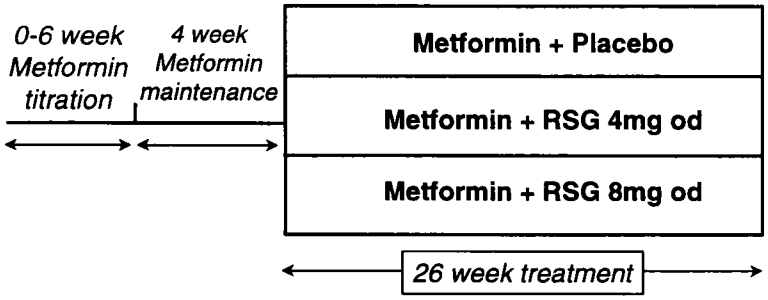
094: Study Design



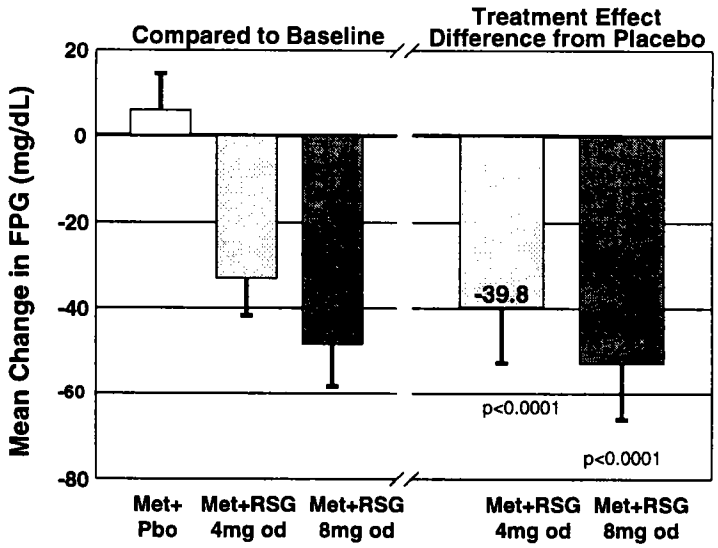
Patients received maximal (2.5g/day) metformin during the maintenance period

094: Baseline Metabolic Characteristics

Baseline Characteristics, n(%)	Treatment Group: Met + Pbo (N = 113)	Met + RSG 4mg od (N = 116)	Met + RSG 8mg od (N = 110)
Baseline HbA1c (%)			
Mean ± SD	**8.6** ± 1.3	**8.9** ± 1.3	**8.9** ± 1.5
Baseline FPG (mg/dL)			
Mean ± SD	**214** ± 52.4	**215** ± 57.1	**220** ± 54.9
Duration of Diabetes (yrs)			
Mean ± SD	7.3 ± 5.7	**7.5** ± 6.3	**8.3** ± 6.3
Previous Therapy			
Diet Only	5 (4)	7 (6)	5 (5)
Single Agent	55 (49)	46 (40)	48 (44)
Combination	53 (47)	63 (54)	57 (52)

(Study 094 - ITT Population)

094: FPG at Week 26

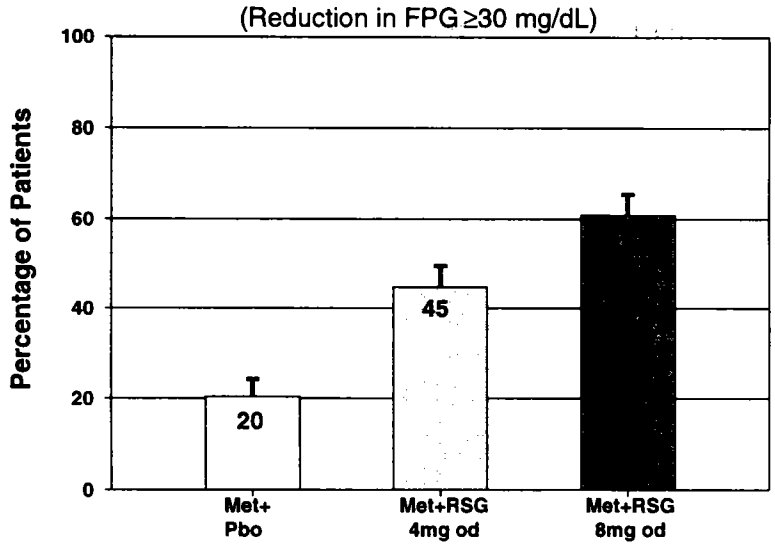


(Study 094 - ITT, LOCF)

