

Overview of Large Prospective Trials of Thiazolidinediones: Study Design and Current Status of Cardiovascular Safety Data

Karen Murry Mahoney, MD, FACE
Medical Officer
Division of Metabolism and Endocrinology Products

Center for Drug Evaluation and Research
Joint Meeting of the Endocrinologic and Metabolic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee
July 30, 2007

1

Content of Presentation

- Overview of studies' characteristics
- Overview of myocardial ischemia safety data for ADOPT, DREAM and RECORD (RSG); and PROactive (PIO)
- ADOPT and PROactive study reports have been submitted to FDA; therefore more detail
- Analyses of similar CV endpoints across data sources
- Summary

Center for Drug Evaluation and Research
Joint Meeting of the Endocrinologic and Metabolic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee
July 30, 2007

2

Transition from Meta-Analysis to Consideration of Large Prospective Randomized Trials

- FDA meta-analysis has signal of increased myocardial ischemic risk for RSG
- Common after meta-analyses to look at other data sources for consistency in signal
- Large, prospective, randomized, controlled trials do not have some of the problems of meta-analyses
- For any drug, all data sources have limitations

Center for Drug Evaluation and Research
Joint Meeting of the Endocrinologic and Metabolic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee
July 30, 2007

3

Tables of Data Source Characteristics

	ADOPT (RSG)	DREAM (RSG)	RECORD (RSG)	PROactive (PIO)	FDA Meta-Analysis (RSG)
Status	Study complete, full report under review	Study complete, no study report to FDA yet	Ongoing	Study complete, review complete	Studies complete, review complete
Question	Durability as monotherapy	Progression from IGT to DM	CV outcome	CV outcome	Glycemic control
# Patients	4351	5269	4447	5238	14,237
Duration	4-6 yrs	Median 3 yrs	Median 6 yrs planned	Mean 34.5 mo	38142 c66 mo; mean appr 6 mo
TZD Pt-Yr Exposure	4954 pt-yr	8014 pt-yr	8369 pt-yr to date	6482 pt-yr	4145 pt-yr

Center for Drug Evaluation and Research
Joint Meeting of the Endocrinologic and Metabolic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee
July 30, 2007

4

Tables of Data Source Characteristics (cont)

	ADOPT (RSG)	DREAM (RSG)	RECORD (RSG)	PROactive (PIO)	FDA Meta-Analysis (RSG)
Pt Pop	DM2 <= 3 y	IGT or IFG	DM2, inad control on MET or SU	DM2 with hx macrovasc dx	DM2, varied pops
Study Drug	RSG	RSG or RSG+RAM	Add-on RSG	Add-on PIO	RSG (mono, coadmin, or add-on)
Control	SU or MET	RAM or PBO (2x2 factorial)	Add-on MET or SU	Add-on PBO	Varied
! Endpt	Monotherapy failure	DM2 or death	Death or CV hosp	Composite of 7 macrovasc events	Myocardial ischemia, broad composite
Isch Event Adjudic?	No	Yes	Yes	Yes	Post hoc for BSK meta-analysis

Center for Drug Evaluation and Research
Joint Meeting of the Endocrinologic and Metabolic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee
July 30, 2007

5

ADOPT A Diabetes Outcome Progression Trial

Center for Drug Evaluation and Research
Joint Meeting of the Endocrinologic and Metabolic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee
July 30, 2007

6

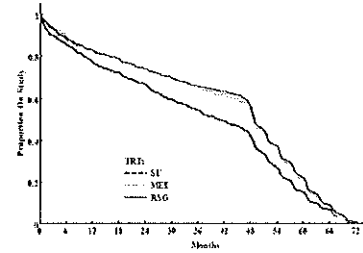
ADOPT Design and Disposition: Key Points

- Objectives: examine time to monotherapy failure, and examine general safety (not a specific CV outcome study)
- High withdrawal rate (monotherapy failure and other reasons)
- Differential exposure (pt-yrs): RSG 4954, MET 4906, SU 4244

Center for Drug Evaluation and Research
 Joint Meeting of the Endocrinologic and Metabolic Drugs Advisory Committee and the
 Drug Safety and Risk Management Advisory Committee
 July 30, 2007

7

Withdrawal Rates in ADOPT: Proportion of Patients on Study by Treatment Group



Center for Drug Evaluation and Research
 Joint Meeting of the Endocrinologic and Metabolic Drugs Advisory Committee and the
 Drug Safety and Risk Management Advisory Committee
 July 30, 2007

