


Avandia® (rosiglitazone maleate)
GlaxoSmithKline

NDA 21-071 Supplement 022
FDA META-ANALYSIS

Joint Meeting of Metabolic & Endocrine Advisory Committee
and Drug Safety & Risk Management Advisory Committee


July 30, 2007

Joy Mele
Statistician
Division of Biometrics 2



Meta-analysis Topics


- Motivation for FDA meta-analysis
- Database of 42 studies
- FDA Methods
- Overall results
- Active-controlled studies
- Add-on to insulin studies
- Placebo-controlled non-insulin studies
 - Subgroups
 - Studies 135, 211 and 352
- Summary



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Motivation for FDA meta-analysis

- GSK overall estimate for total myocardial ischemic events only
- Suggestion of subgroup differences based on GSK analyses
 - Heterogeneous patient populations across studies
- Heterogeneity among the different treatment paradigms
 - Initial FDA pooled estimate of 1 for RSG mono vs. PLA
 - Initial FDA pooled estimate of 3 for MET+RSG vs. MET+PLA
- No results by individual studies were shown by GSK and their analyses were not stratified by study



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The FDA Meta-analysis Database



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**Rosiglitazone Meta-analysis
FDA database compared to NEJM database
Differ on 14 studies**


FDA	NEJM
<ul style="list-style-type: none"> • 42 randomized, controlled trials (ICT) • All double-blind • 4 trials 1-yr+ 38 trials 6 mos or less • 14,237 Type 2 diabetics • Composite endpoints • Patient level data 	<ul style="list-style-type: none"> • 42 randomized, controlled trials • 38 double-blind 4 open-label • DREAM+ADOPT 3-4 years 10 trials 1-yr+; 30 trials ~6 mos • 19,462 Type 2 diabetics 5,269 Pre-diabetics 3,112 Non-diabetics • MI and CV death



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FDA Meta-analysis Database

- RSG monotherapy 15 trials
 - 9 head to head to placebo
- RSG in combination
 - Metformin (MET) 10 trials
 - Sulfonylurea (SU) 14 trials
 - Insulin (INS) 5 trials
 - Run-In period on active control, randomized to RSG or placebo
- RSG added to background medication (BM) 3 trials
 - Patients remained on stable doses of the anti-diabetic medications they were taking at enrollment, randomized to RSG or placebo
- A similar database for pioglitazone was predominantly active-controlled primarily with SU as a head-to-head comparator



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FDA Meta-analysis Database Trials in High Risk Populations

- Study 352
 - Patients on background medications randomized to RSG or placebo
 - 16-weeks
 - 61 CHD patients
- Study 211
 - Patients on background medications randomized to RSG or placebo
 - 1 year
 - 224 CHF patients
- Study 135
 - Run-in on SU, randomized to RSG or placebo
 - 2 years
 - 227 patients with mean age of 68 (range 59-78)

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Myocardial Ischemia Endpoints

- Trials not designed to assess ischemia
 - Efficacy trials with HbA1c endpoint
- Post-hoc adjudication of myocardial ischemic events
 - Non-serious & serious (IHD)
 - Serious (SIHD)
- Composite of myocardial infarction / cardiovascular death / stroke
 - Provided to FDA 5/31/07
 - Identified using pre-defined MedDRA terms
 - No adjudication
 - To compare meta-analysis results to long-term study results

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FDA Meta-analysis Methods

FDA

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Meta-groups for FDA Analysis

Meta-group	Control	Studies	Patients
Monotherapy RSG	PLA or MET or SU	15	4,236
RSG+Background Medications	PLA+BM	3	479
RSG+Sulfonylurea	PLA+SU	14	4,245
RSG+Metformin	PLA+MET or SU+MET	10	3,469
RSG+Insulin	PLA+INS	5	1,530
RSG+Metformin+Sulfonylurea	PLA+MET+SU	1	837

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How FDA dealt with low event rates

- Focus on composite endpoints
 - Results can vary considerably with analytical method when many trials have no events
 - MI OR 1.2 to 1.6 NS CV death OR 1.0 to 1.8 NS
- For plots of OR on a forest plot, added 0.5 to each cell in studies with no events in one arm or both arms
- Exact test drops studies with no events in both arms
 - Performed several sensitivity analyses
 - Stratified on study or meta-group

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Steps in the FDA meta-analysis

- Determine whether computing an overall estimate was sensible
- Assess heterogeneity within meta-groups and compute an overall estimate of risk for each meta-group
 - Exact test stratifying on study
 - Risk difference analysis using both fixed and random effects models
 - Robustness of meta-group results
- Redefine meta-groups creating a separate group for the active-controlled comparisons
- Compute overall odds ratios
 - Differences among meta-groups?
 - High risk subgroups?

