Author's response to reviews

Title: No increased risk of glucose metabolism disorders in adults with growth hormone deficiency undergoing long-term treatment with biosimilar somatropin (Omnitrope®): data from an observational, longitudinal study

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Version: 1 Date: 09 Oct 2019

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Editor comment. Thank you for submitting your work to BMC Endocrine Disorders. Reviewers were very positive about the manuscript; the biggest criticism was the lack of statistical analysis. It is suggested that authors, at minimum, compare groups in addition to the suggestions made by the reviewers.

The primary aim of the manuscript was to report the occurrence of diabetes mellitus and glucose intolerance reported during the PATRO Adults study. As this was an observational study, only descriptive statistical analyses were included in the statistical analysis plan, and no formal statistical testing was defined up front. For this reason, further statistical analysis cannot be included in the manuscript.

Reviewer 1. Comment 1. The diagnosis of diabetes was made by OGTT or HbA1c. HbA1c is used in daily clinical practice, but in general, there are some reasons when OGTT is performed. If a large number of diabetes diagnoses are made by OGTT, it may be a bias in the rate of diabetes diagnosis. If you able to know the conditions under which OGTT was performed, please describe the reason. If you do not know, please describe the "potential selection bias" in the discussion part.

Due to the observational nature of the study, the choice of method used to diagnose diabetes was not recorded, and likely reflected the preference of individual clinicians. It is therefore not possible to describe the conditions under which OGTT was performed. A statement has
been added to the discussion to describe this potential bias (discussion, page 16, lines 326-329).

Reviewer 1. Comment 2. Of the 21 diabetic patients, it is assumed that cortisone has been administered to 14 patients. Is there any report that low dose cortisone causes glucose intolerance in patients with hypopituitarism?

A statement has been added to the discussion (page 15, lines 305-308) to clarify that cortisone has been linked to glucose intolerance in patients with hypopituitarism, although the prevalence decreases when a lower dose is used (McConnell et al. 2001).


Reviewer 1. Comment 3. Table 2 and the discussion describe whether cortisone or statin is given in patients with diabetes. However, with regard to these medications, when these medication rate in patients without diabetes is unknown, it cannot be described the contribution to impaired glucose tolerance in patients with diabetes. On the contrary, it emphasizes the impression that progress to diabetes is not due to GH treatment. Please note whether these medications were given before the start of GH treatment. Also, please state your point of view in the discussion part.

The discussion has been expanded to explain that the relationship between cortisone/statin use and the development of diabetes mellitus could not be confirmed based on the results of our analysis, and that further investigation is therefore warranted (discussion, page 15, lines 302-316).

Unfortunately, due to the observational nature of the study, the start date of concomitant cortisone/statin medications was not collected for all patients included in Table 2. This information therefore could not be added to the manuscript.

Reviewer 1. Comment 4. In Table 2, the body weight and HbA1c before GH treatment are described, but neither is showed at AE onset. It is better to describe comparable metabolic parameters before and after GH administration.

Unfortunately, weight and HbA1c were not specifically recorded at the onset of the diabetes mellitus AE, and therefore this information could not be included in the manuscript.

Reviewer 2. Comment 1. I suggest authors to indicate the study's design in the title, i.e. "prospective cohort".
The title has been amended as suggested.

Reviewer 2. Comment 2. Authors should mention the setting (i.e. primary care), and locations (participant countries).

The setting has been added to the first paragraph of the methods section (page 7, lines 117-118). The participant countries are included at the start of the results section.

Reviewer 2. Comment 3. How did the authors guarantee the veracity of the information? Did the physicians were previously trained to detect EA and SAEs? Did they use an instrument to detect them?

Due to the observational nature of the study, there is potential for information bias (due to incorrect or inexact recording of information). Data underwent regular quality checks by monitors at all sites. The potential for bias due to inaccurate documentation by investigators has now been added to the ‘study limitations’ part of the discussion (page 16, lines 321-324). The relationship between AEs/SAEs and study treatment is made according to investigator and sponsor assessment, and categorised according to the worst case; this information is included in the methods section (page 7, lines 130-134).

Reviewer 2. Comment 4. Describe the participation of each author in the METHODS section.

The role of the authors in the study (members of the global steering committee or employees of the study sponsor) is indicated in Section 7.4 (Competing interests, page 21, line 395). We suggest that this is more appropriate than inclusion in the Methods section.

Reviewer 2. Comment 5. Authors do not establish a statistical analysis planning, including how the statistical data is expressed (i.e. mean and SD, frequencies), and reported (figures, tables, etc.).

The statistical analysis has been added to the method section of the manuscript (page 8, lines 140-142). Since the study uses only descriptive statistics, the statistical information included in the manuscript is sufficient for Table 1 and Figure 1.