Reviewer's report

Title: Actos Now for the Prevention of Diabetes (ACT NOW) Study

Version: 1 Date: 13 May 2009

Reviewer: Sirkka Keinanen-Kiukaanniemi

Reviewer's report:

Comments to the authors

The article presents the protocol and study design of ACT NOW study, which is planned to determine if pioglitazone can prevent/delay progression to diabetes in high risk IGT subjects, and to define the mechanisms via which pioglitazone exerts its effect on glucose metabolism.

The study hypothesis is well justifiable and well defined, and the planned study design is adequate to answer the primary objective of the study.

In addition to primary objective there are seven secondary objectives included in the study. Some of the secondary objectives are focused on effects of pioglitazone on glucose metabolism, insulin sensitivity, beta cell function, i.e. to the questions which have already been answered in previous studies, but which can be ascertained in this study. Some of them are focused on testing the effects of pioglitazone on cardiometabolic risk factors and regression/slowing progression of carotid intima-media thickness and decreasing microalbuminuria. These are interesting questions, and the study will increase and deepen the knowledge of pioglitazone’s long term effects on these factors.

The presented protocol provides sufficient information to allow replication of the work and the comparison with related analyses.

The manuscript is well written, and the allocation and randomisation procedures, inclusion criteria, measurement protocol and intervention are explained in detail. The power calculations for sample sizes are based on sufficient information and accordingly approximately 600 subjects with IGH is required to achieve the 90% statistical power to show that pioglitazone decreases the conversion rate of IGT to type 2 diabetes by 50%.

In addition to these general comments some Minor Essential Revisions are needed and some Discretionary revisions are suggested.

The Minor Essential revisions:
In abstract in Method section line 7 the expression ‘ for FPG determination of FPG’ should be corrected
In abstract in Method section line 9 there is one excessive word (8 ..method. form
On page 6 (starting from the title page) in the middle of the first paragraph line ten, the expression CBC should be opened.
On page 10 in the second sentence, where ‘the add on medication’ in subjects who develop type 2 diabetes is described, a clarification is needed. The authors describe that the open label pioglitazone starting from 30 mg/day and titrated to 45 mg/day is added without opening the randomization code. Does this mean that it is possible that the dosage of pioglitazone can actually increase to 90 mg/day?

On page 13 under the subtitle ‘Calculations’ (page 12) and paragraph starting with the words Sample Size, line 2 second sentence: The DPP (1942) is possibly wrong, it should be corrected.

The Discretionary Revisions

In Method/design section, the subject eligibility is described in detail, but the authors don’t mention any exclusion criteria. A comment on this is recommended.

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

'I declare that I have no competing interests'