Advisory Committee Meeting
Avandia® (rosiglitazone maleate)
July 13-14, 2010

Mary H. Parks, M.D.
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

Outline of Presentation

- **Events leading up to the 2007 AC meeting for Avandia**
- **Data presented at 2007 AC meeting***
- **Recommendations from 2007 AC panel members**
- **Events after 2007 AC meeting**
- **Agenda for July 2010 AC meeting**

*http://www.fda.gov/ohrms/dockets/ac/cder07.htm#EndocrinologicMetabolic

Pre-2007 AC Meeting

- December 2003 WHO report of data mining signal for increased cardiac risk, including heart failure, for the TZDs
- GSK initiated a meta-analysis (MA) of rosiglitazone controlled clinical trials w/ final report of MA on 42 controlled clinical trials submitted to FDA in August 2006
- Separate MA published in NEJM in June 2007 by Nissen and Wolski
- Together, these meta-analyses were viewed as a signal for CV risk associated with rosiglitazone

July 30, 2007 Joint Advisory Committee Meeting on Avandia®

FDA presentations focused on:

- **Meta-analysis of 42 controlled clinical trials***
- **CV safety data from long-term controlled clinical trials**
- **CV safety data from observational studies comparing rosiglitazone to other anti-diabetic therapies**
- **Indirect comparisons between rosiglitazone and pioglitazone**

***For remainder of presentation, reference is made only to the meta-analysis performed by FDA**

Characteristics of MA Presented in 2007

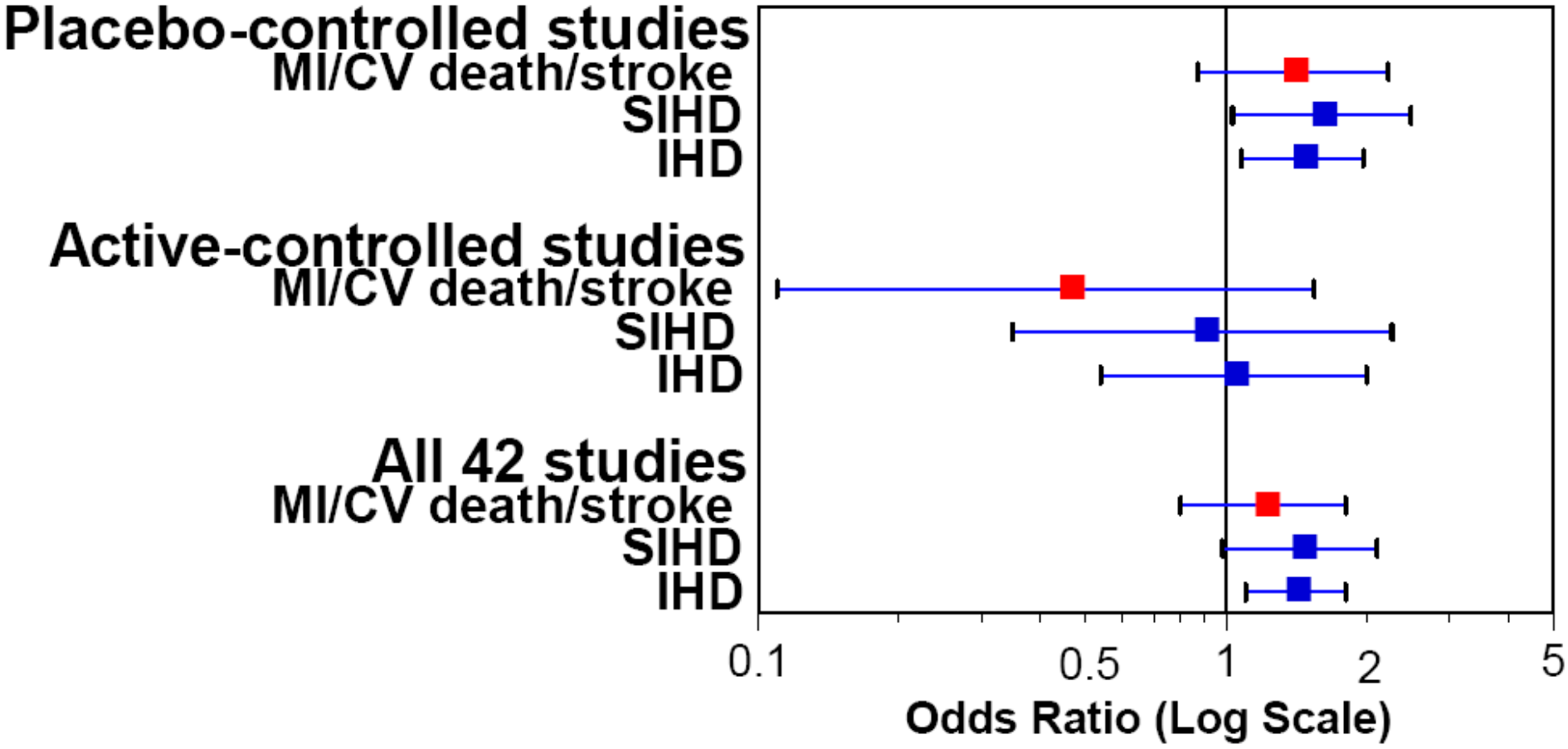
- Comprised of 14,237 patients (8604 RSG; 5633 nonRSG)
- All studies were randomized, double-blind, and controlled
- 38 studies were </= 6 mos; three 1-yr studies; one 2-yr study
- No prospective adjudication of CV events by blinded endpoints committee (except one study) --- trials were designed to assess glycemic control
- CV events were collected from AEs reported on CRFs; reviewed retrospectively – access to patient level data available
  - Nonserious and serious CV events (ischemic heart disease – IHD)
  - Serious CV events (serious ischemic heart disease – SIHD)
  - Heart failure
  - MACE events captured later in preparation for AC meeting
- Many of the adverse event terms considered in the CV endpoints were nonspecific for cardiac ischemia