(Error Bars = 95% CI)

Avandia®

094: FPG Responders

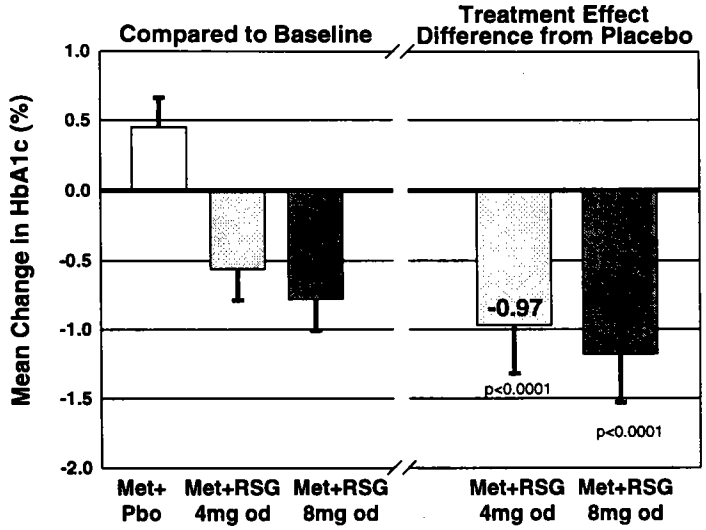


(Study 094 - ITT, LOCF)

(Error Bars = SE)

Avandia®

094: HbA1c at Week 26

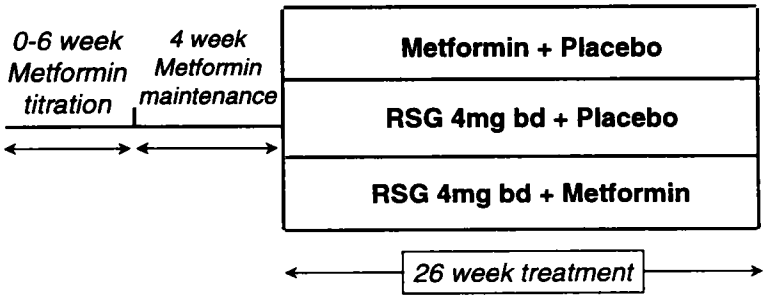


(Study 094 - ITT, LOCF)

(Error Bars = 95% CI)

