Author's response to reviews

**Title:** Randomized, controlled, parallel-group prospective study to investigate the clinical effectiveness of early insulin treatment in patients with latent autoimmune diabetes in adults.

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**Author's response to reviews:** see over
Dear Sir/Madam,

Thank you for the comments and suggestions. Please find our amendments below:

1. **What is the reason not to choose DPP-IV inhibitors or GLP-1 (exenatide for example) have been proposed in impaired beta cell function. What is the reason not to choose them?**

These treatments were not on the market when the proposal was originally designed. This study was designed to inform GP’s as to the best treatment for their LADA patients, to treat with tablets or referral to secondary care for insulin. Currently NICE guidance does not sanction monotherapy use of either exenatide or Sitagliptin in the treatment of type 2 diabetes and were not licensed for use in the UK until 2007. In future DPP-IV inhibitors or GLP-1 could be acceptable alternatives to insulin which need investigating.

2. **What is the expected change in c-peptide with different treatments? Are data available on C-peptide in LADA in the considered population vs Japan? I expect an ethnic difference.**

The studies which have examined C-peptide using different treatments, have very small numbers. The largest study was conducted in China;

Zhu 2004

**Fasting C-peptide**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Baseline</th>
<th>12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin (n=33)</td>
<td>0.84 nmol/L (+/- 0.56)</td>
<td>1.12 nmol/l (+/-0.62)</td>
</tr>
<tr>
<td>SU (n=20)</td>
<td>0.82 nmol/L (+/-0.35)</td>
<td>0.94 nmol/l (+/-0.42)</td>
</tr>
<tr>
<td>Insulin and Chinese Medicine (n=31)</td>
<td>0.87 nmol/L (+/-0.54)</td>
<td>1.16 nmol/l (+/-0.42)</td>
</tr>
</tbody>
</table>

We have amended our sample size calculation to use this projection:

Page 13: The study conducted in China [14] examined fasting C-peptide levels over 12 month, the average difference in C-peptide at 12 months was 0.18 nmol/l (stdev: 0.5 nmol/l) between the insulin vs the SU groups. To find a difference of 0.7% in average HbA1c (standard deviation = 1.5%) we would need 97 analysible people in the insulin and the standard care arms of the study (power 90%, significance = 5%).

This would detect an average difference of 0.2 nmol/l in fasting C-peptide. As the
power calculation is based on patients in China, we will re-calculate the sample size based on the standard deviation of the first 30 patients recruited in our study.

3. The authors stated “As the power calculation is based on patients in Japan, we will re-calculate the sample size based on the standard deviation of the first 60 recruited patients”.

What is the expected drop out rate in each group? How the authors expect to handle this in the randomization and after the analysis of the first 60 recruited patients.

The following has been added:

Page 13: We will examine the standard deviation of the HbA1c and the fasting C-peptide in all 30 patients at 3 months (regardless of treatment) in order to re-estimate the sample size assuming a difference of 0.7% in HbA1c and 0.2 nmol/l in fasting C-peptide.

4. Statistical analysis seems not well described. The authors should perform 2 way ANOVA for repeated measurements, with account for cofactors when variables are normally distributed. Otherwise, log transformations or non parametric tests should be employed.

The following has been added:

Page 11: ANOVA for repeated measurements with be used when variables are normally distributed. Otherwise, log transformations or non parametric tests will be employed.

Figure 1: An algorithm on initial dose of insulin should be reported. This figure only report information on dose adjustment. Usually initial dose of insulin is given based on pre-prandial glycemia and or BMI.

In the UK it is unusual to use algorithms based on BMI or post-prandial glycaemia (or any other parameters). It tends to start at low dose and then be built up according to response. We have used the standard criteria used in the UK.

Figure 2: Sulfonylurea at baseline entry should be discontinued and substituted with another treatment. This is sort of reported at page 6, but should be made clear in this figure if this is the intention (another decision seems unethical based on the results of sulfonylurea reported in the introduction).
We have amended figure 2 to say: **Sulphonylurea discontinued**

*Although rosiglitazone is still on the market, it may increase risk of heart failure and myocardial infarction. Thus, cardiac as well as renal evaluation should be performed before putting a subject on rosiglitazone.*

The suggestion that rosiglitazone increases myocardial infarction is still controversial. In this study patients have a full physical examination at outset where cardiovascular history is taken into account.

*Pioglitazone does not seem to be as harmful as rosiglitazone: an explanation should be reported on why rosiglitazone vs general TZD was chosen.*

Rosiglitazone was chosen on the basis of it being most commonly used market-leader of the two glitazones, this remains the case despite the recent controversies in the literature.

*Second part of figure 2: Sulfonylurea disappeared and rosiglitazone with/without metformin is present. Where rosiglitazone alone has been introduced at baseline?*

Yes this is right. This is for visits 3-11 so sulfonylurea has be discontinued and rosiglitazone may be introduced.

*Only fasting C-peptide was used in screening. Most of these patients have low/normal C-peptide but impaired postparandial response. This should be checked as well and could be a good endpoint.*

We agree that stimulated C-peptide would give a better reflection of beta cell function. However, we did not include this in this trial as some patients are expected to become insulin dependent during the study and we felt that the stimulated C-peptide would be very difficult to perform, interpret and put some patients at risk of hypoglycemia. We have now started recruiting patients to the trial and do not feel this is a component we can now introduce.