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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Author’s response to reviews:

Reviewer #1: Comments:

1. A. Dear Authors, please add the description of the method of HbA1c measurement to the main text (not to the Supplementary materials); some details regarding the reproducibility/accuracy and reference values for HbA1c should be added.
Response:

We agree with this suggestion. We have moved information on the method of HbA1c measurement from the ‘study measurements’ section under the ‘Supplementary materials’ to the main text, under the ‘patients and methods’ section. We have also included information on the reproducibility/accuracy and reference values for HbA1c in the same section. Revised in manuscript.

- HbA1c values should be presented in both % and in mmol/mol.

Response:

We agree with this suggestion. We have revised HbA1c values throughout the manuscript to be presented in both % and mmol/mol. HbA1c values from other studies (lines 51 to 59 on page 8 and lines 1 to 5 on page 9) however have not been calculated to mmol/mol as the conversion cannot be accurately done. Revised in manuscript.

B. Please add information about the blood glucose meters used by patients. Did they all use the same BG meters?

Response:

All the patients used Performa blood glucose meters during the whole course of the study. We have briefly mentioned the type of blood glucose meters used by the patients under the ‘study outcomes’ section. Revised in manuscript.

3. A. In my opinion, as p values (or 95% CI) are missing for some of the results presented in the main text, figures and tables, the conclusions drawn (and information about changes of variables over time) are not fully supported in these points by the data shown, i.e:

- p. 8 lines 32-41 and p. 6 lines 46-48 (the Authors say: "At all study time points and in both treatment groups, the mean HbA1c was lower than at baseline (Fig. 2a.").) - in the fig. 2a - asterisks could be added where appropriate (for time points in which HbA1c differed significantly, i.e. p<0.01, compared to baseline)
Response:

Due to the limited number of patients, this study was not powered to detect statistically significant reductions in HbA1c and asterisks indicating significance have therefore not been added to Fig. 2a. We have, however, revised the lines 32-41 on page 6 to: “At all study time points and in both treatment groups, the mean HbA1c was numerically lower than that at baseline”. The addition of ‘numerically’ to this statement emphasises that it has not been statistically tested. Revised in manuscript.

- In Table 3 and 4 - for each complication (or a group of complications) p values should be presented (eg. in a fourth column) to show that there were no differences or that there were differences (eg. in hypos frequency as stated on p. 9 lines 42-43).

Response:

As mentioned previously, this study was not designed to detect statistic differences in the incidence of hypoglycaemia on account of the limited number of patients. Therefore, P values in tables 3 and 4 cannot be presented. To emphasise the lack of statistical significance of the results, we have revised lines 2-6 on page 8 to read: “However, the insulin glargine group had a numerically lower rate of any hypoglycaemic events per patient year than the NPH insulin group (68.6 ± 69.4 versus 84.6 ± 79.3). The proportion of patients who experienced ≥1 symptomatic hypoglycaemic event and the rate of symptomatic hypoglycaemic events per patient year were also numerically lower in the insulin glargine group than in the NPH insulin group.” Revised in the manuscript.

B. In my opinion it would be enough to present only one measure of central tendency for all variables - either mean (+/-SD) or median (25%-75% quartile)

Response:

We agree that using one measure of central tendency is enough. However in this study on account of the small sample size and an imbalanced randomisation ratio, the mean value is likely to be impacted by extreme values causing a skewed data distribution. Therefore we felt that presenting the median (25%-75% quartile) is still of value. All variables in the ‘results’ section of the manuscript have been described by only the mean (+/-SD). In the ‘discussion’ section
however the mean and median (25%-75% quartile) absolute changes in HbA1c have been briefly mentioned.

The tables describing the various variables also include the mean and median (25%-75% quartile) values. Revised in the manuscript.

C. Minor remarks:

- p. 6/7 lines 53-57/1-2 should be reedited, eg.: "From baseline to Week 24, the mean FBG decreased in patients who received insulin glargine (from … to …) and increased in patients who received NPH insulin (from … to …; Table 1).

