Reviewer's report

**Title:** Different thresholds of tissue-specific dose-responses to growth hormone in short prepubertal children

**Version:** 2  **Date:** 16 August 2012

**Reviewer:** Roland Schweizer

**Reviewer's report:**

**General Comments:**
This is a nice study dealing with the question if there is a different responsiveness to GH in different tissues. This is of interest and till know to my knowlege, not published in this kind of study.

A weakness of the study is the mix up of patients with GHD and patients with ISS and the definition of GHD only on test results. If diagnosis of GHD is done with the criteria given below, according to Binder et al. 2011 (Growth Horm IGF Res. 2011 Aug;21(4):212-8. Epub 2011 Jun 14. Auxology-based cut-off values for biochemical testing of GH secretion in childhood.

Binder G, Huller E, Blumenstock G, Schweizer R.) we would expect a difference in the responsiveness between the GHD and the ISS group, since growth in real GHD is almost everytime better than in ISS. And in GHD we would expect a low muscle mass and increased fat mass before GH treatment, but not in ISS. In GHD in the first years of GH treatment muscle and fat mass normalize, in ISS muscle mass would also increase dose dependent, but to levels higher than normal. Of course one would argue that there is a continuum between GHD and ISS but than we would also expect that the extrems of the continuum in responsiveness to GH in different tissues are one the one side only GHD patients, on the other side only ISS patients, inbetween there may be a little overlap.

**Minor essential revisions**

page 7 (Subjects and study protocol), please clarify that the start of catch-up growth is also the start of GH-therapy for the first time. Since our experience is that growth response is better in the first year of GH therapy, than in the following years.

page 7/8: It is problematic to diagnose GHD only with help of GH levels in tests/spontaneous secretion, since the diagnosis of GHD needs more (in the following order):

1.) slow growth (below 25th percentile of age and sex specific height velocity standards) for et least 6, better 12 months.

2.) Low IGF-I (below -1 SD of sex and age specific references).
3.) Bone age retardation of more than 1.5 years
4.) Low GH secretion in test/spontaneous secretion.

In addition the cut-off chosen (10 ng/ml) seems to be very high

Auxology-based cut-off values for biochemical testing of GH secretion in childhood.
Binder G, Huller E, Blumenstock G, Schweizer R.

page 8 (last paragraph): if possible try to simplify the explanation of the procedure for dose selection.

page 9 (Body composition): is there a reference for fat mass measured with DXA, in the following text and the abstract; it is mentioned a Fat mass SDS. Please give the reference.

page 12 (Effective GH dose at 50% effect): was Delta LVDd low compared to reference values and did it normalize or did it increase within a reference range?

page 15 (line 8): it should be "...33 µg/kg/day..." not 33 ug/kg/day.

Discretionary Revisions

It is possible to shorten the Statistics and Result part, since it is e.g. repeatedly mentioned that .....the GH dose effect is given by the maximum range of the fitted piecewise function.....

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I received lecture fees from Pfizer and Novo Nordisk