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Results of the FDA Meta-analysis



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Summary of the Findings

- Statistically significant overall estimate of risk of a non-serious or serious myocardial ischemic event associated with RSG
 - OR 1.4 95% CI of 1.1 to 1.8 p=0.02
- No evidence of increased myocardial ischemic risk associated with RSG compared to MET or SU
 - OR 1.0 95% CI of 0.5 to 2.0 p=0.3
- Increased myocardial ischemic risk associated with RSG compared to placebo
 - Results are heterogeneous
 - Across treatment paradigms/studies
 - Across subgroups



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Results of FDA meta-analysis All 42 studies

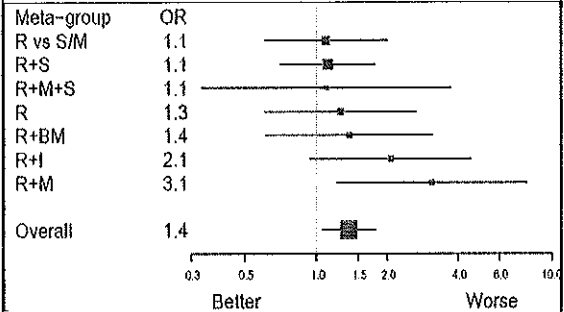
IHD=serious + non-serious ischemia SIHD=serious ischemia

	RSG (n=8804)	Control (n=5633)	OR (95% CI)	p
IHD	2.0%	1.5%	1.4 (1.1, 1.8)	0.02
SIHD	1.0%	0.8%	1.4 (0.98, 2.1)	0.06
MI/CVD/ST	0.73%	0.67%	1.2 (0.7, 1.8)	0.4



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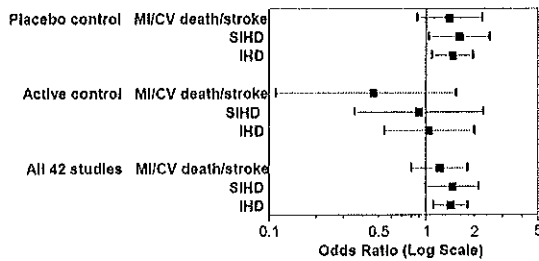
Serious + Non-serious Myocardial Ischemia By Meta-group For All 42 Studies



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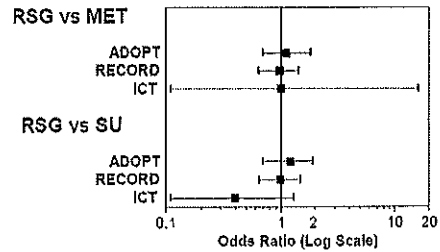
Results For All 42 Studies And For The Placebo And Active Controlled Studies

SIHD=serious ischemia IHD=serious+non-serious ischemia



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Comparison of RSG to SU or MET MI/CV Death/Stroke Meta-analysis database (ICT), ADOPT and RECORD



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Placebo- Controlled Trials Meta-Analysis Database

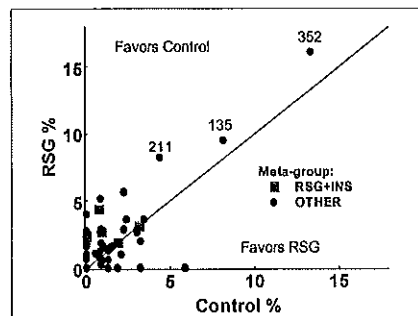
Placebo-controlled Trials N=12,424

- Add-on to insulin trials N=1,530
- Non-insulin trials N=10,894

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Incidence of Serious+Non-serious Myocardial Ischemia