Response:

We agree with the edit suggested. Sentence has been revised to read: “From baseline to Week 24, the mean FBG decreased in patients who received insulin glargine from 10.38 ± 3.38 mmol/l to 9.61 ± 2.63 mmol/l and increased in patients who received NPH insulin from 10.20 ± 2.75 mmol/l to 11.29 ± 3.35 mmol/l (Table 1). Revised in the manuscript.

- Regarding the mean change in FBG, there was a considerable difference between the treatment groups (-0.76 ± 3.56 mmol/l vs 1.07 ± 3.64 mmol/l; 95% CI: -2.6 to -0.76). It seemed that FBG was better controlled with insulin glargine than with NPH insulin at all study time points (see Fig. 2b). - Results section should not include comments.

Response:

We agree with this point and have revised the sentence. Sentence has been revised to read: “FBG was better controlled with insulin glargine than with NPH insulin at all study time points”. Revised in the manuscript.

- p. 9 lines 12-18 should be reedited, eg.: "There was a considerable difference in changes of FBG between the insulin glargine and NPH insulin groups (-0.76 ± 3.56 mmol/l vs 1.07 ± 3.64 mmol/l; 95%CI ………………); […]"
Response:

We agree with the edit suggested and have revised the sentence. Sentence has been changed to: “There was a considerable difference in the change in FBG between the insulin glargine and NPH insulin groups (–0.76 ± 3.56 mmol/l versus 1.07 ± 3.64 mmol/l). Revised in the manuscript.

- p. 6 line 28/29 - should be: microalbuminuria

Response:

We agree with the edit suggested. Revised in the manuscript.

- Table 1 and 2 - "LS" - this abbreviation should be explained

Response:

We agree with the edit suggested. Expansion of LS as 'least square' has been included in the footnote under each table. Revised in the manuscript.

- p. 8 line 53 - references should be added

Response:

We agree with the incorporation suggested. We have added in the references supporting this line. Revised in the manuscript.

- Numbers of figures should be corrected according to those used in the main text.

Response:

We have double checked the figure numbers used in the main text and can confirm that they correctly correlate to the appropriate figures.
A total of 5 figures are used in this manuscript:

- Fig 1: Patient flow diagram
- Fig 2a: Mean HbA1c (%)
- Fig 2b: Mean fasting blood glucose (mmol/l)
- Fig 2c: Mean nocturnal blood glucose (mmol/l)
- Fig 2d: Mean eight-point SMBG (mmol/l).

4. as in point 3A-B and:

…it is not clear for me, if based on the data presented in Table 2 one can conclude about differences in total and basal insulin doses between groups.

Response:

We have taken this into consideration and revised the wording and been more conservative in our interpretation of the data. Description of the Table 2 has been revised to: “Compared with baseline, at Week 24 the NPH insulin group had a greater numerical increase in both the mean daily total and basal insulin doses than the insulin glargine group (6.22 ± 7.54 units versus 11.51 ± 12.06 units for total insulin and 2.03 ± 3.36 units versus 6.10 ± 7.09 units for basal insulin, respectively; ANCOVA, Table 2). Consequently, at Week 24, the insulin glargine group used fewer total and basal insulin doses than the NPH group (41.69 ± 17.43 units versus 47.49 ± 20.35 units for total insulin, and 14.37 ± 6.30 units versus 19.02 ± 9.76 units for basal insulin, respectively). The mean changes in daily bolus insulin from baseline to Week 24 were numerically similar in the treatment groups (4.07 ± 5.52 units versus 4.75 ± 7.07 units for the insulin glargine and NPH insulin groups, respectively).” Revised in the manuscript.

Reviewer #2: Summary

Major comments

1. In the abstract, the conclusion is not entirely correct, and the message may be misleading given that the trial did not have enough statistical power to detect any statistically different in effectiveness and safety data. Please revise.

Response:
We have taken this comment into consideration and revised the conclusion in the abstract. The conclusion of the abstract has been revised to “Initiation of insulin glargine can aid Chinese paediatric patients with T1DM to safely reduce their HbA1c levels.” Revised in the manuscript.