Results of FDA 2007 Meta-analysis

	RSG N=8604	Control N=5633	OR (95% CI)	p-value
IHD	2%	1.5%	1.4 (1.1-1.8)	0.02
SIHD	1%	0.8%	1.44 (0.98-2.1)	0.06
MACE	0.73%	0.67%	1.2 (0.7-1.8)	0.4

IHD = ischemic heart disease; SIHD = serious ischemic heart disease; MACE = CV death, NFMI, NFstroke

RSG vs Placebo or Active Control (met/su)



Increased CV ischemic risk w/ RSG observed in placebo-controlled trials but not observed in active-controlled trials which compared RSG to metformin or SUs

Long-term Controlled Trials (LCCT)

DREAM

- 2x2 factorial design in prediabetics comparing rosi vs pbo and rosi+ramipril vs ramipril in the prevention of T2DM
- N=5269; median duration of f/u 3.0 yrs
- Primary endpoint: composite of progression to diabetes and all-cause mortality
- Secondary endpoints included CV events adjudicated by a blinded CEC

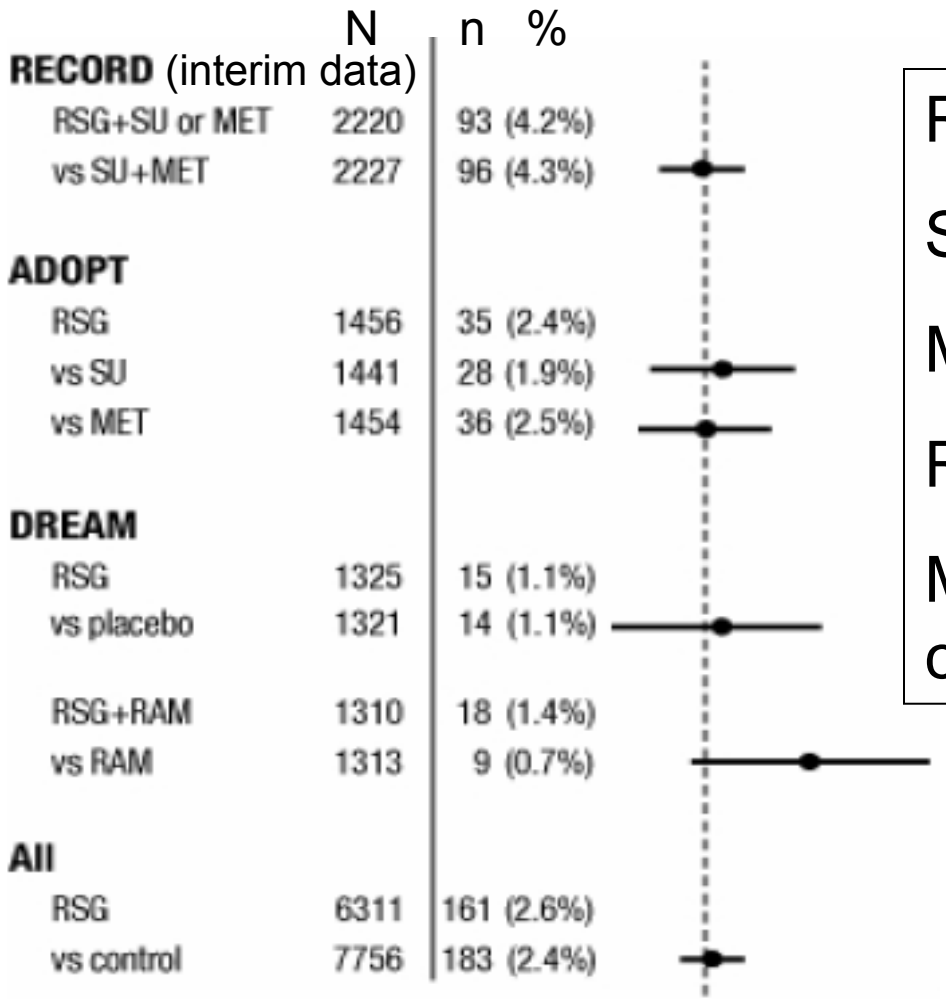
ADOPT

- Active control trial in treatment naïve diabetics to evaluate rate of monotherapy failure (rosi vs metformin or SU)
- N=4351; median duration of tx 4 .0 yrs
- Primary endpoint: time to glycemic control failure of monotherapy
- CV events collected as adverse events, not adjudicated by blinded CEC

RECORD (interim analysis as of 2007)

- Ongoing, active control trial evaluating CV events between Met+RSG vs Met+SU and SU+RSG vs SU+Met
- N=4447, current status 3.75 yrs mean follow-up
- Primary endpoint: composite of CV death and CV hospitalization
- CV events adjudicated by blinded CEC