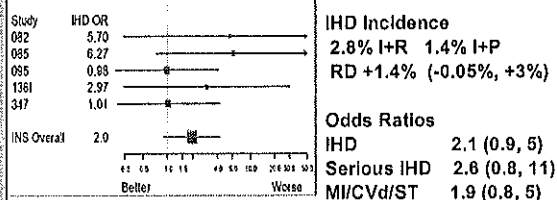
All Placebo-controlled Trials
Study Numbers shown for outliers



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Insulin+RSG vs. Insulin+Placebo

6 month trials
867 I+R 663 I+P



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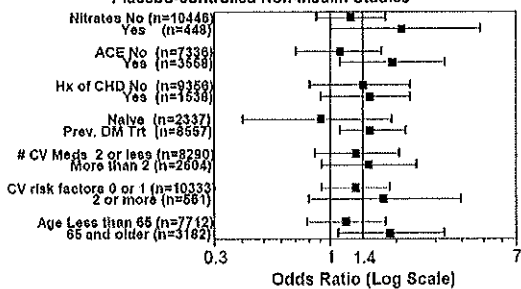
Results for 35 placebo-controlled non-insulin studies (77% of database)

	RSG (n=6447)	Control (n=4447)	OR (95% CI)	p
IHD	1.9%	1.4%	1.4 (1.0, 1.9)	0.06
SIHD	1.0%	0.7%	1.5 (0.9, 2.4)	0.08
MI/CVd/ST	0.68%	0.58%	1.2 (0.7, 2.1)	0.5

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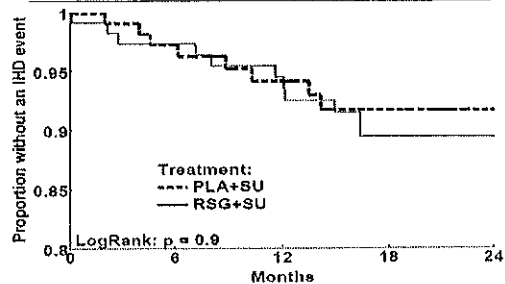
Subgroup Results

Serious + Non-serious Myocardial Ischemia
Placebo-controlled Non-insulin Studies

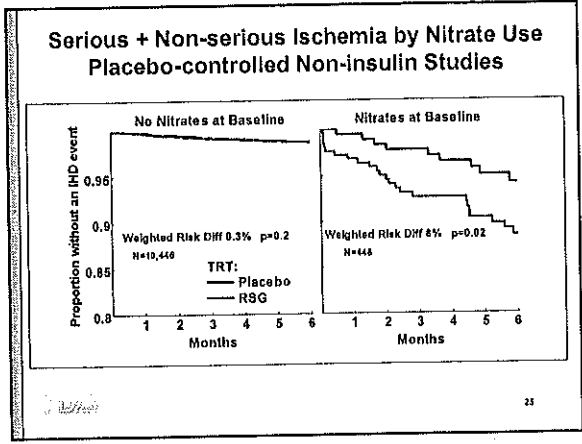


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Study 135 – 227 Patients 60 years+ Serious+Non-serious Myocardial Ischemic Events



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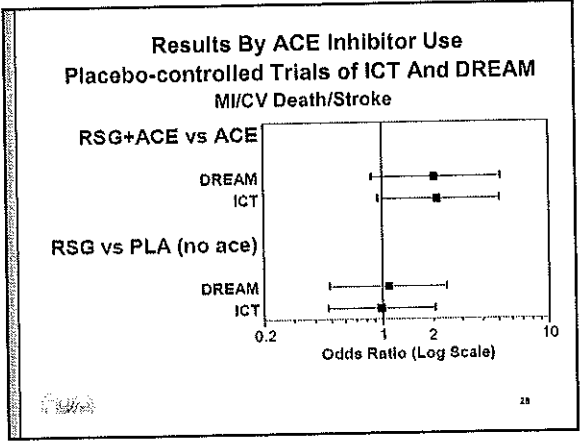
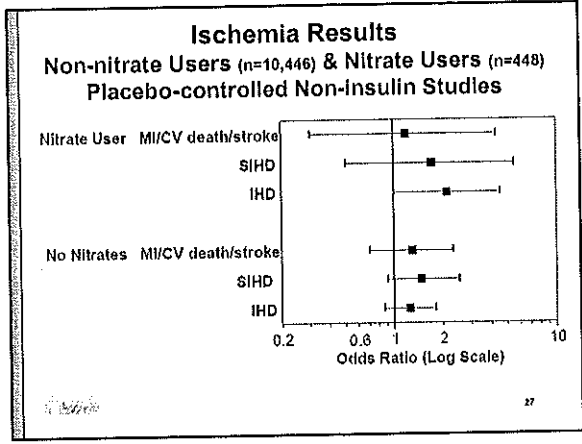


