Author’s response to reviews

Title: A randomised, open-label study of insulin glargine or neutral protamine Hagedorn insulin in Chinese paediatric patients with type 1 diabetes mellitus

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Reviewer 1

Major comments

1. p. 9 line 20 - a measure of significance should be given here - either 95% CI:… or p=… - please consult with your statistician. If there is a statistically significant improvement in FBG - it should be mentioned in the abstract.
Response: We agree with this suggestion and have added in the 95% CI values. However as this study’s design did not include pre-defined measures of statistical significance, strictly speaking, we cannot interpret the 95% CI values to indicate a statistically significant improvement in FBG. Hence, we have not included FBG in the abstract.

2. p. 8 line 46-49 after "... similar..." a measure of significance should be given here (despite there was no statistical significance)

Response: In order to reflect the data more accurately, this sentence has been revised to “The median changes in HbA1c in the treatment groups were numerically similar”. However, since the comparative statistics were not a part of the study design, it is technically not possible to provide a measure of significance such as P values.

3. Data about daily insulin doses in children should be given in units/kg per day

Response: We have revised data on the daily insulin doses to be presented in units/kg/day in both Table 2 and throughout the content of the manuscript.

4. Discussion still requires some linguistic corrections

Response: In accordance with your feedback, we have made several linguistic corrections throughout the discussion section.

Minor comments

1. p.6 line 46 - Performa blood glucose meter - manufacturer and country of origin should be stated

Response: We have provided the manufacturer and country of original of the Performa blood glucose meter.

2. p. 9 line 50 - in my opinion it is not necessary to write that "there were no deaths…"

Response: We agree with this suggestion and have removed the sentence regarding deaths accordingly.
3. p. 11 line 11 - the word "treatment" is double in this sentence

Response: We have revised the above sentence.

4. p. 12 line 10 - "insulin lente"?

Response: Regarding the study from which the above information has been taken, several corrections have been made, they are:

• The study from which the above information has been taken was wrongly referenced in this paper (reference 19). However, we have now corrected the reference to reflect the correct study.

• The study by Chase, et al. is a parallel-group comparison of the long-acting insulin glargine with intermediate-acting insulin NPH or lente insulin. The rapid-acting analog insulin lispro was used as aprandial component in both treatment groups.

We have updated content regarding the above study in this paper to reflect that insulin lispro was a part of both the treatment groups

• We have corrected “insulin lente” to “lente insulin”; Lente insulin is an intermediate-acting human form of insulin i.e. Humulin® L, Novolin® L.

Reviewer 2

1. On Page 5 (Line 21 - 24), the authors indicated that "A 2:1 randomisation ratio allowing a greater number if patients exposure to insulin glargine was used in order to accurately assess and document the safety of insulin glargine in the patient population". Larger sample size or randomization ratio can help improve the precision (but may not affect the accuracy) of the estimate. I would suggest revising the above sentence.

Response: We agree with this correction and have revised the sentence accordingly to highlight that the randomization ratio allowing a larger number of patients exposure to insulin glargine, improves the precision of the safety assessment.

Additional changes

• The link to the “Guideline for the Diagnosis and Treatment of Type 1 Diabetes Mellitus in China” has been updated to present a viable link to the guidelines.
• “medium-acting neutral protamine Hagedorn (NPH) insulin” has been changed to “intermediate-acting neutral protamine Hagedorn (NPH) insulin” throughout the manuscript.

• We have included “Week 24 (not LOCF)” and “Change (not LOCF)” values for the insulin category of “Mean daily bolus insulin” in Table 1.

• We have revised the LS mean values and 95% CI values in Table 1 to be presented to 2 decimal places in order to maintain consistency with the rest of the values in Table 1 as well as the values in Table 2.

• Regarding the comparison of insulin dose between the insulin glargine and NPH insulin groups, we have revised the description in three places:

1. Results: revised from “the insulin glargine group used fewer total and basal insulin doses than the NPH group” to “the insulin glargine group had lower total and basal insulin doses than the NPH group”

2. Discussion: revised from “At the end of the 24-week treatment period, patients in the insulin glargine group used considerably fewer total and basal insulin doses than the NPH group” to “At the end of the 24-week treatment period, patients in the insulin glargine group used considerably lower total and basal insulin doses than the NPH group”

3. Discussion: revised from “and it is likely that a dosing regimen, which achieves glycaemic control with the least number of total/basal insulin doses per day” to “and it is likely that a dosing regimen which achieves glycaemic control with the least amount of total/basal insulin doses per day”