PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Glimepiride monotherapy vs. combination of glimepiride and linagliptin therapy in patients with HNF1A-diabetes: protocol for a randomised, double-blinded, placebo-controlled trial
AUTHORS	Sidelmann Christensen, Alexander; Storgaard, Heidi; Hædersdal, Sofie; Hansen, Torben; Krag Knop, Filip; Vilsbøll, Tina

VERSION 1 – REVIEW

REVIEWER	Henning Beck-Nielsen Odnse University Hospital, Denmark
REVIEW RETURNED	20-Mar-2018

GENERAL COMMENTS	This is a relevant study and a clear written protocol, but the design can be questioned. A adjustment of the glimeperide dose in a treat to target model may make the two groups incomparable. Furthermore, inclusion of patients all ready on glimeperide can be criticised since SU receptors all ready may be saturated with the given dosis. Therefore, the optimal design to me is to use drug naive patients and to give a fixed dose of glimeperide f.ex. 1-2 mg together with the DPPIV inhibitor. The endpoint thus will be A1c and number of hypos. Only if hypos is induced dose of glimeperide should be reduced. That design will show if the DPPIV inhibitor protects against hypos at the same time as BG values are reduced.

REVIEWER	Prof. Andrew Hattersley University of Exeter Medical School Exeter, UK
REVIEW RETURNED	21-Mar-2018

GENERAL COMMENTS	This is a very interesting study which will give interesting results. The protocol is well described and is very clear. I hope you can get enough HNF1A patients to recruit for the study as it may be hard to find the patient numbers. However I accept your centre did a good job with the GLP-1 study. I have a few minor points for clarification. 1. Your suggestion from a very old reference that MODY is 2% of all diabetes is not correct. A recent population study showed it was 3% of all diabetes diagnosed under 30 years (Shepherd MH Diabetes Care 2017). This is a lot less than 2% of all diabetes. 2. In the introduction you are very damming about sulphonylureas and even speculate they may kill you by causing hypoglycaemia (this part is very poorly supported!). however in your study you go on to give a sulphonylurea in both arms of your study. You suggested that GLP-1 agonist is better so why was this not the comparator? Why did you not try an DPP4 inhibitor on its own? My personal

	opinion is that properly titrated SUs are safe and easy to use - unless you do foolish things like give patients glibenclamide, little food and lots of exercise!! I would suggest you might tone down the anti SU section of the introduction or at least give the contrary argument given you are going to use them in your study. 3. My experience of adding a DPP4i to an SU when there is poor control in HNF1A patients is that you need to reduce the dose of the SU to avoid hypos. I think you should emphasise the titration down or up in SU dose that will be carried out when the blinded drug changes and may be the final dose of SU should be documented as a secondary endpoint. 4.I am surprised at the primary clinical endpoint you used using CGM - you could justify this better in the protocol. I would have thought a better HbA1c with no increase in hypos would be the most clinically relevant end point. Why was this not used? 5. In the CGM analysis you have not said what checks you would do for quality of CGM traces before doing the MAGE analysis 6. You do not say you will examine for order effects or carry-over - this would be routine in a cross-over study.

VERSION 1 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:

Reviewer: 1

Reviewer Name: Henning Beck-Nielsen

Institution and Country: Odnse University Hospital, Denmark

Reviewer 1 comment: *This is a relevant study and a clear written protocol, but the design can be questioned. A adjustment of the glimeperide dose in a treat to target model may make the two groups incomparable.*

Authors reply: Thank you very much for your positive comment. We appreciate that you find our study relevant and the text clear.

We have given the “treat to target”-model of the design a lot of consideration. Our primary aim was to design a highly clinical relevant trial. Given the *cross-over* design, where patients are their own controls, we consider the participants as one group. Based on our own clinical experiences and case reports we trust that glimepiride *and* linagliptin will have additive or supra-additive effects on postprandial glucose excursions and that the *treat-to-target* design will not alleviate this difference. To increase the likelihood of capturing differences between treatments we use glycaemic variability measures based on the results from continuous glucose monitors (CGM) and

a meal test evaluation. The *treat-to-target* approach has an advantage compared to a simple

“linagliptin add-on” study (e.g. glimepiride fixed dose +/- linagliptin) as it is more clinical relevant and addresses risk of hypoglycaemia.