Overall Findings from 3 LCCTs: MACE



RSG – rosiglitazone

SU – sulfonylurea

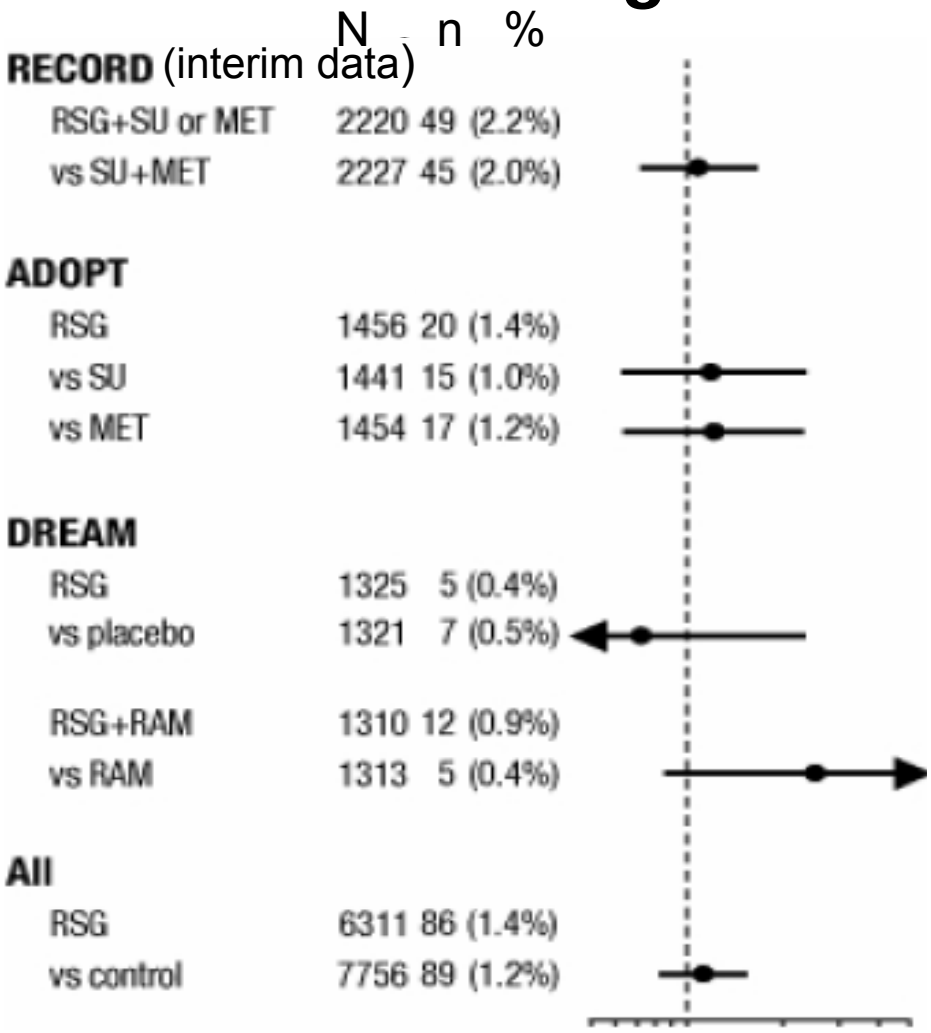
MET – metformin

RAM – ramipril

MACE – major adverse cardiovascular events

favors rosiglitazone ← → favors controls

Overall Findings from 3 LCCTs: MI



RSG – rosiglitazone

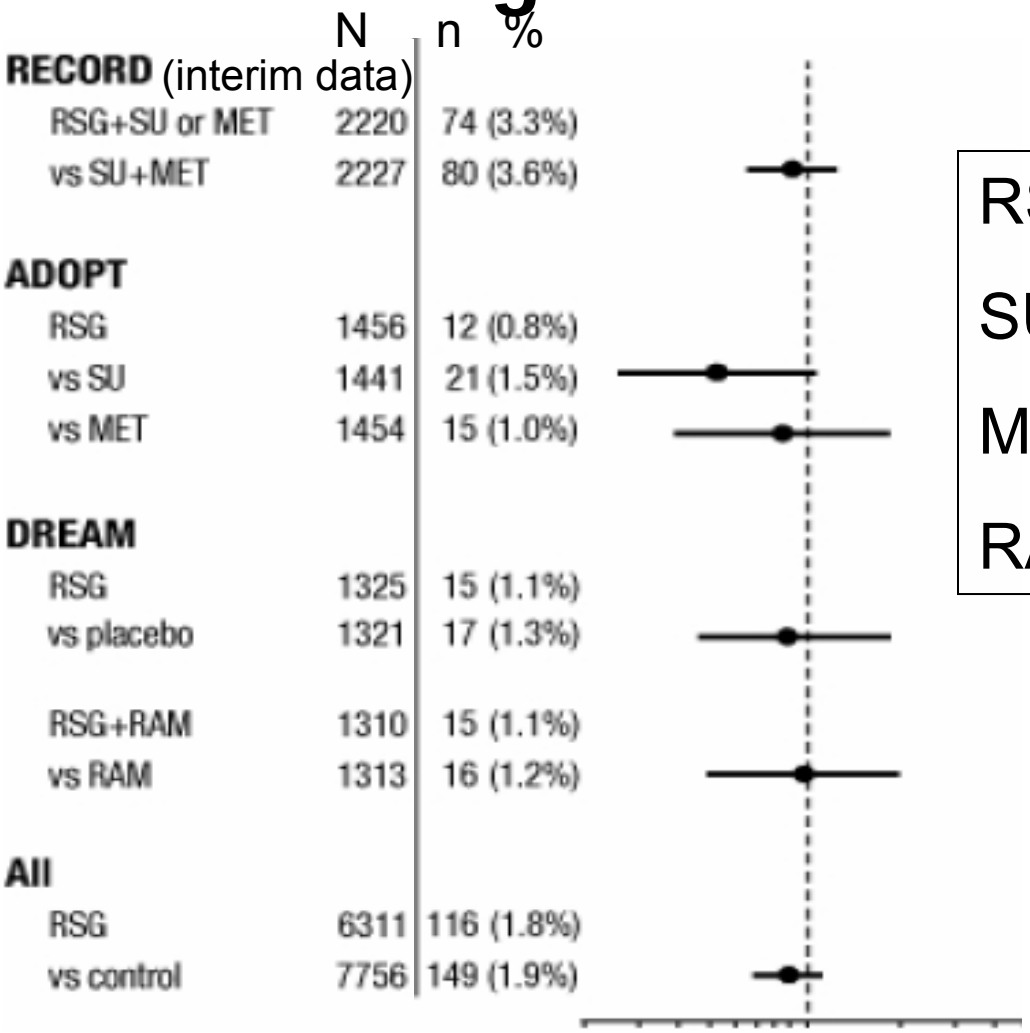
SU – sulfonylurea

MET – metformin

RAM – ramipril

MI – myocardial infarction

Overall Findings from 3 LCCTs: Mortality



RSG – rosiglitazone

SU – sulfonylurea

MET – metformin

RAM – ramipril

Rosiglitazone vs Pioglitazone, 2007

- Pioglitazone (Actos) is the only other marketed TZD
- PROactive (Prospective Clinical Trial in Macrovascular Events)
  - CV outcomes trial in 5238 patients w/ T2DM and macrovascular disease comparing pioglitazone to placebo added on to current anti-diabetic therapies
  - Primary endpoint: composite of all-cause death, NFMI (including silent MI), stroke, ACS, cardiac intervention (CABG or PTCA), major leg amputations (AKA), or bypass surg/revasc procedure in the leg.
  - Late amendment to protocol 4 mos after trial cessation made CV death, NFMI, and stroke a major 2^0 endpoint
  - FDA updated labeling of pioglitazone in 2/07 to include results from PROactive. No claim of CV benefit granted but labeling noted 'no increase in mortality or in total macrovascular events with Actos'

