Reviewer's report

Title: Disease progression and genetic contribution in autoantibody negative type 1 diabetes Results from The Hvidore Study Group

Version: 2 Date: 12 May 2010

Reviewer: Ashok Balasubramanyam

Reviewer's report:

I have reviewed the revised ms carefully. I believe this paper is worth publishing, as it provides new and longitudinal information regarding "antibody negative" type 1 diabetes. However, I am concerned that the authors have paid scant attention to one my major comments, and have chosen to gloss over another.

1. They acknowledge that they have not measured the ZnT8 autoantibody in their cohort, and apparently will not do so to strengthen their conclusions in this paper. This is fine, if they want to limit the scope of the paper to an investigation of patients who are GAD65 Ab-negative, ICA-negative and IA-2-negative. However this should be made clear in the title and introduction, as well as in the discussion. It is not enough to insert one sentence (line 14 on page 9). ZnT8 is a well-accepted and important autoantibody that defines autoimmune type 1 diabetes, and one cannot call this a study of "antibody-negative" type 1 diabetes if one excludes this measurement.

I agree that the investigators have done a lot of work, and a longitudinal study is welcome, but the omission of ZnT8 antibody measurement definitely limits the scope of the conclusions, and this should be make clear in the way the results are presented and discussed.

2. My point in the previous critique about the lack of association with HLA risk alleles was specifically in connection with the absence of ZnT8 antibody measurement. The authors have not addressed this point.

3. Again, I feel that the methods in regard to GADA measurement are lamentably skimpy. It is not enough to tell the reviewers in the response letter that it was done in a specific lab in Copenhagen - just as they have provided details in the ms texxt on the ICA and IA-2 measurement methods, they should do so for GADA.