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Title	Growth hormone treatment of Canadian children: results from the GeNeSIS phase IV prospective, observational study
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Reviewer 1	Nancy Gagné
Institution	Pediatrics-endocrinology service, Centre Hospitalier Universitaire de Sherbrooke, Sherbrooke, Que.
General comments (author response in bold)	Interesting findings overall. It would have been interesting to compare the Canadian data to the non-Canadian data (all sites minus Canada instead of including Canada). Following these results one wonders if we should be recommending higher growth hormone doses for our Canadian patients… **Many thanks to the reviewer for their comments.** **• Unfortunately we do not currently have analyses for all countries minus Canada. We believe that providing data for all countries combined (incl Canada) versus Canadian data alone provides the reader with an appropriate indication of how the Canadian data compares to other countries.** **• While data from pharmaceutical company sponsored studies, such as GeNeSIS provides real-world insights into outcomes of treatment (entirely at the discretion of investigators), we do not believe it appropriate to make recommendations regarding GH dosage based on such data.**
Reviewer 2	Paola Luca
Institution	Department of Pediatrics, Cumming School of Medicine, University of Calgary, Calgary, Alta.
General comments (author response in bold)	Dear Dr. Deal and co-authors, I really enjoyed reading your article "Growth hormone treatment of Canadian children: results from the Genesis surveillance program", and found it to be very well written, clear and, most importantly, very informative. **Many thanks to the reviewer for their comprehensive and thoughtful comments.** I have a few suggestions and comments. In the Results section, page 7, line number 8-9, how many GH-treated children had data that was not evaluable? **Per the existing text, there are 848 in the effectiveness evaluable population and then a further 2 patients eligible only for the safety analysis, so 2 not evaluable for effectiveness** On page 7, lines 21-22, suggest putting the % in brackets for the subcategories of organic GHD. **Text updated as suggested** On page 9, line 5-9, it might be helpful to specify this information is for Canadian patients only. **Text updated as suggested** For Safety Outcomes (page 9, lines 25-29), there is a discrepancy between the number of deaths possibly related to GH treatment in the text vs Supplemental Table 2. Here 3 possible deaths are listed, however, in Supplemental Table, 2 deaths are possibly related to GH. Further, on page 12, lines 20-24, three deaths are reported as being possibly related to GH. **Thank-you for spotting this inaccuracy; Supplemental Table 2 has been updated to indicate 3 of the cases as being considered related to GH by the investigator.** In addition, is it possible to expand on why the investigators attributed the recurrence of medulloblastoma in 2 patients to GH and not the recurrence of astrocytoma in 2 (or one) patient? **The assessment of causality to study drug (GH) is in the opinion of the investigator. Although the literature has consistently found no evidence of increased risk of intracranial tumour recurrence in GH treated patients, many investigators are cautious in assessing such events in the absence of other defining factors and often state something like that a relationship of the event to GH treatment cannot be ruled out. Conversely others may reject the possibility of a causal relationship based on temporal association or risk factors.** On page 12, line 48, I believe 'GH-treatment' should be written as 'GH treatment'. **Text corrected as suggested** For Table 1, the superscript 'g' is below 'h', 'I' and 'j'. **Thank you – corrected, but footnotes have also been harmonised to a certain extent** For Table 1, did the 30 patients with Prader Willi Syndrome listed under GHD organic clinical syndrome have documented GHD. I assume yes. This does not require clarification in the article as it is implied. **Yes they did have documented GHD.** For Figure 1a, suggest putting a legend for height velocity (open square) and height SDS (closed circle) directly on the figure. **Corrected as suggested.** For the legend of Figure 1, suggest describing Figure 1a-d in the text. For example: "for all patients (1a) and for evaluable diagnostic groups (1b, 1c, 1d)". **Text updated as suggested**
Reviewer 3	Jonathan Meyer
Institution	Department of Pediatric-Endocrinology, University of Oklahoma Health Sciences Center, Oklahoma City, OK
General comments (author response in bold)	Growth hormone therapy is used widely in the field of endocrinology for many different indications, and there is still much to learn about the benefits and risks of this medication. The GeNeSiS trial sought to answer many of these questions on a global scale. The authors of this paper review the data of the Canadian cohort of this study to see if there is a country-specific difference that should be noted. The ultimate question stemming from this paper is whether a country-specific data set is more valuable than a larger, more heterogeneous global cohort. I think in most cases this is not true. However, there is some valuable information within this data set that the authors note. Despite only being the 6th largest contributor of patients to the study, the sample size of 848/850 is robust. This sample size allowed for identification of differences in the Canadian cohort vs the US and global patients. The paper is well organized and flows well, and methods and results are clearly stated. The major overall weakness was inconsistency throughout comparisons. Some of the Canadian results were compared to US and some to the global cohort, and the tables had different columns that did not match. The interpretations were also interesting but in my opinion, incomplete. I'd like to know more about why, for instance, Canadian prescribers are more conservative with both growth hormone prescriptions and growth

	hormone dose, yet there were more adverse events among Canadian patients. Overall, the data may provoke discussion regarding usage and funding of GH in the population, especially in a Canadian journal. **Thanks to the reviewer for the comprehensive and helpful comments** Specific comments: 1. Appreciate the last paragraph page 4 describing the potential impact of this study 2. 2. Unclear why on page 7 comparisons with US made for diagnostic criteria and then (even in the same paragraph) comparisons made with global cohort. This goes for table 1 as well. I would either stick with Canada vs global or clearly state why the comparison to US for only these data. **We have included global data in Table 1 for demographic and GH treatment parameters.** 3. End of page 8, might say "as per previous studies" or something similar rather than "as expected." **Adding as per previous studies would demand several reference citations, therefore we have elected to delete this.** 4. Appreciate information on Canadian indications for GH on page 10, as well as information on funding for GH. **Thank you** 5. On page 11 line 14, what is the actual difference between the accepted values for GHD between Canada and US? And is this a global trend? **As the maximum GH peak recorded during stimulation testing may be affected by a variety of factors including age, BMI and agent used and the accepted cut-offs subject to geographic variation we have deleted this sentence.** 6. On figure 1/2 caption, +1 SD % is missing and unsure if this was overlooked 7. Tables 2 and 3 are similar data but in table 2 SGA is listed and in table 3 "all" is listed. Think both tables should have the same catagories. **Thank you. +1 SD % has been added to the legend for both figures. Table 3 shows data for those patients who attained near-adult height – SGA was omitted as only 1 Canadian patient with SGA reached final near-adult height during GeNeSIS. For Table 3 the near-adult height outcomes for the combined "all" diagnoses group may be of interest for some, but use of such data for just baseline demographics in table 2 is of much lower interest – hence only the individual indications are shown.** 8. Table 3 should also probably have "Males (%)" like table 2 does, rather than several footnotes. **Thank-you. Now updated per your suggestion.** 9. Smaller sample size compared to global cohort makes it easier to view all deaths in more detail, as in supplementary table 2. Appreciate this for looking at AEs. **Thank you** 10. There are a lot of tables/figures but all give at least some relevant information so I think it is fine to have them as is. **Thank you**