2. The major limitation of this study is a small sample size due to recruitment failure. Since the trial did not have enough power to assess the difference in outcomes across arms, the objective should be revised from "...to assess the safety and efficacy of …" to "...to describe the safety and efficacy of…".

Response:

We agree with the edit suggested. Revision has been made as follows in the abstract and background:

-“We aimed to describe the safety and efficacy of insulin glargine in Chinese paediatric patients with type 1 diabetes mellitus (T1DM).”

-“Therefore, the purpose of the present study was to describe the safety and efficacy of once-daily insulin glargine over a period of 24 weeks in Chinese paediatric patients with T1DM”

Revised in the manuscript.

3. Why the authors chose to conduct an open label as opposed to single or double blinded trial? Why a randomized 2:1 design was used? Please provide the justification under the methods section.

Response:

As insulin glargine was q.d. dosing and NPH insulin q.d. or b.i.d dosing, it was not feasible to conduct a blinded study. However assessment of the outcomes were based on objectively collected data, wherein HbA1c measurements were conducted by central laboratories blinded to the treatment and SMBG was used for the collection of blood glucose data.

The unbalanced 2:1 randomisation was used for the purpose of having a greater number of patients exposed to insulin glargine in order to better document the safety of insulin glargine in the population. Information has been included under the methods and discussion sections explaining the rationale behind the 2:1 randomisation and open-label design of the trial, respectively. Revised in the manuscript.
4. It is unclear how patients were randomized. How the randomization sequence was generated? Was the allocation concealed? What was the unit of allocation? Please describe allocation process.

Response:

As randomisation and patient allocation is a large and complicated process, we have provided the some basic information which covers the key randomisation scheme.

The following information has been included under the methods section explaining the key randomisation scheme: “Patients were centrally randomised in a block size of six and in a 2:1 ratio to receive insulin glargine (Lantus, Sanofi, Paris, France) by subcutaneous injection once daily at bedtime (20:00–22:00), or NPH insulin (Novolin N, Novo Nordisk, Copenhagen, Denmark) by subcutaneous injection either once daily at bedtime or twice daily: once before breakfast and once at bedtime. Investigators were allowed to select which of these two methods was more appropriate for their patients. Randomisation was conducted using an interactive voice response system and patients were stratified according to screening age (<12 years, ≥12 years) and screening HbA1c (<9% [<74.9 mmol/mol], ≥9% [≥74.9 mmol/mol]). A 2:1 randomisation ratio allowing a greater number of patients exposure to insulin glargine was used in order to accurately assess and document the safety of insulin glargine in the patient population.” Revised in the manuscript

5. On Page 4, Line 5-11, why NPH insulin was used by investigator's discretion. Why its use was not guided by local clinical practice guidelines?

Response:

Local clinical practice guidelines state that NPH insulin can be administered at any time of the day. However administration of NPH insulin twice a day is more common in real-life clinical practice in China. Therefore this trial allowed for the subcutaneous administration of NPH insulin either once daily at bedtime (20:00 to 22:00), to be consistent with the administration timing of insulin glargine, or twice daily in the morning (before breakfast) and at bedtime (20:00 to 22:00). The investigators were allowed to select which of these two methods was more appropriate for the patients.

The number and timing of the NPH insulin injections were also not altered from the time of randomisation until the end of the study, unless deemed necessary by the investigator.

We have revised the methods section to stress that the investigators practice was in line with the clinical practice guidelines, as such: “Patients were centrally randomised in a block size of six and in a 2:1 ratio to receive insulin glargine (Lantus, Sanofi, Paris, France) by subcutaneous injection once daily at bedtime (20:00–22:00), or NPH insulin (Novolin N, Novo Nordisk,
Copenhagen, Denmark) by subcutaneous injection either once daily at bedtime or twice daily: once before breakfast and once at bedtime. Investigators were allowed to select which of these two methods was more appropriate for their patients.”

Revised in the manuscript

6. Under the enrollment section, clearer justification for the decision to reduce the sample size from 366 to 150 patients should be added. As well, original sample size should be included.

