Reviewer's report

Title: Safety and tolerability of sitagliptin in clinical studies: A pooled analysis of data from 10,246 patients with type 2 diabetes

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Reviewer: Zachary Bloomgarden

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The authors report a pooled safety and tolerability analysis of 10,000+ persons randomized to sitagliptin vs. control treatment for 12-104 weeks (mean 282 vs. 259 days of treatment, total 4700+ sitagliptin vs. 3900+ comparator patient-years of follow-up). The analyses were based upon the time to the first (incident) event, calculated as follows: incident event rate = 100 * (total number of patients with >1 event during eligible exposure period per total patient-years of exposure).

Question: was there also capture of individual events, in case some persons had >1 event? The observations “included data after initiation of glycemic rescue therapy” – Question: was the sitagliptin (or comparator) always continued after such treatment was initiated?

The noteworthy findings, such as they are, are in table 4:

Blood and Lymphatic System Disorders 1.1 vs. 0.6 mean diff 0.4 (0.0, 0.8) – the authors explain this is because of increased likelihood of anemia with sitagliptin

Metabolism And Nutrition Disorders 9.3% of sitagliptin vs. 16.3% of comparator mean diff 6.8 (-8.5, -5.2) – the authors explain this is because of increased likelihood of hypoglycemia with sulfonylurea comparators to sitagliptin

Skin And Subcutaneous Tissue Disorders 8. 6% of sitagliptin vs. 7.3 mean diff 1.3 (0.1, 2.5) – the authors state that this appears to reflect several different skin conditions, none occurring with high frequency.

Also somewhat noteworthy are the gastrointestinal conditions in table 5, more diarrhea and abdominal pain occurring with comparators, and related to effects of metformin, while more constipation occurred with sitagliptin, and although the authors do not comment on it this likely reflects what is in effect a “therapeutic” effect of metformin for persons who would without such treatment have constipation.

The cardiovascular analysis is of interest in suggesting no evidence of adverse effect of sitagliptin, with the 95% CI showing an upper bound < 1.3-fold above comparators.

While none of the findings are earth-shaking, the authors have satisfactorily addressed the goals of the manuscript.