Author’s response to reviews

Title: The effect of insulin degludec on risk of symptomatic nocturnal hypoglycaemia in adults with type 1 diabetes and high risk of nocturnal severe hypoglycaemia (the HypoDeg trial): study rationale and design

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Author’s response to reviews:
Dear Editor-in-chief,

Thank you for the review and some very relevant comments. Enclosed please find the revised version of our manuscript “The effect of insulin degludec on risk of symptomatic nocturnal hypoglycaemia in subjects with type 1 diabetes and high risk of nocturnal severe hypoglycaemia (the HypoDeg trial): study rationale and design”

Below we have provided a detailed response to each of the referees’ comments.

All changes to the manuscript have been highlighted.

Editor Comments:

I) We noticed that there is overlapping text between this manuscript and your 2015 article (http://www.biomedcentral.com/1472-6823/12/10). We understand that the two articles are related, but we would ask that you reduce the overlap in text particularly in the i) visit procedures and ii) lab analysis sections:

Reply I:
The overlap in i) Visit procedures and ii) Laboratory analysis has been reduced as requested. In revised manuscript see section: ‘Visit procedures’, page 10, line 18-57 and page 11, line 1-40 and section: ‘Laboratory analyses’, page 16, line 40-56 and page 17, line 1-14.

II) Please clarify if written or verbal consent will be obtained from participant

Reply II:

Written informed consent was obtained by all participants prior to any protocol-related procedures. In revised manuscript see section: ‘Visit procedures’, page 10, line 30-31.

Reviewer reports:

Frier Brian (Reviewer 1):

I) This paper describes the protocol for a multicentre clinical trial, HypoDeg, that is being performed in Denmark. This trial compares two long-acting basal insulin analogues, insulin degludec and insulin glargine, in adults with type 1 diabetes with a high risk of nocturnal hypoglycaemia who are being treated with basal-bolus regimens, to ascertain
whether insulin degludec is more effective in limiting the frequency of nocturnal events. As it is a cross-over trial, this insulin cannot be said to be "reducing" the frequency of hypoglycaemia, unless insulin glargine is always the first insulin to be used, which would not be a randomised trial and would introduce an order effect. This inaccurate terminology should be corrected.

Reply I:

Thank you for your comment. We understand your point of view. Insulin glargine was of course not always the first insulin to be used since this study is a randomised trial. In the new manuscript we have rephrased our paragraph in the abstract and in the section ‘Aims’ using the words compare, risk and limiting instead of reducing, see ‘Abstract’ page 3, line 14, line 21 and line 48-55, and the section: ‘Aims’, page 6, line 26-31. In the section ‘Discussion’ we have changed the expression reducing to limiting, see page 17, line 28-29.

II) Patients were recruited for the trial between 2015 and 2017, and the trial will be completed this year (2019). As the trial is near completion, it is not feasible to provide constructive criticism of the detailed protocol. This raises the question as to why the protocol was not published earlier, and preferably before the study commenced?

Reply II:

We are aware of this unfortunate situation and would have preferred a publication sooner. We are, however, not able to change the circumstances and believe that a publication is still relevant before publication of our primary results.

Some points require consideration and modification.

III) In the present politically correct climate, it is no longer acceptable to use the term "subjects" (title and throughout the text), and this should be changed to "adults" in the title and either participants, patients or people with type 1 diabetes, should be used in the manuscript.

Reply III:

We have changed the term “subjects” in the title to “adults” (see page 1, line 4). Throughout the manuscript we have changed the term “subjects” to either participants or patients (see highlighting).
IV) This is a randomised trial with two treatment arms and a cross-over design. Was the randomisation counterbalanced? This should be stated.

Reply IV:

Thank you for your question. This was previously stated in the section: ‘Visit procedures’. We have decided to emphasize the randomisation procedure by its own section which is now to be found in the revised manuscript in section: ‘Randomisation’, page 10, line 1-14.

V) Many participants in SWITCH-1, who were at high risk of severe hypoglycaemia, would have experienced severe hypoglycaemia at night, so it should be made clear how the present comparative trial is substantially different.

Reply V:

Thank you for your important comment. This is exactly our concern, but it remains undocumented in the SWITCH-1 baseline data, which is why this comparative trial with patients having documented problematic nocturnal hypoglycaemia is important.

The idea for the HypoDeg study arose from the results of the BEGIN trial programme. This programme demonstrated lower rates of nocturnal hypoglycaemia (secondary endpoints) in both individual trials and in meta-analyses. The difference between insulin degludec and insulin glargine manifested itself during the night. With our knowledge from the HypoAna trial demonstrating superiority of insulin detemir compared with NPH insulin on occurrence of both severe and non-severe nocturnal hypoglycaemia we wanted to study the possible superiority of insulin degludec on occurrence of nocturnal hypoglycaemia as compared with insulin glargine (comparator in the BEGIN programme) in the high-risk type 1 diabetes population.