8

Preliminary Review of Cardiovascular Safety Results: Death

	RSG N=1456, PY=4954 n (%) [rate/100 PY]	SU N=1441, PY=4244 n (%) [rate/100 PY]	MET N=1454, PY=4906 n (%) [rate/100 PY]
All deaths up to 30 days p Tx (end of routine AE collection)	12 (0.8%) [0.2/100 PY]	21 (1.5%) [0.5/100 PY]	15 (1.0%) [0.3/100 PY]
All reported deaths (not routinely collected >30 d p Tx)	34 (2.3%) [0.7/100 PY]	31 (2.2%) [0.7/100 PY]	31 (2.1%) [0.6/100 PY]

Center for Drug Evaluation and Research
 Joint Meeting of the Endocrinologic and Metabolic Drugs Advisory Committee and the
 Drug Safety and Risk Management Advisory Committee
 July 30, 2007

9

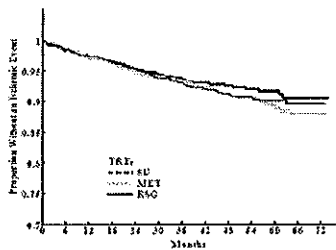
ADOPT Serious CV Adverse Events (Rates/100 PY)

- Cardiac MedDRA® System Organ Class Events: RSG 1.6, SU 1.2, MET 1.7
- Individual CV SAE terms:
 - 1/104 observed SAE terms had rate/100 PY ≥ 0.1 higher for RSG than for SU and MET.
 - 0/104 terms had rate/100 PY ≥ 0.2 higher for RSG than for MET and SU.
 - "Myocardial infarction" (not all terms for MI), RSG 0.4, SU 0.2, MET 0.3
- Myocardial Ischemia event grouping by GSK:
 - No significant difference between groups for overall myocardial ischemic events or components.
 - MI SAEs RSG 0.5, SU 0.3, MET 0.4. Not stat sig.
- FDA cardiologist event groupings (>49,000 records, >40 endpoints): No significant imbalances; overall rate of MI seemed low in proportion to rate of strokes.

Center for Drug Evaluation and Research
 Joint Meeting of the Endocrinologic and Metabolic Drugs Advisory Committee and the
 Drug Safety and Risk Management Advisory Committee
 July 30, 2007

10

ADOPT KM Curves: Time to Myocardial Ischemic Event



Center for Drug Evaluation and Research
 Joint Meeting of the Endocrinologic and Metabolic Drugs Advisory Committee and the
 Drug Safety and Risk Management Advisory Committee
 July 30, 2007

11

Limitations of ADOPT

- Was an efficacy and general safety trial, and not a CV endpoint trial; no predefined CV event adjudication
- High withdrawal rate
- Differential pt-yr exposure (lower for SU)
- Active comparator may obscure absolute risk
- Adverse event ascertainment only out to 30 days after cessation of study drug
- Early diabetic population may not be generalizable
- Small numbers of cardiovascular events increase uncertainty of estimates

Center for Drug Evaluation and Research
 Joint Meeting of the Endocrinologic and Metabolic Drugs Advisory Committee and the
 Drug Safety and Risk Management Advisory Committee
 July 30, 2007

12

Strengths of ADOPT

- Duration much longer than mean duration of studies in meta-analysis
- Large number of patients
- Treatment groups well-matched at baseline; less heterogeneity than in meta-analysis
- Randomization maintained for adverse event analyses
- Review revealed few problems in ascertainment and coding
- Active comparator design consistent with "real-world" treatment decisions

Center for Drug Evaluation and Research
 Joint Meeting of the Endocrinologic and Metabolic Drugs Advisory Committee and the
 Drug Safety and Risk Management Advisory Committee
 July 30, 2007

13

Summary of Preliminary CV Safety Findings from ADOPT

- Has not detected a significant difference in myocardial ischemic event rates between RSG and MET or SU
- Cannot rule out a difference in myocardial ischemic risk
- Higher rate of heart failure events with RSG than with SU
- Study has limitations, including high withdrawal rate

Center for Drug Evaluation and Research
 Joint Meeting of the Endocrinologic and Metabolic Drugs Advisory Committee and the
 Drug Safety and Risk Management Advisory Committee
 July 30, 2007

14

Possible Contributions of ADOPT to Evaluation of Myocardial Ischemic Risk for Rosiglitazone

- More patient-year exposure for this single trial than for all trials in meta-analysis combined
- Provides information in a population with relatively early diabetes
- Provides information regarding risk relative to the two most commonly prescribed diabetes drug classes

Center for Drug Evaluation and Research
 Joint Meeting of the Endocrinologic and Metabolic Drugs Advisory Committee and the
 Drug Safety and Risk Management Advisory Committee
 July 30, 2007

