Reviewer’s report

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

Version: 0 Date: 29 Apr 2019

Reviewer: Frier Brian

Reviewer's report:

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. 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?

Some points require consideration and modification.

1. 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.

2. This is a randomised trial with two treatment arms and a cross-over design. Was the randomisation counterbalanced? This should be stated. 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.

3. 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? 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. 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 carer or observer. What the authors are attempting to identify and measure, needs to be clarified.

4. 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? 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?

5. 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.

**Are the methods appropriate and well described?**
If not, please specify what is required in your comments to the authors.

No

**Does the work include the necessary controls?**
If not, please specify which controls are required in your comments to the authors.

Yes

**Are the conclusions drawn adequately supported by the data shown?**
If not, please explain in your comments to the authors.

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I have received honoraria for serving on advisory boards and as a speaker at scientific meetings for Novo Nordisk, which has funded this study. Favourable results for insulin degludec in this study would be of benefit to this pharmaceutical company, but a paper on the protocol will not have any financial benefit. I have had no involvement with this study in any way.

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