Reviewer 1 comment: *Furthermore, inclusion of patients all ready on glimeperide can be criticised since SU receptors all ready may be saturated with the given dosis. Therefore, the optimal design to me is to use drug naive patients and to give a fixed dose of glimeperide f.ex. 1-2 mg together with the DPPIV inhibitor."*

Authors reply: Thank you for raising an important issue and suggesting another very relevant trial to be conducted. We find that patients eligible for our study represent typical patients for whom intensified glycaemic control is needed; i.e. a patient with HNF1A-diabetes on glimepiride monotherapy and HbA1c >48 mmol/mol. And that the research question (is linagliptin a good option to provide a better glycaemic control vs. "just" increasing the dose of glimepiride?) is justified. Indeed, we agree with the reviewer that a trial with inclusion of treatment naïve individuals would be interesting. However, this would not be possible in our hands as a single-centre trial. We are currently planning a large trial designed as a multicentre trial with initiation of glucose-lowering drugs (glimepiride, DPP-4 inhibitor, placebo) early in HNF1A-diabetes (e.g. at the age of 18-years).

With respect to the dose of glimepiride it is approved in Europe in daily doses up to 6-8 mg daily. To our knowledge, the most appropriate, effective and/or highest recommended dose has never been finally determined in patients with HNF1A-diabetes. We have added this as a limitation in the manuscript, p. 11, Strengths and Limitations (please bear in mind that SUR1=sulphonylurea receptor 1):

"Another limitation is that participants at randomisation will receive different baseline doses of glimepiride. This may cause different levels of saturation of the SUR1 and thereby potentially inter-individual differences to an increment of the glimepiride dose".

Reviewer 1 comment:*" The endpoint thus will be A1c and number of hypos. Only if hypos is induced dose of glimeperide should be reduced. That design will show if the DPPIV inhibitor protects against hypos at the same time as BG values are reduced."*

Authors reply: The proposed combined endpoint of reduction of HbA1c and hypoglycaemia has its merits and has been discussed in detail in our group. We expect to see better or at least equal HbA1c levels in the treatment with glimepiride + linagliptin compared to glimepiride + placebo without an increase in hypoglycaemia. Indeed, several of the secondary endpoints in this study e.g. HbA1c and episodes of hypoglycaemia are going to be almost just as important as our primary endpoint. Please note that we will indeed reduce the dose of glimepiride if episodes of hypoglycaemia occur. Furthermore, we are confident that the CGMs will provide sound information on both glycaemic control and risk of hypoglycaemia. Many patients with HNF1A- diabetes only have mildly deranged fasting plasma glucose values and primarily a postprandial insulin secretory impairment with rising postprandial glucose values as the major problem. An improvement of postprandial glucose values should correspond nicely with an improvement of the mean amplitude of glycaemic excursions (MAGE). Given the repeatable measurement of CGM we expect to obtain more knowledge than 'just' measuring HbA1c would provide, and thereby be able to distinguish even minor but clinical relevant differences between treatments. In addition, CGM will provide sound information on hypoglycaemia, which is not only limited to the reports from patients. However, we do agree that it is a very good point that a composite endpoint of HbA1c and hypoglycaemia sums up important information and thus we have added a composite secondary endpoint the manuscript p. 7, "Secondary outcome measurements":

- *"Differences between treatments in the proportion of patients achieving HbA1c <48 mmol/mol (or a decrease in HbA1c more than 5 mmol/mol compared to baseline) and have no episodes of hypoglycaemia during the study"*

Reviewer: 2

Reviewer Name: Prof. Andrew Hattersley

Institution and Country: University of Exeter Medical School, Exeter, UK

Reviewer 2 comment: "*This is a very interesting study which will give interesting results. The protocol is well described and is very clear. I hope you can get enough HNF1A patients to recruit for the study as it may be hard to find the patient numbers. However, I accept your centre did a good job with the GLP-1 study"*

Our comment: We are very happy to hear that you find the study interesting and the protocol well described and clear.