15

DREAM Diabetes Reduction Assessment with Ramipril and Rosiglitazone

Center for Drug Evaluation and Research
 Joint Meeting of the Endocrinologic and Metabolic Drugs Advisory Committee and the
 Drug Safety and Risk Management Advisory Committee
 July 30, 2007

16

DREAM Status, Design and CV Events

- Prospective, R, DB, PC
- 2x2 factorial design; both RSG and ramipril studied
- Examined progression from impaired glucose tolerance to overt DM
- 2635 pts RSG; 2634 pts non-RSG
- Total mortality equal for RSG and non-RSG
- Numerically more CV composite (macrovasc + HF) events for RSG than for non-RSG
- Significantly more HF events for RSG than for non-RSG

Center for Drug Evaluation and Research
 Joint Meeting of the Endocrinologic and Metabolic Drugs Advisory Committee and the
 Drug Safety and Risk Management Advisory Committee
 July 30, 2007

17

DREAM Angiotensin Converting Enzyme (ACE) Inhibitor Interaction

Table D8: CV Outcomes in DREAM Presented by Factorial Groups

	Rosiglitazone/Rosiglitazone N=1310		Rosiglitazone/Rosiglitazone N=1313		Rosiglitazone/Rosiglitazone N=1325		Placebo N=1321	
	N	%	N	%	N	%	N	%
CV Composite	45	3.4	24	1.8	32	2.4	32	2.4
MI	11	0.8	3	0.2	5	0.4	4	0.3
Stroke	7	0.5	2	0.1	5	0.4	3	0.2
All Death	15	1.1	16	1.2	15	1.1	17	1.3
CV Death	7	0.5	9	0.7	3	0.2	5	0.4
Revascularization	15	1.1	10	0.8	19	1.4	19	1.4
Non Anginal CHF	15	1.1	9	0.7	9	0.7	11	0.8
CHF	11	0.8	1	0.1	5	0.4	1	0.1

Center for Drug Evaluation and Research
 Joint Meeting of the Endocrinologic and Metabolic Drugs Advisory Committee and the
 Drug Safety and Risk Management Advisory Committee
 July 30, 2007

18

Possible Contributions of DREAM to Evaluation of Myocardial Ischemic Risk for Rosiglitazone

- Almost double the patient-year exposure for this single trial than for all trials in meta-analysis combined
- Provides information in a “prediabetic” population
- Provides information regarding risk relative to placebo
- Raises the question of the contribution of an interaction between RSG and ACEI for CV risk

Center for Drug Evaluation and Research
 Joint Meeting of the Endocrinologic and Metabolic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee
 July 30, 2007

19

RECORD Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycemia in Diabetes

Center for Drug Evaluation and Research
 Joint Meeting of the Endocrinologic and Metabolic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee
 July 30, 2007

20

Status and Design

- Ongoing; mean follow-up 3.75 yrs; interim analysis published
- Prospective, R, open-label, CV outcome study
- Pt pop = DM2 with inadequate control on MET or SU
- BL MET pts randomized to add-on RSG (1117 pts) or add-on SU (1105 pts)
- BL SU pts randomized to add-on RSG (1103 pts) or add-on MET (1122 pts)
- Primary endpoint = death or cardiovascular hospitalization
- Lower-than-expected event rate has affected planned statistical power

Center for Drug Evaluation and Research
 Joint Meeting of the Endocrinologic and Metabolic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee
 July 30, 2007

21

Interim Cardiovascular Safety Data from RECORD (Adjudicated Events)

Endpt	RSG n (%)	Contr n (%)	HR (95% CI)	p-value
I* (Death or CV Hosp)	217 (9.8)	202 (9.1)	1.08 (0.89, 1.31)	0.43
Heart Failure	38 (1.7%)	17 (0.8%)	2.24 (1.27, 3.97)	0.005
All-cause Mort	74 (3.3)	80 (3.6)	0.93 (0.67, 1.27)	0.63
CV Mort	29 (1.3)	35 (1.6)	0.83 (0.51, 1.36)	0.46
Acute MI	43 (1.9)	37 (1.7)	1.16 (0.75, 1.81)	0.50

Center for Drug Evaluation and Research
 Joint Meeting of the Endocrinologic and Metabolic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee
 July 30, 2007

22

Conditional Power Calculations for RECORD

- When evaluating Interim trial data, conditional power is the probability that the trial will demonstrate statistical significance for an endpoint at the end of the trial *conditional* on the data observed in the trial thus far.
- Calculations dependent on what one has *already* seen in the trial (e.g. HR, SE, information fraction)
- Calculations also dependent on what one *expects* regarding the rest of the data to come (e.g. what the future HR might be)