PROactive Results*

Endpoint	Add-On PIO N=2605 n (%)	Add-on PBO N=2605 n (%)	HR (95% CI), p-value
Primary composite	514 (19.7%)	572 (21.7%)	0.90 (0.80, 1.02), p=0.0954
CV mort (predefined II°)	127 (4.9%)	136 (5.2%)	0.94 (0.74, 1.20), p=0.6163
All-cause mort + MI + stroke (II°)	301 (11.6%)	358 (13.6%)	0.84 (0.72, 0.98), p=0.0277

***Presented by Dr. Karen Mahoney at July 2007 Avandia AC meeting**

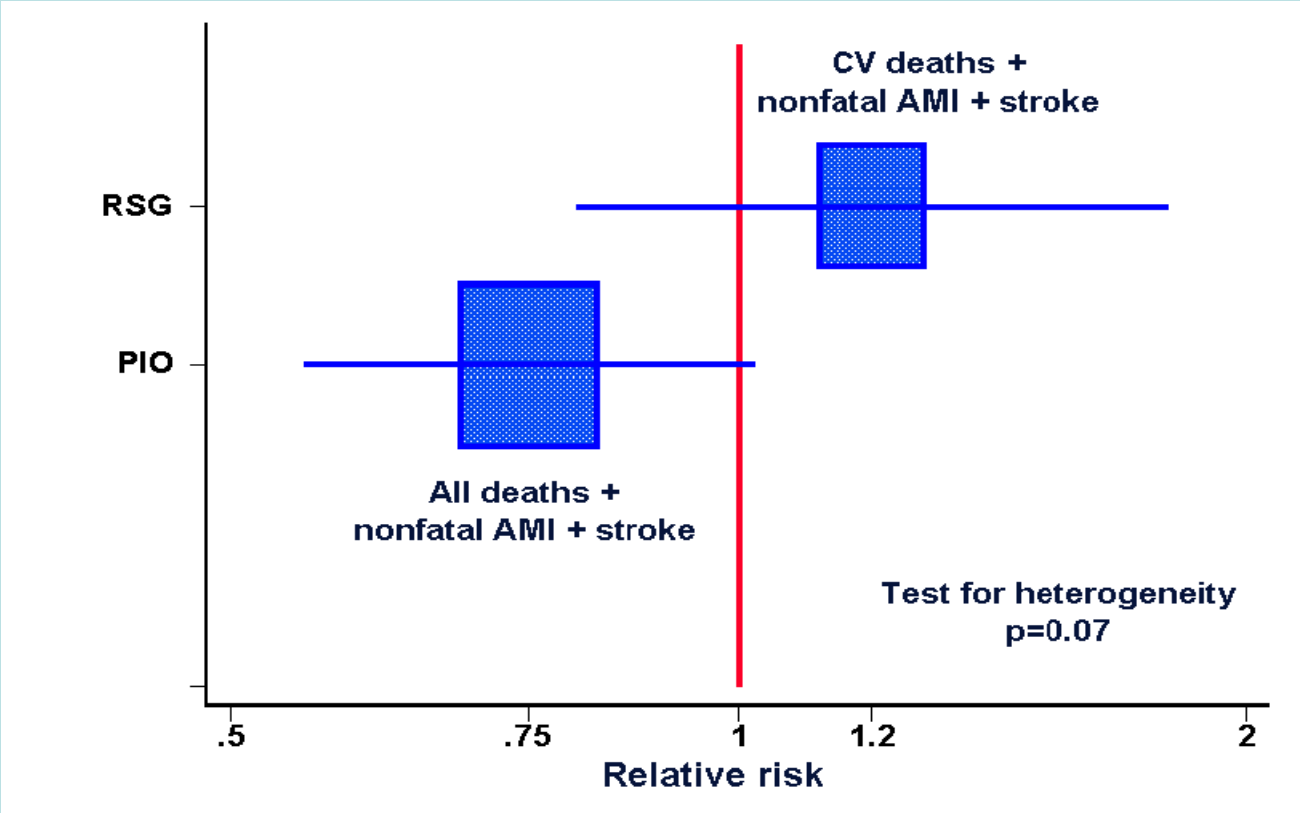
Rosiglitazone vs Pioglitazone, 2007

- **No CV outcomes trial directly comparing the two marketed TZDs**
- **Takeda submitted a meta-analysis of 19 pioglitazone trials**
- **Differences in trial design between the pio and rosi MA, including duration and controls, should be considered in making indirect comparisons b/w the two TZDs**

