ASSESSING THE CARDIOVASCULAR RISK OF ANTI-DIABETIC THERAPIES IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

Richard C. Zink, JMP Life Sciences, SAS Institute on behalf of the ASA Biopharmaceutical Section Safety Working Group:
Aloka Chakravarty, Christy Chuang-Stein, Qi Jiang, Chunlei Ke, Haijun Ma, Jeff Maca, Olga Marchenko, Estelle Russek-Cohen & Matilde Sanchez-Kam

Introduction

- Type 2 diabetes mellitus (T2DM) accounts for 90-95% of all diabetes patients. These individuals are characterized with insulin resistance and/or insulin deficiency.
- FDA called for assessment of cardiovascular (CV) risk for non-insulin therapeutics for T2DM. Asked that hazard ratio (HR) of treatment compared to control be < 1.8 in pre-market evaluation (122 events, two-sided, α=0.05) [1]. Further, guidance suggested additional data collected post-market to show HR of Major Adverse Cardiovascular Event (MACE: CV death, nonfatal myocardial infarction and nonfatal stroke events) be < 1.3 (611 events, two-sided, α=0.05).
- Figure 1 displays the α-spending functions for a hypothetical sequential trial using OBF-like boundaries.
- Reviewed drugs approved by U.S. FDA to treat T2DM during 2002-2014. Main objective was to understand the impact of FDA guidance on assessment of CV risk in T2DM development programs.

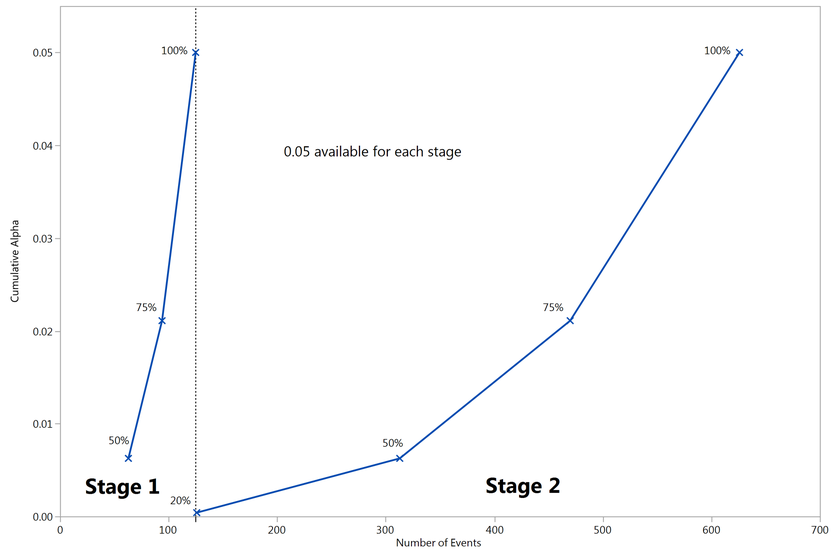

Figure 1. Cumulative α for Hypothetical Sequential Design Across Two Recommended Stages for T2DM

Methods

- Majority of information taken from www.clinicaltrials.gov, advisory committee materials, and Drugs@FDA: FDA Approved Drug Products.
- Review included drug name and class, initial US NDA submission and approval dates, initial MAA submission and approval dates, and strategy to address CV risk.
- Details on pre-marketing meta-analysis such as primary endpoint, whether prospectively adjudicated, study population, size of database, statistical hypotheses and methods, primary outcome, subgroup analyses, and major issues identified in FDA briefing documents.
- Details from CV outcome trial (CVOT) included whether initiated to address post-marketing commitment and/or contributed to pre-marketing CV analysis, study design, population, treatment groups, sample size, duration, primary endpoint and how adjudicated, primary objectives, completion date, and primary outcome.

Results

- CV risk assessment population typically consists of all randomized patients who received at least one dose of double-blind study therapy.
- For NME, CVOT usually required. Many sponsors started studies during late phase 3. Products whose individual components have been or currently evaluated for CV risk exempt from CV requirements.
- At NDA submission, sponsors typically proposed to conduct CV meta-analysis (MA) that included completed phase 2-3 studies. Because MA at submission stage, development programs often included plan to prospectively adjudicate CV events. In some cases (canagliflozin, alogliptin), MA included interim data from CVOT.