Center for Drug Evaluation and Research
 Joint Meeting of the Endocrinologic and Metabolic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee
 July 30, 2007

23

RECORD Conditional Power Calculations

True hazard Ratio (HR) ^a	Conditional power to exclude HR = 1.2 ^b	Conditional power to exclude HR = 1.1 ^b	Conditional power to exclude HR = 1.0 ^b
Primary endpoint			
1.00	16%	94%	>99%
1.08 ^c	22%	80%	99%
Composite endpoint of CV death, MI and stroke (secondary endpoint)			
1.00	43%	82%	97%
0.97 ^c	50%	87%	98%

^a Hazard ratio (HR) for data following the interim analysis

^b Non-inferiority margin specified in the protocol

^c Assumes HR for data after the interim analysis is equal to the HR at interim analysis

Center for Drug Evaluation and Research
 Joint Meeting of the Endocrinologic and Metabolic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee
 July 30, 2007

24

Possible Contributions of RECORD to Evaluation of Myocardial Ischemic Risk for Rosiglitazone

- Is a cardiovascular outcome study
- To date, over twice the patient-year exposure for this single trial than for all trials in meta-analysis combined
- Provides information in a diabetic population failing monotherapy
- Provides information regarding risk with add-on RSG vs add-on MET or SU
- Has high conditional power to exclude a hazard ratio of 1.4 (similar to the HR point estimate in the meta-analysis), or 1.3; but lower power to exclude a hazard ratio of 1.2

PROactive Prospective Pioglitazone Clinical Trial in Macrovascular Events

PROactive Design: Key Points

- CV outcome study
- Add-on PIO = 2605 pts
Add-on PBO = 2633 pts
- All had history of macrovascular disease
- Excluded HF NYHA FC II or higher
- Excluded pts on insulin monotherapy
- Other meds, including other DM meds, were to be titrated or added to achieve IDF goals for DM, Htn and lipids; however, differences at endpoint favored PIO.

Primary Efficacy Endpoint

A composite of:

- All-cause mortality
- Nonfatal myocardial infarction (including silent MI)
- Stroke
- Acute coronary syndrome
- Cardiac intervention (CABG or PCI)
- Major leg amputation (above ankle)
- Bypass surgery or revascularization in the leg

No endpoints included heart failure.

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=0.8163
All-cause mort + MI + stroke (II*)	301 (11.6%)	358 (13.6%)	0.84 (0.72, 0.98), p=0.0277

PROactive Subgroups by Baseline Oral Diabetes Therapy (for Endpoint of All-cause Mortality, Stroke and MI [Excluding Silent MI])

Baseline OHA	Add-on PIO n/N (%)	Add-on PBO n/N (%)	HR (95% CI)
Neither MET nor SU	29/212 (13.7%)	23/214 (10.7%)	1.29 (0.75, 2.23)
MET only	76/769 (9.9%)	107/793 (13.5%)	0.72 (0.54, 0.97)
SU only	104/800 (13.0%)	116/791 (14.7%)	0.89 (0.68, 1.15)
MET + SU	92/824 (11.2%)	112/835 (13.4%)	0.82 (0.62, 1.08)

PROactive Addendum with Pooled Studies

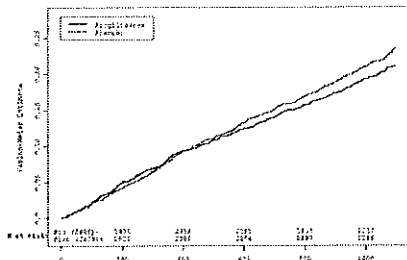
- Submitted analysis of their later secondary endpoint (all-cause mort + MI + stroke) across pooled clinical trials database
- Overall HR 0.78 (95% CI 0.58, 1.06), p=0.12
- Datasets not submitted
- No analyses by treatment comparator (e.g. placebo, active comparator)
- Takeda has agreed to do meta-analysis for PIO similar to that done for RSG, with meta-groups by treatment comparison

Differences Between Rosiglitazone and Pioglitazone Clinical Trials Pools: Implications for Overall Risk Estimates

- | | |
|---|------------------------------------|
| RSG: | PIO: |
| • Appr 85% pbo-controlled (where higher risk difference seen) | • Appr 20% pbo-controlled |
| • Appr 15% head-to-head against SU (where less risk seen) | • Appr 62% head-to-head against SU |