Reviewer 2 comment: 1. *Your suggestion from a very old reference that MODY is 2% of all diabetes is not correct. A recent population study showed it was 3% of all diabetes diagnosed under 30 years (Shepherd MH Diabetes Care 2017). This is a lot less than 2% of all diabetes.*

Authors reply: Thank you very much for pointing this out. To estimate the exact prevalence of MODY is challenging and the prevalence differ from country to country. We appreciate that 3.7% of all diabetes patients diagnosed before 30 years of age, where due to MODY mutations (Shepherd MH Diabetes Care 2017) and now uses this as the reference. A recent not yet published Danish study has found approximately 1.5% of an unselected cohort of 3,000 newly diagnosed patients with type 2 diabetes had a GCK or a HNF1A MODY-mutation. Thus, we believe it is fair to write a minimum of 1% of diabetes may be attributed to MODY-mutations.

The Introduction (manuscript p. 4) has been changed: "*A minimum of 1% of all cases of diabetes is due to heritable monogenetic subtypes of diabetes collectively named maturity-onset diabetes of the young (MODY) [2]*"

Reviewer 2 comment: *2. In the introduction you are very damming about sulphonylureas and even speculate they may kill you by causing hypoglycaemia (this part is very poorly supported!). however in your study you go on to give a sulphonylurea in both arms of your study. You suggested that GLP-1 agonist is better so why was this not the comparator? Why did you not try an DPP4 inhibitor on its own? My personal opinion is that properly titrated SUs are safe and easy to use - unless you do foolish things like give patients glibenclamide, little food and lots of exercise!! I would suggest you might tone down the anti SU section of the introduction or at least give the contrary argument given you are going to use them in your study.*

Authors reply: Thank you for your comment. We agree that SU is the treatment of choice for patients with HNF1A-diabetes. They are indeed well tolerated and in general safe to use. We hypothesise that given the pathophysiology of HNF1A-diabetes that a small dose of SU and incretin-based therapy augments each other in terms of better glycaemic control. This is also our clinical experience, which initiated the current study. The choice of linagliptin and not a GLP-1 receptor agonist (GLP-1RA) rely on several things: 1) DPP-4 inhibitors are easier to use vs. GLP-1RA (injections), 2) they are well tolerated, 3) good case-based clinical experience with DPP-4 inhibitors, 4) HNF1A-diabetes patient may have retained some effect of GIP on the late-phase insulin response (*Vilsbøll T, J Clin Endocrinol Metab, 2003*) and 5) potential protection against hypoglycaemia with GIP.

Based on the very relevant reviewer comment and to make the introduction more balanced we have changed the text regarding SU and hypoglycaemia in the introduction. The manuscript, p.4 "Introduction" now states:

Thus, SU treatment is currently the recommended first-line therapy in patients with HNF1A-diabetes and is in general well-tolerated and considered safe [12,13]. However, due to the glucose-independent action of SUs, they confer a risk of hypoglycaemia even when relatively low doses are used [11]. In 2006, Tuomi et al. [12] demonstrated that 40% of their patients with HNF1A-diabetes developed hypoglycaemia during physical exercise (i.e. light cycling for 30 minutes two hours after meal ingestion) when treated with SU (glibenclamide). One patient experienced prolonged hypoglycaemia for 12 hours. In a clinical setting, some patients with HNF1A-diabetes have recurrent episodes of hypoglycaemia on SU treatment. In these patients, a reduction of SU dosing may protect against hypoglycaemia, however this may be at the expense of good glycaemic control. Therefore, patients with HNF1A-diabetes with recurrent hypoglycaemia on SU treatment and unsatisfactory HbA1c levels may benefit of a more effective treatment with a lower risk of hypoglycaemia.

Reviewer 2 comment: *3.* My *experience of adding a DPP4i to an SU when there is poor control in HNF1A patients is that you need to reduce the dose of the SU to avoid hypos. I think you should emphasise the titration down or up in SU dose that will be carried out when the blinded drug changes…*

Authors reply: Thank you for pointing this out. Given the inclusion criteria with HbA1c ≥6.5% (HbA1c ≥48 mmol/mol) our experience is that it is safe to introduce a DPP-4 inhibitor, but we do agree that lowering the dose of SU may be necessary in some cases. This may also be the case in our study given our protocol. When included, patients will continue on the same dose of glimepiride as they are treated with at inclusion. When linagliptin/placebo is initiated patients are instructed to daily measure fasting plasma glucose and report hypoglycaemia the following week. If average fasting plasma glucose values are <4.5 mmol/l or in case of hypoglycaemia, the daily glimepiride dose will be reduced with 0.5 mg. The glimepiride dose will only be increased if average fasting plasma glucose > 6.0 mmol/l without episodes of hypoglycaemia.

