Reviewer's report

**Title:** Randomised Prospective Study for the Effect of Therapy on Residual Beta Cell Function in Type-1 Diabetes Mellitus

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**Reviewer:** ERIFILI HATZIAGELAKI

**Level of interest:** A paper of considerable general medical or scientific interest

**Advice on publication:** Accept without revision

**General comments**

This paper describes the design of a study of the effect of intensive diabetes therapy on the preservation of residual beta cell function. Other aims are to find out whether there is an association between C-peptide concentration and glycosylated hemoglobin and the albumin excretion in urine. Apart from these surrogate parameters insulin reserve is related also to important clinical endpoints such as neuropathy and retinopathy.

The question of intensive diabetes therapy protecting insulin reserve in diabetes was addressed by other studies, but is not settled due to statistical considerations. All other studies including the DCCT landmark study had not chosen insulin reserve as major endpoint hypotheses but were designed for other reasons. Therefore this new trial is clearly needed since it will address the role of insulin reserve in a statistically sound way. In my opinion the ethical considerations of the study and the manner in which it is being conducted are appropriately described. The design and methodological issues and the decisions behind them are presented in a detailed way to the reader.

**Specific comments**

1) Are non-compliant patients continued to be followed and C-peptide levels assessed in accordance with the intent-to-treat principle?
2) The mix of a randomized study and an observational study based upon the participant's willingness or lack thereof to be randomized was first proposed by Zelen and is intriguing to be utilized for a diabetes study. But this design may present a number of problems. Unless participants are encouraged to join the randomized trial, why wouldn't virtually everyone opt to be simply followed and not randomized? Also it tends to be a problem for the site investigators, as to their own ethical viewpoints with regard to the value of intensive treatment and therefore willingness to encourage people to be randomized.
3) You define non-compliance, but do not state how it will be addressed in the collection, analysis or reporting of the data

**Competing interests:**
None declared.