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

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Reviewer: Holstein Andreas

Reviewer's report:

General comments

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.

Specific Comments

1. 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.

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.

2. 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.

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

4. 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.

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

Yes

Does the work include the necessary controls?
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Yes

Are the conclusions drawn adequately supported by the data shown?
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