In order to make this clear for the readers we have update the manuscript accordingly (p. 6 "Intervention"):

"… Each treatment period is divided into a drug-titration period (week 1-4) and a maintenance period (week 5-16). After initiation of linagliptin/placebo patients will continue on the initial dose of glimepiride at screening for one week. Patients are instructed to measure fasting plasma glucose values daily. After the first week of linagliptin/placebo the glimepiride dose will be adjusted for the first time. Target fasting plasma glucose (average during at least five days) is between 4.5 and 6.0 mmol/l (both inclusive) without episodes of symptomatic or biochemical hypoglycaemia (plasma glucose ≤3.9

mmol/l). In case of no hypoglycaemia and an average fasting plasma glucose >6 mmol/l the glimepiride dose will be increased with 0.5 mg. In case of hypoglycaemia or average fasting plasma glucose <4.5 mmol/l, the dose of glimepiride will be decreased by 0.5 mg. In the remaining titration period the glimepiride dose will be up or down-titrated once-weekly in the same treat-to-target manner with a maximum daily dose of 6 mg in both groups. A total daily dose of glimepiride ≥1 mg will be divided and administered as two daily doses: one dose in the morning and one dose in the evening. If target fasting plasma glucose is not achieved during the drug-titration period, the dose of glimepiride will be adjusted after week 4 at the investigators discretion. In case of hypoglycaemia outside of the drug titration period, glimepiride dose will be down-titrated 0.5 mg."

Reviewer 2 comment: "*… and may be the final dose of SU should be documented as a secondary endpoint."*

Authors reply: Excellent suggestion. Now included in the manuscript p. 7, "Secondary outcome measurements":

- ***"Dose of glimepiride at the end of each treatment period"***

In addition, we have also updated the manuscript, p. 8 Box 1: Definition of outcome parameters:

"Dose of glimepiride at the end of each treatment period *as total daily dose of glimepiride"*

Reviewer 2 comments: 4) *"I am surprised at the primary clinical endpoint you used using CGM - you could justify this better in the protocol. I would have thought a better HbA1c with no increase in hypos would be the most clinically relevant end point. Why was this not used?"*

Authors reply: Thank you for this comment. Please read our answer to a similar comment by reviewer 1 (the bottom on page 3) regarding a combined endpoint of HbA1c and episodes of hypoglycaemia. We have added in the manuscript a brief explanation for the use of MAGE as a primary endpoint as suggested (p. 5, Study Objective):

… The primary endpoint is the difference in glycaemic variability defined as mean amplitude of glycaemic excursions (MAGE) between the two treatment arms at end of treatment. MAGE has been chosen as most patients with HNF1A-diabetes have only mildly deranged fasting glucose values and marked postprandial hyperglycaemia. An improvement in MAGE corresponds with an improvement of postprandial hyperglycaemia. Secondary endpoints consist of… "

Reviewer 2 comment: *5). In the CGM analysis you have not said what checks you would do for quality of CGM traces before doing the MAGE analysis*

Authors reply: This is an excellent and important question. In general the CGM recordings from Medtronic Ipro2 are reliable. We are using the quality checks as recommend in the newest consensus paper on CGM (Danne T, Diabetes Care 2017). In the supplementary material appendix

3 from the consensus paper on CGM it states that:

"CGM accuracy is dependent on SMBG test results for calibration. Therefore, it is important to have an accurate glucometer."

We use a well validated glucometer Contour XT which have been validated together with Medtronic Ipro2 CGMs.

In addition we will do the following quality checks according to the consensus paper on CGM:

"CGM sensors can be also affected by occasional, transient faults which need to be excluded prior to systematic analysis. Two common faults of are disconnection and the so-called 'compression artifact".

Reviewer 2 comment: *"6. You do not say you will examine for order effects or carry-over - this would be routine in a cross-over study."*

Authors reply: We do indeed plan to examine for a potential carry-over effect and obviously it should be mentioned in the manuscript. Thank you pointing this out. We have updated the manuscript (p. 10, "Statistical Analysis") accordingly by adding the following:

"Interaction between treatment and treatment period will be performed in linear mixed models to test for potential carry over effect"