Serious+Non-serious Myocardial Ischemia Treatment by Nitrate Use Interaction (INT) 1-year Study 211 (CHF) & 16-week Study 352 (CHD)

Study	RSG	PLA	OR (95%)	INT p-value
352	5/31 (16%)	4/30 (13%)	1.2 (0.2, 6.9)	0.21
211	9/110 (8%)	5/114 (4%)	1.9 (0.6, 7.5)	0.11

211 By Nitrate use

Nitrates	3/31 (10%)	0/37 (0%)	p=0.09
No Nitrates	6/79 (8%)	5/77 (6%)	p>0.9



- ### Summary
- Placebo-controlled trials in meta-analysis database
- Nominally statistically significant increased risk of a myocardial ischemic event associated with RSG compared to placebo
 - High risk treatment paradigms
 - RSG add on to Insulin
 - RSG add on to metformin: Avandamet?
 - High risk subgroups
 - Nitrates
 - Ace Inhibitors?
- Active-controlled trials in meta-analysis database
- No definitive evidence of increased risk associated with RSG compared to metformin or sulfonylurea

- ### Summary
- Meta-analysis results have generated additional hypotheses
 - Formal FDA review of DREAM needed to examine the ACE Inhibitor interaction
 - Results for nitrates and ace inhibitors should be examined in RECORD, a study with prospectively adjudicated CV endpoints

Acknowledgements

Review team of DMEP and OSE

Statistical Colleagues:

Todd Sahlroot Tom Permutt Lee Pian

Bob O'Neill Ed Nevlus

Mat Soukup Chris Holland Mark Levenson

John Lawrence Cynthia Liu Janice Derr

Qian Li Japo Choudhury



HANDOUT FOR PRESENTATION OF FDA META-ANALYSIS OF ROSIGLITAZONE RANDOMIZED CONTROLLED TRIALS

Joint Meeting of Metabolic & Endocrine Advisory Committee and Drug Safety & Risk
Management Advisory Committee

July 30, 2007

Joy Mele
Statistician
Division of Biometrics 2
CDER

Attached are 3 forest plots showing the individual study results for the composite
endpoint of serious and non-serious myocardial ischemic events.

The studies are grouped as follows:

- Active-controlled studies
- Rosiglitazone add-on to insulin studies
- Placebo-controlled non-insulin studies

