acceptable for publication. I look forward to hearing from you.

Yours sincerely

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