Response:

We have taken this comment into consideration and revised the appropriate sections. Further explanation behind the reduction in sample size from 366 to 150 patients has been included under the enrolment section. The original sample size for each of the treatment groups has also been included. Additionally, rationale behind the reduction in sample size included under the discussion and supplementary sections have been cut down in order remove repetition in the manuscript. Revised in the manuscript.

7. Page 4, Line 46 should be study outcomes instead of study objectives. This section should also describe how the primary outcome was measured.

Response:

We agree with the edit suggested. Revised in manuscript.

- Detailed descriptions of outcome measures in the supplementary information should be moved to this section.

Response:

We agree with the edit suggested. We have moved information on the method of the outcome measurement from the ‘study measurements’ section under the ‘Supplementary materials’ to the main text, under the ‘patients and methods’ section. Additionally and in accordance with reviewer 1’s comments we have included information on the reproducibility/accuracy and reference values for HbA1c in the same section. Revised in manuscript.
8. Page 5, Line 53, why minimum and maximum values were used to represent the dispersion of median as opposed to an interquartile range?

Response:

As reviewer 1 suggested, we have revised the manuscript and only used mean ± SD to describe all the variables in the results section. However in the ‘discussion’ section the median (25%-75% quartile) absolute changes in HbA1c have been briefly mentioned and the tables have been updated to include the 25%-75% quartile values for the median. Revised in the manuscript.

9. How many patients did not have outcome data at Week 24? Given that LOCF ignores whether the participant's condition was improving or deteriorating at the time of dropout, this technique may inappropriately stop the increase in glycemic measures or artificially stabilize glucose level in those who dropout. This may introduce bias to the trial's results. The use of LOCF should be discussed as one of the limitation.

Response:

The number of patients without outcome data can be gleaned from Tables 1 and 2 of the manuscript. We have taken this comment into consideration and the use of LOCF has been discussed as one of the limitations under the discussion section. The following information has been included under the methods section highlighting the limitation of LOCF:

“Another one of the limitations of this study arose from patients discontinuing treatment prematurely during the treatment period, resulting in outcome data not being reported for Week 24. Assessment of the primary and secondary endpoints for these patients was therefore conducted using their last post-baseline on-treatment measurement for the calculation of Week 24 (Last Observation Carried Forward [LOCF]). Given that LOCF does not take into consideration whether a patient’s condition was improving or deteriorating at the time of dropout, the analysis may have incorrectly increased, decreased or stabilised patients’ glycaemic measures thereby introducing bias.”

Revised in the manuscript

- In addition, Table 1 should present data for Week 24 WITH and WITHOUT LOCF.

Response:
We agree with the suggested data inclusion. Table 1 has been revised to include data for Week 24 with and without LOCF. Revised in the manuscript.

10. On Page 11, the authors claims that there is no competing interest; however, two co-authors (LS and XLD) are employers of Sanofi, the company that produces and sells insulin glargine. Both authors also contributed to the analysis and interpretation of the data. Competing interest section should be revised.

Response:

We have taken this comment into consideration and updated the competing interest section. The competing interest section has been revised to state that LS and XYD are employees of Sanofi. Revised in the manuscript.

Minor comments

1. Page 6, Line 20-21, the authors indicate that demographic and baseline characteristics were shown in Table 1, but they were included as a supplementary information. Please verify.

Response:

We agree with the edit suggested. ‘Table 1’ has been updated to ‘Supplementary Table 1’. Revised in the manuscript.

2. Page 6, Line 57, please delete an extra word (between) at the end of Line 57.

This sentences has been revised according to Reviewer 1’s comments. The sentence has been revised to “There was considerable difference in change in FBG between the insulin glargine and NPH treatment groups (–0.76 ± 3.56 mmol/l versus 1.07 ± 3.64 mmol/l)”. Revised in the manuscript.

Other additions

Footnotes under tables 1 and 2 have been updated in order to more accurately explain the data and abbreviations used in the tables.
- Table 2 has been revised to include data pertaining to Week 24.
- The words “randomized” and “summarized” have been revised throughout the manuscript to adhere to UK spelling.
- The words “being overweight” on page 7 line 44 has been rephrased to “weight gain”
- Throughout the manuscript: “vs” has been expanded to “versus”