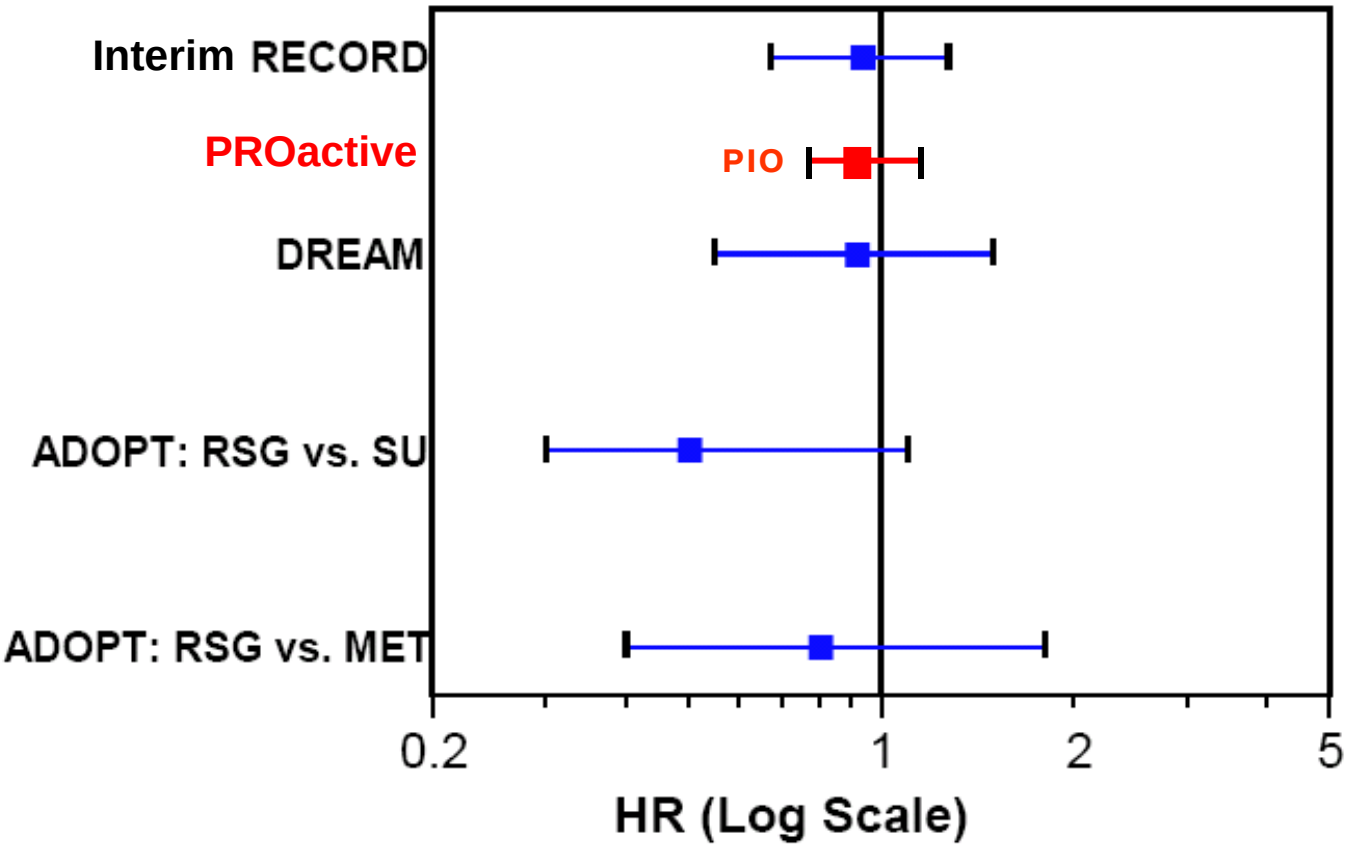
Examples:	Rosi	Pio
Duration	38/42 ≤ 6 mos	10/10 ≥ 1 yr
Comparator	85% pbo 15% SU	18% pbo 63% SU