Avandia®

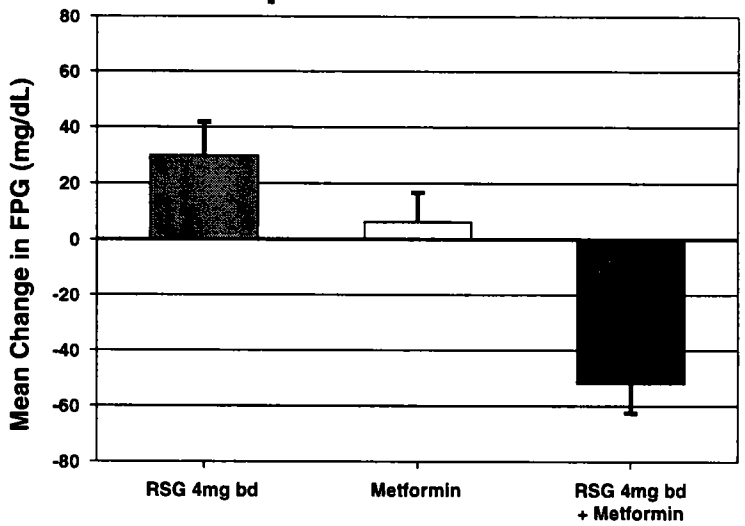
093: Study Design
The "Synergy" Study



Patients received maximal (2.5g/day) metformin during the maintenance period

Avandia®

093: FPG at Week 26 Compared to Baseline



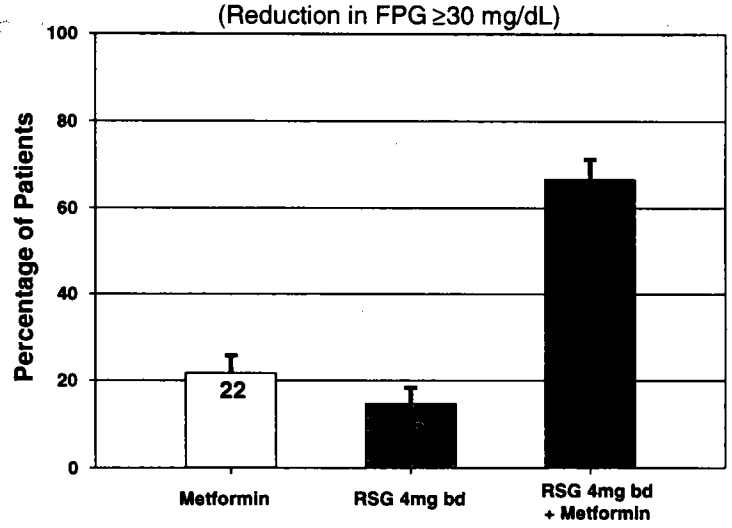
(Study 093 - ITT, LOCF)

(Error Bars = 95% CI)

Avandia®

093: FPG Responders

(Reduction in FPG ≥30 mg/dL)

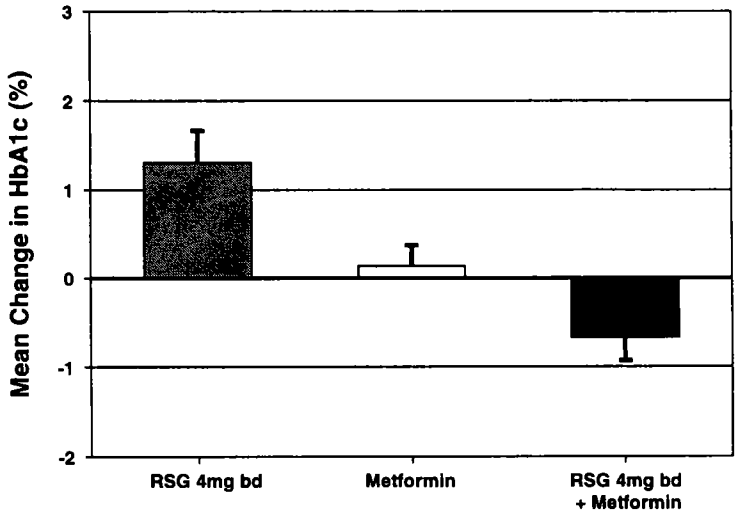


(Study 093 - ITT, LOCF)

(Error Bars = SE)

