Reference name: An independent evaluation of the cardiovascular risk of rosiglitazone: meta-analysis of GSK's publicly available clinical trial data

SECTION A: RESEARCH PLAN

A.1 Title of Proposed Research (limit: 200 char)

An independent evaluation of the cardiovascular risk of rosiglitazone: meta-analysis of GSK's publicly available clinical trial data.

A.2 Lay Summary (limit: 3000 char)

- The background to this research

    o Why does this research need to be done now?

    o How many patients / members of the public are affected?

- How the research will add to medical science or improve patient care

- The aims and objectives of the research

- How the research will be conducted

    o What design and methods have you chosen and why? (in brief)

- How the findings will be interpreted and communicated to patients and /or the public

Rosiglitazone (Avandia), manufactured by GSK, was approved for use by the U.S. Food and Drug Administration in 1999 for the treatment of type 2 diabetes mellitus. The approval was based on clinical trials that demonstrated the effectiveness of the medication at lowering serum blood glucose concentrations. Use of rosiglitazone grew rapidly in the ensuing years and annual sales peaked at approximately $2.5 billion in 2006.

However, concerns were raised about the medication when, in May 2007, a meta-analysis suggested it increased risk of myocardial infarction. These findings led to widespread public and regulatory scrutiny of the medication, triggering a safety alert by the FDA that same month and Congressional hearings on the topic shortly thereafter in June 2007. In September 2007, a second meta-analysis of this data using a slightly different statistical approach was published, which identified no increased risk. Despite these conflicting findings, in September 2010, the FDA updated rosiglitazone's product label to include

information on cardiovascular risks and in May 2011, the FDA implemented a risk evaluation and mitigation strategy (REMS), which restricts the drug's availability and applies specified criteria for use.

In 2013, FDA eased the restrictiveness of the rosiglitazone REMS after an updated analysis of the Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of glycaemia in Diabetes (RECORD) study that compared heart attack risk of standard diabetes treatments found the medication's risk to be in line with that of other diabetes drugs. However, even with eased restrictions, the previous boxed warning may instill a lingering apprehension in doctors and patients for prescribing rosiglitazone. While fewer patients today are using rosiglitazone, with eased restrictions and upcoming availability of rosiglitazone in a cheaper, generic formulation, we can expect rosiglitazone utilization to increase in the future.

One key limitation of both prior meta-analyses on this topic has been the use of summary-level data from the identified clinical trials for meta-analysis. However, the recent announcement by GSK to make patient-level clinical trial data available to external investigators in an effort to facilitate further research that can help advance medical science or improve patient care presents a unique opportunity to address the question of rosiglitazone's cardiovascular risk through the meta-analysis of all of GSK's clinical trial program data of this medication.

Our research objective is to conduct a meta-analysis of GSK's rosiglitazone clinical trial program data to better understand the cardiovascular risk associated with use of the medication, including risk of heart failure events, acute myocardial infarction, cardiovascular-related deaths, and all-cause deaths. Results from this research will be submitted for publication to a peer-reviewed biomedical journal.

A.3 Study design (limit 2500 char):
We will conduct a meta-analysis of GSK's rosiglitazone clinical trial program patient-level data to better understand the cardiovascular risk associated with use of the medication, including risk of heart failure events, acute myocardial infarction, cardiovascular-related deaths, and all-cause deaths.

A.4 Studies selected and study populations (limit: 2500 char):
We have selected all phase II, III, and IV clinical trials of rosiglitazone being made available by GSK through ClinicalStudyDataRequest.com.

A.5 Primary and secondary endpoints for the study (limit: 2500 char)

Our primary endpoint is a composite outcome of the following events: heart failure events, acute myocardial infarction events, cardiovascular-related deaths, and all-cause deaths. We will examine each of these events independently as secondary endpoints.

A.6 Statistical analysis plan (limit: 25000 char)

Please provide the statistical analysis plan for the proposed research. The following is provided as guidance for items to include in the statistical analysis plan:

- Effect measure of interest (e.g. for inferential studies: risk or rate ratio, risk or rate difference, absolute difference; for descriptive studies: rate with confidence intervals)
- Methods to control for bias (e.g. restriction, matching, stratification, covariate adjustment)
- Assumptions and any planned adjustments for covariates or meta-regression or modelling of covariates
- The statistical approach (e.g. Bayesian or frequentist (classical), fixed or random effects)
- Meta-analysis approach where applicable (e.g. random effects meta-analysis, stratified meta-analysis)
- Statistical tests and methods (e.g. Fisher's exact test, Kaplan-Meier curves, log-rank test to compare groups, multiplicity adjustments)
- Power to detect an effect, or the precision of the effect estimate given the sample size available
- Statistical power calculations and levels of significance
- Model fit tests, sensitivity or heterogeneity analyses (e.g. Chi-Squared Test, I squared statistic)
- Analysis of subgroups (e.g. by age, disease status, ethnicity, socioeconomic status, presence or absence or co-morbidities); different types of intervention (e.g. drug dose)
- Handling of missing data

We will use a random effects model to conduct a meta-analysis across trials to estimate the relative risk associated with rosiglitazone use for our primary endpoint, a composite outcome of the following events: heart failure events, acute myocardial infarction events, cardiovascular-related deaths, and all-cause deaths, as well as each of these events independently as secondary endpoints. The random-effects model will assign a weight to each study on the basis of an individual study's inverse variance.

Statistical heterogeneity across the trials will be tested with the use of Cochran's Q statistic. A P value of more than the nominal level of 0.10 for the Q statistic will be used to indicate a lack of heterogeneity across trials. Relative risk estimates will be reported with 95% Confidence Intervals. Differences will be considered significant at 2-sided $P < .05$.

For additional analyses, the active comparator control groups will be categorized into the following four classes for comparison with rosiglitazone: metformin, sulfonylurea, insulin, and placebo. Odds ratios and 95% confidence intervals will be calculated for each subgroup with the use of methods similar to those used in the overall pooled analyses described above.

For the primary endpoint, we anticipate all trials will have sufficient endpoints for meta-analysis. However, if there are trials with few overall events, odds ratios and 95% confidence intervals will be calculated with the use of the Peto method. For the secondary endpoint, not all trials will have sufficient endpoints for meta-analysis and thus odds ratios and 95% confidence intervals will be calculated with the use of the Peto method. Trials with no events will be handled in two ways. First, meta-analysis will be conducted that exclude these trials. Second, meta-analysis will be conducted that assigns one event to each arm (rosiglitazone and comparator).

As a sensitivity analysis, we will conduct a one-study-removed analysis to assess the effect of each study on the combined effect. Calculation of I2 and meta-regression will performed using the study as the unit of analysis to assess heterogeneity among studies.

A.7 Publication plan (limit: 2500 char)

Results from this research will be submitted for publication to a peer-reviewed biomedical journal and will be submitted to GSK in order to inform their understanding of the cardiovascular risk associated with use of rosiglitazone.