Slide Presented at 2007 AC Meeting

Comparison of CV risk observed in meta-analyses of RSG and PIO



Total Mortality in LCCTs of Rosi and Pio



Results of 2007 AC Panel Voting Questions

Panel was asked to comment on the strengths and limitations of the MAs, observational studies, and LCCTs followed by two voting questions:

1. **Do the available data suggest a conclusion that Avandia increases cardiac ischemic risk in T2DM?**

   20 voted yes; 3 voted no

2. **Does the overall risk-benefit profile of Avandia support its continued marketing in the U.S.?**

   22 voted yes; 1 voted no

Post 2007 AC Meeting

- **October 2, 2007 - Representatives from OND and OSE presented before Drug Safety Oversight Board:**
  - **OSE recommended withdrawal of drug from market**
  - **OND did not believe there was sufficient evidence to support withdrawal. Recommended strengthened labeling for CV risk and the conduct of a prospective CV outcomes trial**
- **October 13, 2007 –Center-Level Decision**
  - **Rosiglitazone would remain on the market**
  - **Updated labeling including discussion of CV ischemic risks under Boxed Warnings**
  - **Postmarketing trial required to prospectively study rosiglitazone CV safety**

Post 2007 AC Meeting

- **In a memo dated January 2, 2008, to OND and OSE Directors, the Center Director concluded that:**
  - **Rosiglitazone should not be withdrawn from the market**
  - **A boxed warning to discuss the risk of MI was needed**
  - **A Medication Guide was needed**
  - **The Warnings section of labeling needed to discuss individual risk factors which might contribute to excess CV harm with rosiglitazone**

"The firm should be required to begin and promptly execute a study comparing their drug to pioglitazone…"

- **This directive formed the basis for the required postmarketing trial, Thiazolidinedione Intervention and Vitamin D Evaluation (TIDE)**

Updated Boxed Warning 11/07

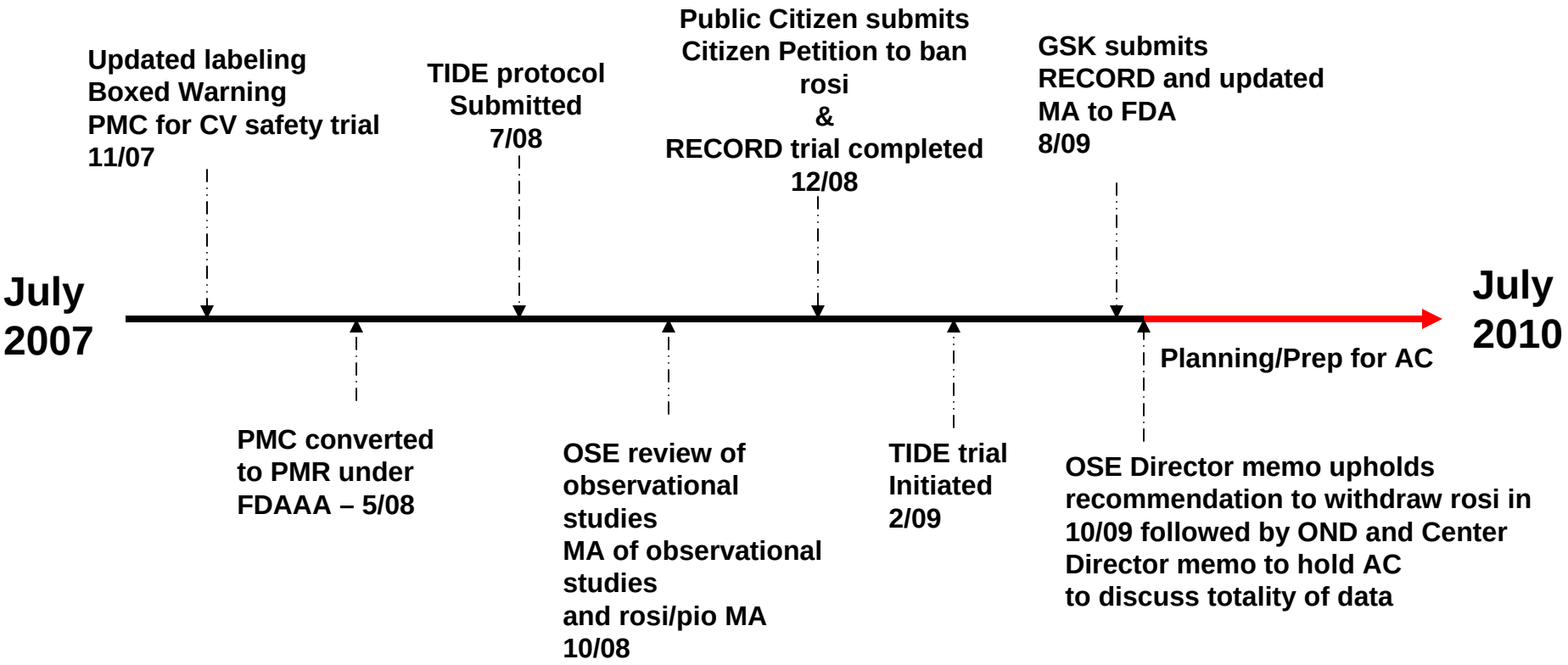
"a meta-analysis of 42 clinical trials (mean duration 6 months; 14,237 patients), most of which compared Avandia to placebo, showed Avandia to be associated with an increased risk of myocardial ischemic events such as angina or myocardial infarction. Three other studies (mean duration 41 months; 14,067 patients), comparing Avandia to some other approved oral antidiabetic agents or placebo, have not confirmed or excluded this risk. In their entirety, the available data on the risk of myocardial ischemia are inconclusive."