Avandia®

093: HbA1c at Week 26 Compared to Baseline

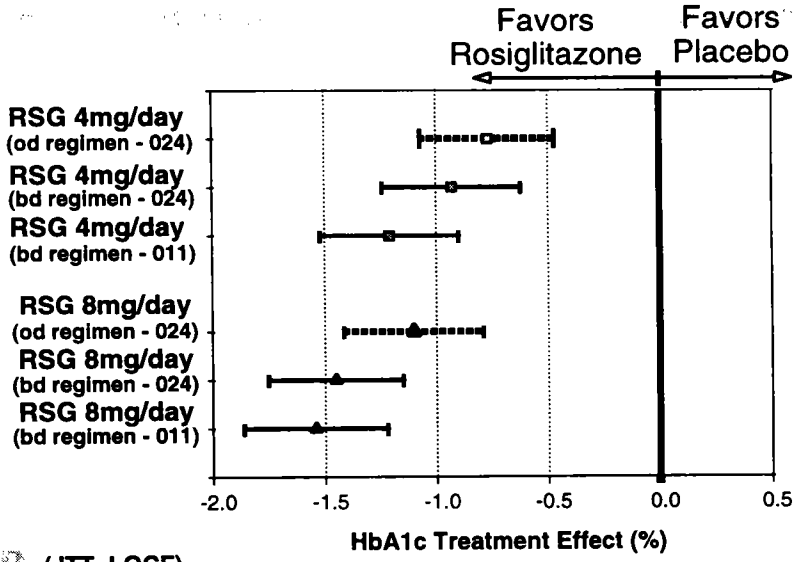


(Study 093 - ITT, LOCF)

(Error Bars = 95% CI)

Avandia®

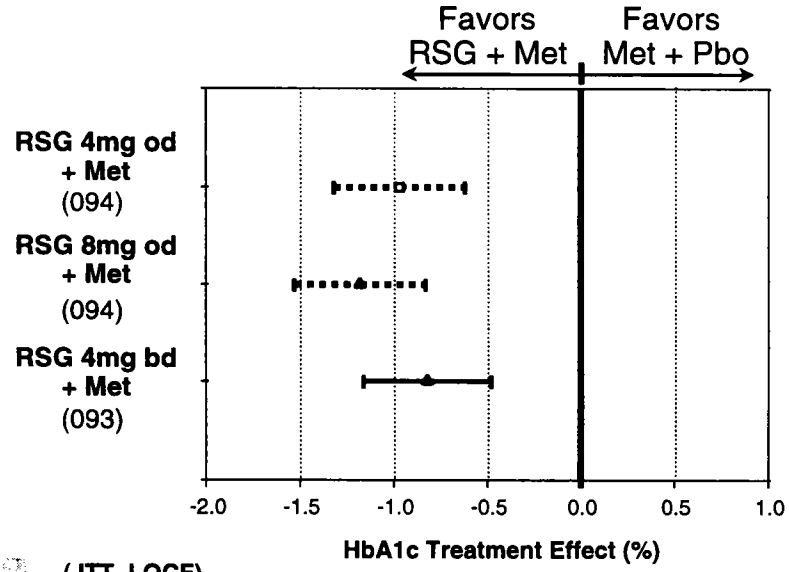
HbA1c - Treatment Effect (95% CI) Monotherapy



(ITT, LOCF)

Avandia®

HbA1c - Treatment Effect (95% CI) - Avandia® + Metformin



(ITT, LOCF)

Conclusions

- **Avandia® used as monotherapy, or in combination with metformin, is effective in improving glycemic control at doses of 4mg/day and 8mg/day**

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- Recommended starting dose of Avandia® is 4mg/day

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- Avandia® may be administered as a single daily dose or in divided doses

Conclusions

- Avandia® used as monotherapy, or in combination with metformin, is effective in improving glycemic control at doses of 4mg/day and 8mg/day
- Recommended starting dose of Avandia® is 4mg/day
- Avandia® may be administered as a single daily dose or in divided doses
- Avandia® in combination with metformin is more effective than either agent alone, consistent with a synergistic effect based on different mechanisms of action

Conclusions

- Avandia® has a durable effect for up to 12 months

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- Improvements in glycemic control are associated with reductions in endogenous insulin, c-peptide, proinsulin, and insulin split products

Conclusions

- Avandia® has a durable effect for up to 12 months
- Improvements in glycemic control are associated with reductions in endogenous insulin, c-peptide, proinsulin, and insulin split products
- Avandia® reduces free fatty acids and preserves the LDL/HDL cholesterol ratio

Avandia®

SmithKline Beecham Pharmaceuticals

David E. Wheadon, MD
VP & Director, North American Regulatory Affairs
Introduction and Preclinical Highlights