The results of the SWITCH-1 study was published after initiation of the HypoDeg study, and although SWITCH-1 included patients at risk of experiencing hypoglycaemia, only 25% of participants had experienced severe hypoglycaemia in the preceding year, and only 20% had hypoglycaemia unawareness defined by a history of impaired autonomic responses, but not determined according to one of the acknowledged methods of awareness classification, and as mentioned previously SWITCH-1 did not state previous occurrence of nocturnal hypoglycaemia. In the HypoDeg study we include only participants who have experienced at least one episode of nocturnal severe hypoglycaemia during the last two years, and we expect at least 80% to have impaired awareness of hypoglycaemia or to be unaware of hypoglycaemia with reference to the HypoAna study where more than 90% had impaired awareness or were unaware of hypoglycaemia.
One may speculate that the risk of hypoglycaemia is very different in a patient having experienced one or more episodes of severe hypoglycaemia in the preceding years compared to a patient having had diabetes for more than 15 years as the only risk factor for hypoglycaemia.

Finally, the SWITCH-1 study has been criticized for pooling their hypoglycaemic endpoints (severe and non-severe combined), for short maintenance periods of 16 weeks, for not assessing nocturnal asymptomatic hypoglycaemia by CGM and for using titration regimens that probably exceed common clinical practice.

The HypoDeg study embraces all these criticized points.

VI) The primary aim is to examine the effect of basal insulins on symptomatic nocturnal hypoglycaemia. This would imply that the participants are awake while experiencing hypoglycaemia at night, as sleeping patients are generally asymptomatic when blood glucose is low, though they may awaken as a result. Do the authors mean that they intend to study the frequency of hypoglycaemia during sleep, which is taking place at night?

Reply VI:

Thank you for your question. We intend to include all episodes of symptomatic hypoglycaemia which awaken the patients during night-time. These are the hypoglycaemic episodes that the patients fear the most. Furthermore, taking our definitions of night into considerations episodes can occur both late night before patients go to sleep, during sleep when patients are awakened by symptoms until morning bolus of aspart or the conventional time cut of night. We believe that night-time is individual, and we want to capture the true effect of the long-acting insulin analogues without overlapping effect of the short-acting analogue. In the hypoglycaemia diary patients are asked to register if they were awake or asleep when the episode occurred. We will, hereby, be able to take the state of awake or asleep in to account in our analyses. Symptoms must of course be present in all cases.

The occurrence of asymptomatic hypoglycaemia will be evaluated in our CGM data.

VII) Much nocturnal hypoglycaemia is asymptomatic and is therefore unrecognised. This is unlikely to be reported by the patients or to be detected by random capillary blood glucose testing and requires continuous glucose monitoring to identify all low glucose values. To ensure robust identification of nocturnal hypoglycaemia, the use of CGM, or overnight admission to hospital for glucose profiles, should have been fundamental for all participants and not offered as an optional measure. This is a potential weakness of the study protocol and should be acknowledged in the Discussion.
Reply VII:

Thank you for highlighting the important topic of complete assessment of hypoglycaemia. Assessing frequency of hypoglycaemia by blinded CGM in clinical diabetes trials provides information unattainable by intermittent capillary blood glucose monitoring.

The CGM and overnight admissions to hospital for glucose profiles were optional for feasibility and recruitment purposes - the assessment methods could not be offered at all centers due to geographical/logistical issues and having these assessment methods as fundamental parts of the study could have hampered the inclusion.

These limitations will of course be acknowledged in the discussion when publishing the primary and secondary endpoints.

VIII) A severe nocturnal event that causes coma and/or seizure may not waken the patient who cannot give any subsequent description of the event, may have complete amnesia afterwards and some such events may certainly go undetected. When they are overt, they are usually identified by a career or observer. What the authors are attempting to identify and measure, needs to be clarified.

IX) A severe event is to be reported by phone by the patient within 24 hours. This could create a potential problem with the documentation and may result in under-reporting of severe events. How can the authors verify when a severe event has occurred, that this did require external assistance and how can missing data be identified?

X) Experience from previous studies has shown that it is desirable that severe hypoglycaemia events are confirmed and reported by an observer (often a family member), and ideally by the individual who assisted recovery. How confident are the authors that the described arrangement of self-report by the patient in the present study is robust?