Warnings and Precautions

- **Co-administration with insulin and nitrates not contraindicated but recommendations against use placed under Warnings and Precautions**

- **21CFR201.57**
  - **Contraindications: "drug should not be used because the risk of use clearly outweighs any possible benefit**
  - **Warnings and Precautions: "a clinically significant hazard as soon as there is reasonable evidence of a causal association w/ a drug; causal relationship need not have been definitely established"**

Timeline of Events Since July 2007



Planning/Prep for 2010 AC

- **Review of RECORD**
  - **Final study reports and complete datasets submitted in 8/09**
  - **Comprehensive review of RECORD performed including consultation to Division of Cardiovascular and Renal Products, Office of Biostatistics, and Division of Scientific Investigations**
- **Review of Observational Studies**
  - **Update on new data since 2007 with studies specifically evaluating rosiglitazone and pioglitazone**
  - **Retrospective cohort study of claims data from CMS to compare rosiglitazone to pioglitazone on selected CV endpoints**

Planning/Prep for 2010 AC

- **Meta-analyses of Rosiglitazone and Pioglitazone Trials**
  - **For rosi: undertaken to update 2007 MA of rosi to include 10 additional studies**
  - **For pio: to determine whether a comparably conducted MA to rosi would enable indirect comparisons of safety b/w the two TZDs**
  - **Long-term trials not included due to marked differences in study designs and their data would dominate overall MA findings**
  - **Long-term trials were reviewed separately**

Planning/Prep for 2010 AC

- **Role of Guest Presentations**
  - Several guest speakers invited by FDA to enable a comprehensive view of CV safety data for rosiglitazone
  - Data presented by several guest speakers have not been reviewed by FDA

July 2010 Agenda

Day 1

- **GSK presentation**
- **Guest presentation by Dr. Steven Nissen (Cleveland Clinic) FDA presentation of RECORD trial**

FDA Presentation of RECORD

- **Dr. Thomas Marciniak (Medical Team Leader/Division of Cardiovascular and Renal Products**
- **Dr. Ellis Unger (Deputy Director, Office of Drug Evaluation I)**
- **Dr. Karen Mahoney (Medical Officer, Division of Metabolism and Endocrinology Products)**
- **Dr. David Hoberman (Biostatistician, Office of Biostatistics)**
- **Dr. Susan Leibenhaut (Medical Officer, Division of Scientific Investigations, Office of Compliance)**

July 2010 Agenda

FDA presentation of Observational Studies

- **Dr. Kate Gelperin (Medical Officer, Office of Surveillance and Epidemiology)**
- **Dr. David Graham (Epidemiologist, Office of Surveillance and Epidemiology)**

July 2010 Agenda

FDA Presentation of Meta-analyses of Rosiglitazone and Pioglitazone Trials

- **Dr. Fiona Callaghan (Biostastitician, Office of Biostatistics)**
- **Dr. Brad McEvoy (Biostastitician, Office of Biostatistics)**

July 2010 Agenda

- **Guest presentation by Dr. Maria Brooks (University of Pittsburgh)**
- **Guest presentation by Mr. Thomas Moritz (Edward Hines Jr. VA Hospital)**

Day 2

- **Guest presentation by Dr. Hertzel Gerstein (McMaster University)**
- **Guest presentation by Dr. Dean Follman (NIH Biostatistics Research Branch)**
- **IOM Report**
- **Open Public Hearing**
- **Charge to the Committee**
- **Advisory Committee Panel Discussion and Votes on FDA Questions**