Reviewer’s report

Title: A prospective randomised cross-over study of the effect of insulin analogues and human insulin on the frequency of severe hypoglycaemia in patients with type 1 diabetes and recurrent hypoglycaemia (the HypoAna Trial): Study rationale and design

Version: 1 Date: 16 May 2012

Reviewer: James Shaw

Reviewer’s report:

This manuscript describes a protocol for a prospective randomised cross-over study comparing the effect of insulin analogues and human insulin on severe hypoglycaemia in individuals with type 1 diabetes with a history of recurrent severe hypoglycaemia.

The rationale and unmet need for the study is well-justified. The study is investigator-initiated by a team of Danish researchers experienced in the field. Funding has been provided by Novo Nordisk and several of the investigators have some links with this company which have been acknowledged. It is noted that the study has already been completed and the Editors may wish to confirm that analysis has not been commenced prior to submission of this manuscript.

I am supportive of publication subject to addressing the following points although there are no major 'compulsory revisions':

Page 4: suggest ‘Insulin analogues have been developed….Short acting insulin analogues…were designed…long-acting insulin analogues were designed…with minimal peak action…with a presumed lower risk of hypoglycaemia...for several reasons the impact of insulin analogues…This renders the trials insufficiently…'


In describing effect of insulin analogues in large trials suggest inclusion of reference: ‘Hypoglycemia rates with basal insulin analogs.


Page 6: Cite pilot study showing reduction in severe hypoglycaemia in type 1 diabetes complicated by impaired awareness of hypoglycaemia in an RCT including non-analogue MDI and short-acting analogue / glargine arms (A randomized pilot study in Type 1 diabetes complicated by severe hypoglycaemia, comparing rigorous hypoglycaemia avoidance with insulin analogue therapy, CSII or education alone.)

Page 7: suggest ‘insulin analogue and human insulin over the preceding 9 months…’

Page 8: Add further details on insulin regimens including number of injections per day and timing of basal insulins; whether prandial insulins were given before, during or after meals (number of injections per day), injection devices used and injection sites used.

Page 9: ‘hypothyroidism’ not ‘myxoedema’. Study ‘will be’ or ‘was’ conducted in accordance…

‘Participants attend the outpatient clinic every three months. After informed consent participants attend fasting…’

Page 10: Suggest inclusion also of validated Clarke or Gold hypoglycaemia awareness questionnaires (clearly may now be too late). Why fasting C-peptide not stimulated or at least taken with concomitant plasma glucose with confirmation that this is not <4mmol/l.

Was insulin given after breakfast?

Clarify whether 19887 or revised Adult Low Blood Sugar Survey version of Hypoglycaemia Fear Survey was used.

Page 12 Clarify whether truly blinded or real time CGM was employed.

Page 15 ‘repeated after 1 year (before changing insulin...is measured centrally at Steno...An ACTH stimulation test was undertaken...analyses are performed...’

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

Member of an ad hoc Novo Nordisk Advisory Board on insulin degludec. Travel support to attend American Diabetes Association Conference from Novo Nordisk.