Author's response to reviews

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

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- Definitions of neuropathy and retinopathy (B4) should be specified

Overall examination of the patients will include all the items of the St. Vincent Declaration data collection form (1). This includes foot examination with palpation of pulses and screening sensation loss with the Rydel-Seiffer-Tuning fork as described by Liniger et al (2). A sensational loss of < 6/8 will be denominated neuropathy". Moreover, will be recorded. Handling of the tuning fork and symptom questionnaire are described by the Foot Working Group of the Deutsche Diabetesgesellschaft (http://www.ag-fuss-ddg.de).

This information is also included into the manuscript.

Retinopathy is diagnosed by ophthalmologists according to a standardized procedure (3) used previously in a population based study in the city of Wolfsburg, Germany on more than 2,800 diabetic patients (4).


- The section on statistical methods should include the account of the complex methods needed to be applied in the analysis of change of C-peptide" with the redundancy of C-peptide levels (B3)

Two primary endpoints will be investigated. First we are interested in failure defined by glycated hemoglobin level, C-peptide-decrease, and occurrence of late-diabetic syndrome biomarkers such as urine albumine, second in the insulin reserve measured by C-peptide-level at the end of the
3-year study period.
As the C-peptide curve is a monotone decreasing function, our main interest is not the trend of C-peptide during follow-up but the remaining C-peptide level at the end of the study. C-peptide level is also determined every six month in order to describe the course and to get the necessary information for the second primary endpoint 'failure'. If 'failure' occurs and the patient changes therapy the method of 'last-value-carried-forward' will be applied for analysis of the first primary endpoint 'C-peptide-change'.

- The problem of potential bias due to diagnostic misclassification (B2) remains unsolved by the mere inclusion of autoantibodies or a relatively small fraction of the patients. How will this information be managed to address the problem?

At the end of the pilot study we observed that some patients originally classified as Type-1” had no C-peptide decay and developed insulin resistance and a metabolic syndrome following the initiation of insulin therapy. Based on these data we expect 5-10% of the patients having to be re-classified after initial diagnosis. The continuous 3-year observation with measurement of C-peptide will make it possible to eliminate bias by initial misclassification.

- And, how will the potential confounders BMI, age and sex be managed statistically?

We agree that BMI and age should be considered during planning phase and analysis of data. In this study we include a specific kind of the minimization procedure sometimes called 'biased coin' for randomization. As result of this procedure we expect homogenous therapy groups regarding BMI and age. Therefore BMI and age will not be used as covariates in the statistical analysis.

- It remains unclear what is meant by the term familywise" frequently used particularly in conjunction with statistical aspects (B8)

With two primary endpoints it is necessary to use a method avoiding failure arising from multiple testing. The familywise error rate is the probability of making any error in the given family of inferences. Therefore we have to use procedures which control the familywise error. In the situation of multiple testing this term is often used to demonstrate that the overall probability of the error of the first kind does not exceed the determined alpha level.

For a reference see:
Multiple Comparison Procedures, Yosef Hochberg, Ajit C. Tamhane. Wiley Series in Probability and Mathematical Statistics, Wiley and sons, USA.