Results

- Cox proportional hazard models stratified by study were often the primary analysis method for more recent MA.
- CMH methods treating endpoints as binary often used as sensitivity analyses. MH and CMH methods stratified by study used as primary analysis for earlier submissions. Extensive subgroup analyses, pre-planned and ad hoc, conducted with consistency of results examined.
- Requirements at post-approval stage may include another MA including completed phase 2-3 studies plus CVOT; or analyzing CVOT as stand-alone study if planned with enough events.
- CVOTs designed as large, randomized, double-blinded, placebo-controlled in T2DM patients with high CV risk. T2DM drugs where development program was designed and/or completed but drugs not yet approved prior to FDA guidance held to same standards. FDA proposed post-hoc evaluations of CV events collected during development (liraglutide, saxagliptin hydrochloride, and exenatide XR).
- Steady increase in number of treated subjects included in pre-marketing CV risk assessment since 2008 (Figure 2). Observed two strategies to assess CV risk since the guidance.
- Substantial similarity in CV endpoints, adjudication, population, and statistical methods across recent CVOTs. No substantial delay in time between submission and approval due to addressing CV risk in recent programs. Did not review duration of development programs to determine if increased from first study in human to regulatory submission. All completed CVOTs ruled out HR > 1.3.

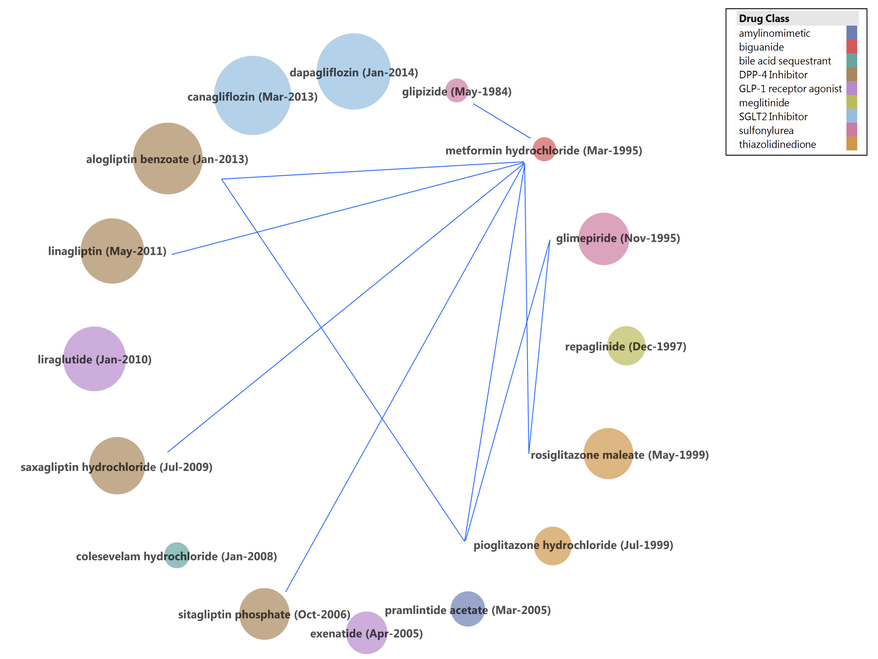

Figure 2. Drugs for Type 2 Diabetes Approved by the FDA up to Jan 2014

Conclusions

- Lot of similarities in approaches taken and subsequent analyses for T2DM programs thus far.
- Balance between evidence on CV safety and excessive delay of novel therapies.
- Access to interim data critical for CV assessment strategies. Releasing interim data when full approval granted (Stage 1) can undermine integrity for ongoing CVOTs. Guidance and buy-in from other regulatory agencies needed.
- Questions yet to answer: Can stop CVOT early? Post-market studies to assess CV risk instead of CVOT? Active-controlled CVOTs? Possible for indirect comparisons for CV risk among T2DM products?
- Additional details on this topic found in [2].

References

1.U.S. Food and Drug Administration. (2008). Guidance to Industry: Diabetes Mellitus — Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes.

2.Chakravarty A, Chuang-Stein C, Jiang Q, Ke C, Ma H, Maca J, Marchenko O, Russek-Cohen E, Sanchez-Kam M & Zink RC. (2015). Evaluation and review of strategies to assess cardiovascular risk in clinical trials in patients with type 2 diabetes mellitus. Submitted to *Statistics in Biopharmaceutical Research*.