Reply VIII, IX and X:

We aim to identify severe hypoglycaemic events, which are events requiring assistance of another person to restore normoglycaemia. A structured interview questionnaire is applied to every episode in order to validate the event according to Whipple’s triad. The questionnaire included questions on who assisted recovery.

We will work with self-reported outcomes and encourage the participants at every visit to report severe events within 24 hours. By quarterly catch-up at the outpatient clinics the investigators
were instructed to encounter all episodes of severe hypoglycaemia that had not been reported within 24 hours.

We are of course challenged and limited by the patients’ willingness to report severe hypoglycaemic events. This limitation will be discussed in the primary article. However, we did not expect willingness to report to change between the treatment arms.

We have supplemented the text in section: ‘Severe hypoglycaemia’, page 13, line 30-45 by:

‘Like in daily clinical practice investigators must encourage patients to report all episodes of severe hypoglycaemia at the quarterly visits at the outpatient clinics, hereby minimizing the risk of missing events.

A structured interview questionnaire will be applied to all possible severe hypoglycaemic episodes in order to validate episodes according to Whipple’s triad. All episodes will be adjudicated by an independent endpoint committee consisting of diabetes specialists blinded to the individual patient insulin regimen.’

XI) The current definition of biochemical hypoglycaemia (<3.0 mmol/L), which post-dated the start of this trial, has been acknowledged (p. 13) and will be used in analysis of the results, which is appropriate and desirable. However, reference 42 is cited for the new definition. At present there are 28 references listed, with no reference 42. This should be included in the reference list, and the reference numbering updated in the paper.

Reply XI:

Thank you for making us aware of this mistake. The reference numbering has been updated in the revised paper, see section ‘Endpoint registration’, page 13, line 1.

Holstein Andreas (Reviewer 2): General comments

I) The manuscript "The effect of insulin degludec on risk of symptomatic nocturnal hypoglycaemia in subjects with type 1 diabetes and high risk of nocturnal severe hypoglycaemia (the HypoDeg trial): study rationale and design" by R.M. Agesen et al. addresses an important issue in current diabetology.

Moreover, the comprehensive, very detailed design (PROBE) of this ambitious study represents the conditions of real-life by including a selected cohort of people with type 1 diabetes at high
risk of severe hypoglycaemia that is generally explicitly excluded from RCTs. Overall, the originality of this study is high.

Study rationale and design are presented clearly and well-structured providing a variety of precise definitions of hypoglycaemia and clock times as well as an adequate assessment of the state of hypoglycaemia awareness.

Reply I:
Thank you for your positive feedback.

Specific Comments

II) The HypoDeg trial is a further development of the SWITCH1 trial that included in 75% patients with substantial risk factors for hypoglycaemia. The SWITCH1 study has demonstrated that insulin degludec is partly superior to the first-generation basal analogue glargine with regard to the occurrence of hypoglycaemia. Thus, the results of the HypoDeg trial are quite predictable as this study is performed in a cohort of patients with even more pronounced risk conditions for hypoglycaemia.

Reply II:
Thank you for your comment. Please see Reply V reviewer 1.

III) The investigator-initiated HypoDeg trial has clearly been planned before 2015 as first subjects were included in January 2015. Insulin glargine U300 was approved by the European Medicines Agency in 02/2015. However, results of the EDITION 4 trial comparing the risk of nocturnal hypoglycaemia between insulin glargine U100 versus insulin glargine U300 in patients with type 1 diabetes have already been published in abstract form in 2014 (Home PD et al.; Diabetologia). Thus, it would have been preferable and highly topical to compare head-to-head insulin degludec versus insulin glargine U300 representing two second-generation long-acting insulin analogues. The authors should give a short comment with regard to this point.

Reply III:
Thank you for your relevant comment. The HypoDeg study was planned throughout 2014 and pre-screening/pre-selection approaches were initiated during the last months of 2014 with inclusion of the first participant on January 5, 2015. We agree that a head-to-head comparison between insulin degludec and insulin glargine U300 is highly topical, but as you mention insulin glargine U300 was approved by the European Medicines Agency in February 2015 when the
HypoDeg study was already initiated. The idea for the HypoDeg study arose from the results of the BEGIN programme investigating insulin degludec compared to insulin glargine U100 and from the HypoAna study including, as the first insulin study, only high-risk type 1 diabetes patients.

IV) According to a power calculation and to results from the HypoAna trial, this two-year cross-over study will include approximately 175 subjects with type 1 diabetes prone to severe hypoglycaemia. The study avoids a treat-to-target design which could itself increase the number of hypoglycaemic events. I wonder whether the number of completed patients with experienced nocturnal hypoglycaemic episodes will be sufficient in order to show statistically significant differences between the two insulin formulations. Hopefully, repeated ambulatory CGMs will provide sufficient hypoglycaemic events.