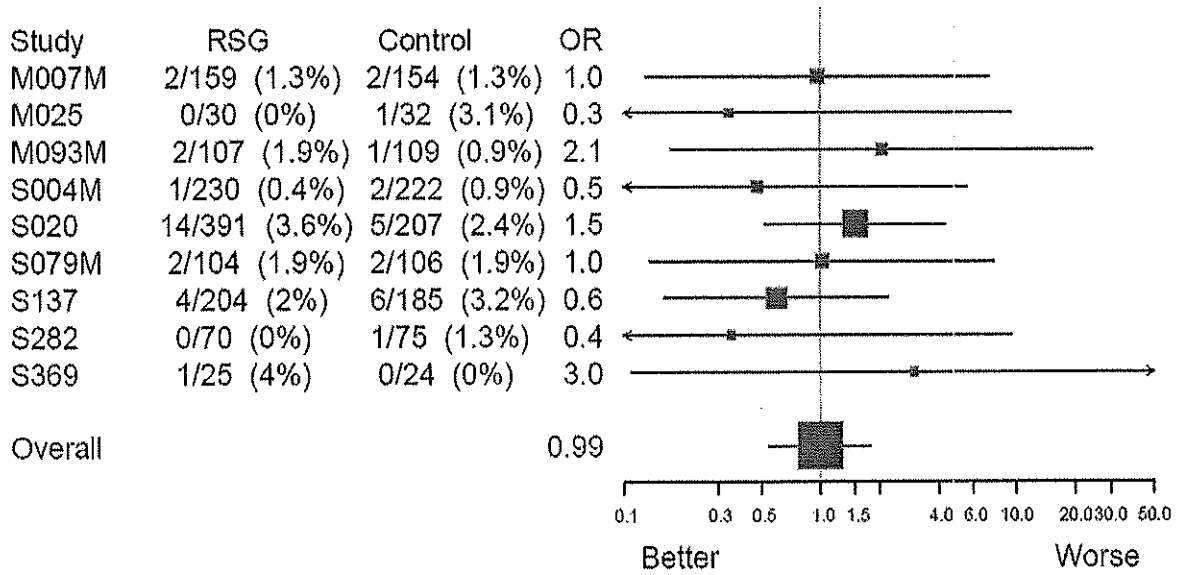
To plot odds ratios for studies with zero events in one arm or both arms, 0.5 was added to
each cell of those studies.

For the active-controlled studies, the letter preceding the study numbers indicates the
active control where M=metformin and S=sulfonylurea.

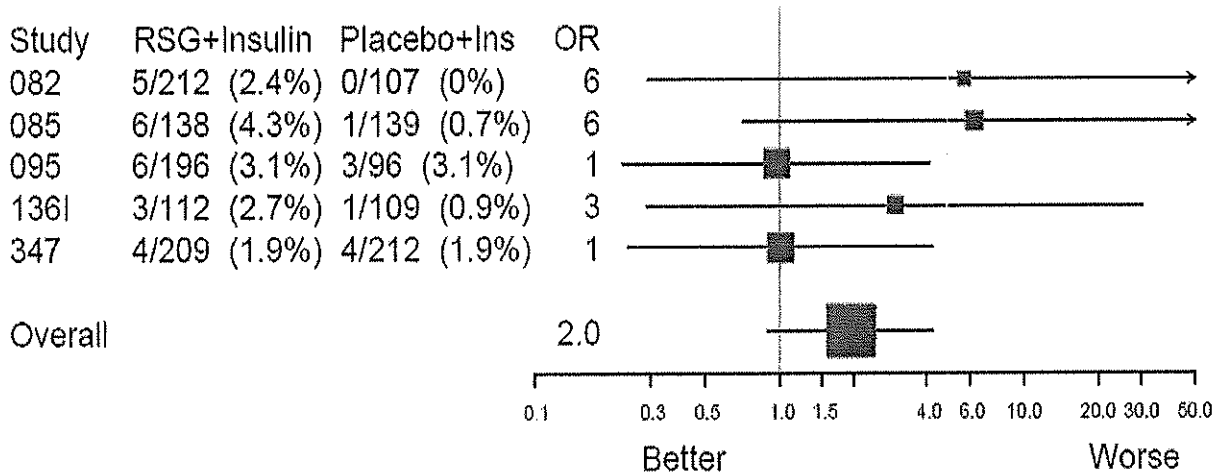
For the placebo-controlled non-insulin studies, the abbreviations used on the plots are:

BM	Add-on to background anti-diabetic medications
METa	Avandamet combination
MET	Add-on to metformin
M	Rosiglitazone monotherapy
SU	Add-on to sulfonylurea
TRI	Add-on to sulfonylurea and metformin

Studies of rosiglitazone compared to active control of metformin (M) or sulfonylurea (S)
 Results for composite endpoint of serious and non-serious myocardial ischemic events



Studies of rosiglitazone added to insulin compared to placebo added to insulin
 Results for composite endpoint of serious and non-serious myocardial ischemic events



Studies of rosiglitazone compared to placebo

Results for composite endpoint of serious and non-serious myocardial ischemic events

(See page 1 for description of abbreviations.)