Possible Importance of Duration of Study

Time to PROactive Primary Composite Endpoint



Contribution of PROactive to TZD Myocardial Ischemic Event Risk Evaluation

- Long-term CV outcome trial of TZD with statistically neutral and numerically favorable results for add-on PIO
- HF risk for add-on PIO > add-on PBO, but HF not included in endpoint composites; HF was included in DREAM and RECORD composites
- Showed possible importance of duration of study
- Analysis using favorable PROactive secondary endpoint also favorable in PIO pooled studies analysis
- Takeda working with FDA to perform pooled studies meta-analysis comparable to that done for RSG

USE OF SIMILAR ENDPOINTS ACROSS DATA SOURCES

Cardiovascular Mortality + Myocardial Infarction + Stroke ("MACE")

Data Source	Comparison and Analysis Source	"MACE" HR (95% CI), p	CV Mort HR (95% CI), p	MI HR (95% CI), p	Stroke HR (95% CI), p
Pooled Shorter-term DM Studies	All RSG vs All CONTR, FDA	1.2 (0.8, 1.8), p=0.4	1.7 (0.7, 5.0), p=0.2	1.6 (0.9, 2.7), p=0.1	0.6 (0.2, 1.2), p=0.1
	RSG vs SU, FDA	1.2 (0.7, 1.9), p=0.3	5.6 (2.1, 1.9), p=0.4	1.6 (0.6, 3.1), p=0.2	0.9 (0.4, 2.1), p=0.9
ADOPT	RSG vs MET, FDA	1.1 (0.7, 1.8), p=0.6	1.3 (0.4, 5.0), p=0.7	1.3 (0.7, 2.3), p=0.4	0.6 (0.4, 0.8), p=0.3
	RSG vs PBO, FDA	1.1 (0.6, 2.4), p=1.0	1.0 (0.2, 4.3), p=1.0	0.6 (0.2, 2.3), p=0.6	1.7 (0.3, 10.7), p=0.7
DREAM	RSG + RAM vs RAM, FDA	2.0 (0.9, 5.1), p=0.1	1.4 (0.4, 5.6), p=0.6	3.7 (0.87, 20.7), p=0.03	1.0 (0.1, 13.8), p=1.0

Cardiovascular Mortality + Myocardial Infarction + Stroke ("MACE"), cont

Data Source	Comparison and Analysis Source	"MACE" HR (95% CI), p	CV Mort HR (95% CI), p	MI HR (95% CI), p	Stroke HR (95% CI), p
RECORD Interim	ALL RSG vs ALL CONTR, GSK	0.97 (0.73, 1.29), p=0.83	0.83 (0.51, 1.36), p=0.46	1.16 (0.75, 1.81), p=0.60	np
PROactive	Add-on PIO vs Add-on PBO, Takeda	0.82 (0.70, 0.97), p=0.02	0.94 (0.74, 1.20), p=0.62	np	0.81 (0.61, 1.07), p=0.14

Incidence of All-Cause Mortality

Trial	TZD	Control
ADOPT	RSG 0.8%	SU 1.4% MET 1.0%
DREAM	RSG 1.1%	PBO 1.3%
RECORD interim	RSG 3.3%	MET/SU combo 3.6%
PROactive	PIO 6.8%	PBO 7.1%

SUMMARY

Similarities Between the FDA Meta-Analysis and the Large Long-Term RSG Trials

- Similar total sample size (>14,000 each)
- All trials randomized
- All trials controlled
- Small numbers of events increased uncertainty of estimates

Differences Between FDA Meta-Analysis and Large Long-Term Trials of RSG

	RSG FDA Meta-Analysis of Shorter-Term Trials	RSG Longer-Term Trials
Objectives	41/42 glycoemic control trials (not CV outcome), 1 ECHO trial.	RECORD CV outcome; DREAM and ADOPT not.
Heterogeneity	PI pops, RFs, comparators, background meds, et al	BL characteristics well-matched
Total RSG Exposure (pt-yrs)	Appr 4000	Appr 20,000
?ACEI Interaction for Risk of Myocardial Ischemic Events	Yes	Yes for DREAM; not seen in ADOPT
Myocardial Ischemic event risk	Significant increased risk for total myocardial ischemic events composite	Total myocardial ischemic events: not signif incr -MI terms per se: several HRs >1

Acknowledgments

- Sandra Kweder, MD, Deputy Director, OND
- John Jenkins, MD, Director, OND
- Hylton Joffe, MD, Acting Diabetes Team Leader, DMEP
- Joy Mele, MS, Biometrics Reviewer
- Robert Meyer, MD, Director, ODE II
- Robert Misbin, MD, Medical Officer, DMEP
- Mary Parks, MD, Director, DMEP
- Todd Sahlroot, PhD, Biometrics Team Leader
- Joanna Zawadzki, MD, Medical Officer, DMEP
- Colleagues in OSE