Reply IV:
Thank you for your reasonable concern. Rates and distributions of hypoglycaemic events are unpredictable and formal power calculations are, therefore, not feasible. From the HypoAna prescreening questionnaire a skewed distribution of severe hypoglycaemia was demonstrated – a minority of subjects accounted for a large proportion of episodes, 6% had five or more episodes corresponding to more than 63% of all episodes. Around 20% had 2 or more episodes per patient-year. Concerning non-severe hypoglycaemia 18% of the participants accounted for 52% of all events occurring in the study.

According to the power calculation and results from the HypoAna-trial with a significant relative difference between treatment regimens of approximately 30-40% concerning both primary and secondary nocturnal endpoints we found it appropriate to include and randomize 175 type 1 diabetes patients prone to severe hypoglycaemia (1 or more episodes of nocturnal severe hypoglycaemia during the preceding two years). The BEGIN Basal-Bolus Type 1 study had a 3:1 (472:157) assignment to insulin degludec and insulin glargine and found a significant relative difference (25%) concerning nocturnal hypoglycaemia similar to the HypoAna study. This substantiates our estimate of 175 type 1 diabetes patients prone to nocturnal severe hypoglycaemia being appropriate for inclusion and randomisation for the HypoDeg study.

V) The number of participants experiencing >1 hypoglycaemic event should explicitly be recorded in the endpoint registration.

Reply V:
This will of course be reported as part of the primary endpoint article.
VI) It should be considered to expand the second standard nocturnal window (23:00-06:59) to 22:00-08:00 with a pre-breakfast SMPG measurement. Of course, this clock time extension is also arbitrary but would increase the number of hypoglycaemic events. In the EDITION- and BEGIN trials a substantial number of hypoglycaemic episodes occurred within this time period.

Reply VI:

Thank you for a relevant input. By our arbitrary definition of night from 4 hours after evening bolus of short-acting insulin until time for actual morning bolus insulin administration we strive for individuality and for inclusion of the substantial hypoglycaemic episodes that may occur in the extra hours that this definition in most cases added. This definition also included the pre-breakfast SMPG measurement by default.

Baqiyyah Conway (Reviewer 3): This is an important concept paper describing an ongoing the purpose and methods of an ongoing case-cross over clinical trial of hypoglycemic events among persons with Type 1 diabetes using the insulin degludec vs. glargine. A couple of concerns are that

I) The article is written more like a grant proposal than an article manuscript. Please write the manuscript in article manuscript style.

II) The paper needs to be better organized. For example, it may be more logical to place the description of the study population before visit procedures rather than after it

III) It needs to be better emphasized in the Introduction that the purpose of this paper is to Introduce this study, providing the rationale and study design for this ongoing study. I had to go back to the title to figure out the purpose of this paper.

Reply I, II, III:

Thank you for your initial thoughts and thank you for your comments. We have tried to make a better organization of the paper. In the revised manuscript we have placed the section: ‘Participants’, page 8, line 45-55 and page 9, line 1-57 before the section: ‘Randomisation’ and ‘Visit procedures’, page 10, line 1-14, page 10, line 18-57 and page 11, line 1-40, respectively. As mentioned previously in the answer to Reviewer 1, question IV, the section ‘Randomisation’ is new in order to emphasize the randomisation procedure.
We have tried to emphasize the rationale in the section ‘Background’ by including the sentence: ‘The effect of insulin degludec in limiting nocturnal hypoglycaemia remains undocumented in this high-risk type 1 diabetes population’. See ‘Background’, page 6, line 8-11.

This article is an overview of our protocol why we find it difficult to provide further classic article manuscript style. We have chosen not to describe the design in the introduction, but rather chosen to provide a detailed aim and study design section striving for an easy overview of the study.

IV) On page 10, please spell out CRF

Reply IV:

Thank you for making us aware of this mistake. CRF has been spelled out. In the revised paper see section: ‘Randomisation’, page 10, line 6.

V) On page 11, line 55. Where the authors state: "Subjects were included", do they mean "recruited" or do they mean "seen"

Reply V:

This paragraph is now to be found on page 9, line 54-57 in the section ‘Participants’.

We are sorry that this paragraph is not clear. We are referring to the recruitment period. Last patient, first visit was in February 2017. Last patient, last visit was in February 2019.

Landgraf Wolfgang (Reviewer 4):

I) The authors should clearly use throughout the manuscript incl. abstract the term „insulin glargine 100U/mL or Gla-100 instead of „insulin glargine" only.

Reply I:

This has been corrected in the abstract and throughout the manuscript (see highlighting).