Endocrinologic and Metabolic Drugs Advisory Committee

and

Drug Safety and Risk Management Advisory Committee

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Outline of GSK Presentation

• Introduction	Ronald Krall, MD
• Data Review	Murray Stewart, DM, FRCP
• Conclusion	Ronald Krall, MD
• Questions	

Meta Analyses of Rosiglitazone Controlled Clinical Trials

	Myocardial Infarction	Cardiovascular Mortality
GSK Integrated Clinical Trials	1.59 (0.93 – 2.71)	1.91 (0.79 – 4.64)
FDA[1]	1.5 (0.9 – 2.5)	1.7 (0.7 – 4.0)
Nissen & Wolski[2]	1.43 (1.03 – 1.98)	1.64 (0.98 – 2.74)

[1] FDA Briefing Document, Statistical Review, J Mele, Table 3.1.2
[2] Nissen and Wolski *NEJM* 2007;356:2457-71

Questions for Today

- Is there an increase in the risk of cardiovascular mortality associated with rosiglitazone?
- Is there an increase in the risk of myocardial infarction associated with rosiglitazone?

Factors that increase the robustness of meta-analyses

- Component trials are similarly designed
  - Objectives
  - Patient population
  - Primary endpoint
  - Event definition
- Absence of bias in allocation to treatment with respect to the meta-analysis endpoint
- Number of events

Evidence to Address ICT Questions

- Large, long term outcome studies
  - RECORD interim analysis
  - ADOPT
  - DREAM
- Epidemiology studies
- Other sources of information
  - Study in high risk patients
  - Ongoing studies

RECORD: Design & Objectives

Design:

- Open label, randomized, RSG+met/SU vs met+SU
- 4447 patients w/ T2DM failing met or SU monotherapy
- 4-6 yr follow-up

Primary Endpoint:

- Time to first occurrence of cardiovascular hospitalization or cardiovascular death
  - Adjudicated
  - Event adjudication committee blinded to treatment

RECORD

- Comprehensive primary endpoint
  - MACE components assessed
- Use of insulin makes blinding impractical
- Event adjudication committee blinded to treatment
- Largest number of observed events

ADOPT: Design & Objectives

Design:

- Double-blind, randomized study; RSG vs met and glyburide
- 4351 patients with T2DM, drug naïve
- 4yr follow-up

Primary Endpoint:

- Time to monotherapy failure

CV Events:

- Non-adjudicated SAE and AE investigator reports

DREAM: Design & Objectives

Design:

- Double-blind randomized, 2X2 factorial, RSG and ramipril
- 5269 patients with IGT and/or IFG
- 3 yr follow-up

Primary Endpoint:

- Prevention of incident T2DM or death

CV Events:

- Adjudicated

How Are Events Assessed in Rosiglitazone Clinical Studies?

In Stream Adjudication

Post-Study Adjudication

Adverse Events (AE)

Data Presentation

- Myocardial Ischemia
- MACE
  - Myocardial Infarction
  - Stroke
  - CV Mortality

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