Cardiovascular Outcomes Associated with Second-Line Agents for Type 2 Diabetes Mellitus:

Industry Expert Perspectives

A PCORI Stakeholder Workshop
October 8, 2018

pcori
PATIENT-CENTERED OUTCOMES RESEARCH INSTITUTE

Agenda

- Welcome
- Background and Goals for the Day
  - PCORI's Exploration of Second-Line Treatments for T2DM
  - Focus on Observational Study: Examination of Feasibility
  - Questions to Guide Our Discussion
- Discussion
- Summary and Closing Remarks

Welcome

Housekeeping

- Participants' lines are live
  - Please mute your line when you are not speaking to reduce background noise
- This conversation is being recorded and will be posted to the PCORI web site
- We will take comments in the order indicated on the agenda
- Comments and questions from the public may be submitted via the chat window
  - We will attempt to include submissions in the discussion when feasible
  - We cannot guarantee a question or comment will be addressed

Background

PCORI's Exploration of Second-Line Treatments for Type 2 Diabetes Mellitus

Scientific Rationale for Interest in Topic

- Decisional dilemma faced by patients and clinicians when choosing appropriate second-line treatment among 6+ classes of drugs
- Varying risks and benefits across drugs/classes of drugs including weight gain and potentially increased CV risk with some drugs/classes
- Ongoing NIDDK-funded GRADE study does not include an SGLT2 inhibitor arm and is not assessing CV outcomes
- Newer agents shown in CV outcome trials to have benefit among patients with established CVD and those at very high risk
  - SGLT2 inhibitors: empagliflozin and canagliflozin
  - GLP-1 receptor agonists: liraglutide and semaglutide
- **Key question:** *What is the comparative effectiveness of older versus newer agents for CV outcomes in individuals at moderate CV risk?*

Comparative Effectiveness Study of Interest

Comparators

- SGLT2 inhibitors
- GLP1 receptor agonists
- Sulfonylureas
- DPP-4 inhibitors

Patient population: Moderate CV risk (approximate risk for CV events of 2-3% per year)

Primary endpoint: Composite CV outcome (3-point MACE; may also include revascularization and/or heart failure)

Secondary endpoints: Side effects, changes in weight, QOL, and other patient-centered outcomes

Key Challenges to CER Trial

- Large sample size required would necessitate significant investment of resources
- Conducting trial in moderate-risk population would require ≥4 years of follow-up
- Feasibility of recruitment uncertain
- Feasibility of conducting trial pragmatically uncertain
- Ability to accurately estimate effect size in moderate risk population is unclear
- Selecting appropriate comparators presents a challenge

Background

Focus on Observational Study: Examination of Feasibility

Why consider an observational analysis?

- Investment and uncertainty associated with a clinical trial make an observational study appealing.
- **Key caveat:** To be useful, an observational analysis must be robust, applying appropriate causal inference analytics.
- **Response:** Emulate a target trial using observational data.

Emulating a Target Trial

- Define the causal question that we would like to answer through a clinical trial.
- Define the protocol for the hypothetical clinical trial (eligibility criteria, treatment strategies, random assignment, outcomes, analysis plan).
- Emulate the protocol for the hypothetical clinical trial using observational data.
- While limitations associated with observational data remain, emulating a target trial minimizes the addition of further problems that undermine the reliability of observational analyses (e.g., selection bias and immortal time bias).

Example: Observational v. randomized studies of hormone therapy and heart disease

- Discrepancy in findings between observational studies and RCT
  - Nurses' Health Study: >30% lower risk in current users of hormone therapy (HRT) v. never users (HR: 0.68)
  - Women's Health Initiative: >20% higher risk in initiators v. non-initiators (HR: 1.24)
- **Why the difference?**
  - WHI trial randomly assigned women to initiate HRT or placebo and compared **incident** users
  - NHS observational study compared **prevalent** users to never users

Example: Observational v. randomized studies of hormone therapy and heart disease (cont.)

- **Solution:** Reanalyze NHS data by restricting inclusion to those women who meet eligibility criteria similar to those of WHI
- **Result**: Findings much more similar to WHI
  - HRs of CHD among initiators of HRT were:
    - 1.42 (0.92-2.20) for the first two years in emulated trial versus 1.68 (1.15-2.45) in the WHI
    - 1.00 (0.78-1.28) for the first eight years of follow-up in the emulated trial versus 1.24 (0.97-1.60) in the WHI
  - Hernán et al. *Epidemiology* 2008; 19(6):766-779

Questions to Guide Our Discussion

Scoping Question 1

- Are there real world practice and use patterns for second-line treatments for type 2 diabetes that may need to be considered in drafting a target protocol?
  - Distribution
  - Payment
  - Clinical
  - Patient

Scoping Question 2

- Are there remaining uncertainties associated with this question (e.g., specific subpopulations that might benefit more or less) which would be important to consider or prioritize for closer examination?

Scoping Question 3

- What additional published studies or literature would be informative of this effort?

Scoping Question 4

- To your knowledge, are there new or ongoing studies addressing this question that would be important to consider?

Scoping Question 5

- Is there anything we have not asked about or discussed that you feel we may have missed?

Discussion

Order of Comments

Comments are not required of participants.
Any participant may pass on the opportunity to comment.

- Boehringer Ingelheim
- Janssen Pharmaceuticals
- Merck
- Novo Nordisk
- Sanofi

Order of Comments
Industry

- Boehringer Ingelheim
  - Jonathan Pak, PharmD, MBA
    Director, Metabolism, Clinical Development & Medical Affairs
- Janssen | Johnson & Johnson
  - Brahim Bookhart, MBA, MPH
    Senior Director, Health Economics and Outcomes Research - Metabolics
- Merck
  - Swapnil Rajpathak, MD, MPH
    Executive Director, Center for Observational and Real World Evidence

Order of Comments
Industry

- NovoNordisk
  - Anders Hvelplund, MD, PhD
    Executive Director, Clinical Development and Research

- Sanofi
  - Kyle Hvidsten, MPH
    Global Head of Health Economics and Value Assessment

Summary and Closing Remarks

THANK YOU!