Anthony S. Rebuck, MD
VP & Director, Pulmonary and Diabetes Therapeutic Unit
Efficacy Profile

Elizabeth B. Rappaport, MD
Group Director, Diabetes and Metabolism
Safety Profile

Douglas A. Greene, MD
Professor, Internal Medicine; Director, Michigan Diabetes Research Center
University of Michigan
Risk/Benefit Assessment

Tadataka Yamada, MD
Chairman, Research & Development, SmithKline Beecham Pharmaceuticals
Summary

SB

SmithKline Beecham Pharmaceuticals

Avandia®
(rosiglitazone maleate)

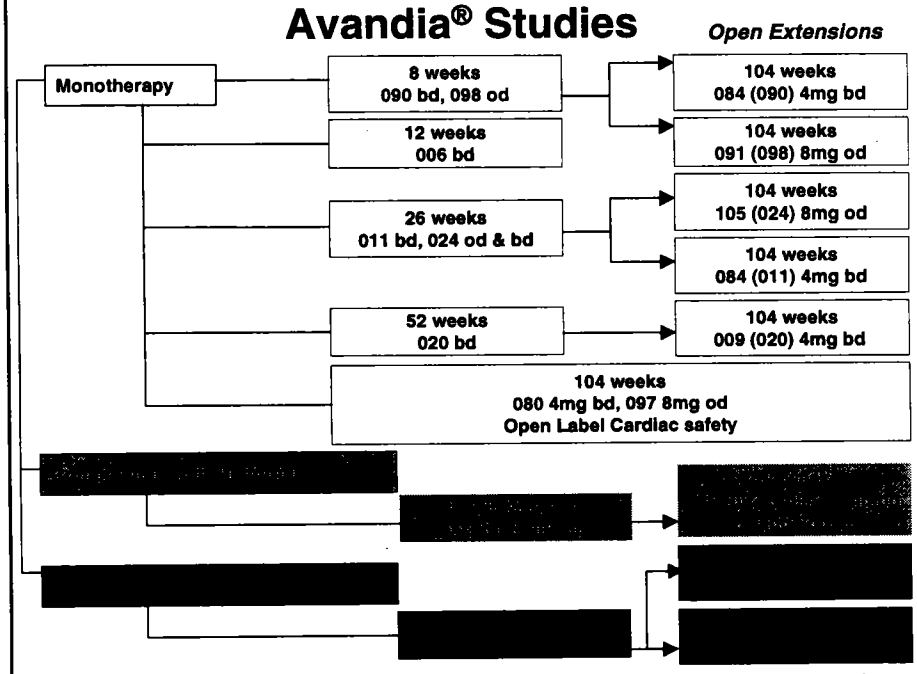
Safety Profile

Elizabeth B. Rappaport, MD
Group Director
Diabetes and Metabolism

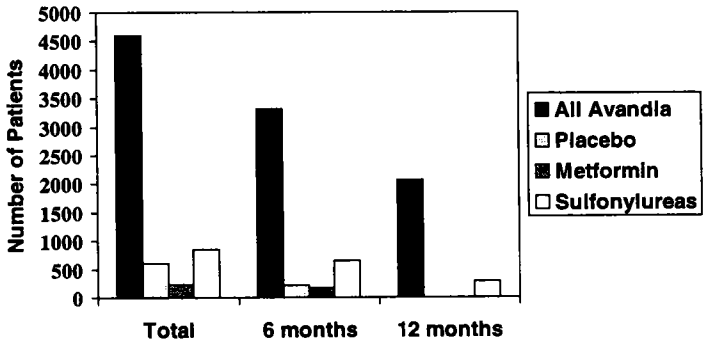
Avandia® Clinical Program Safety Profile

- Scope of safety database
- Demographic and clinical characteristics
- General adverse event findings
- Areas of interest based on pre-clinical findings
  - hemodynamic / cardiovascular
  - hematology
  - weight
- Area of special interest- liver

Avandia® Studies

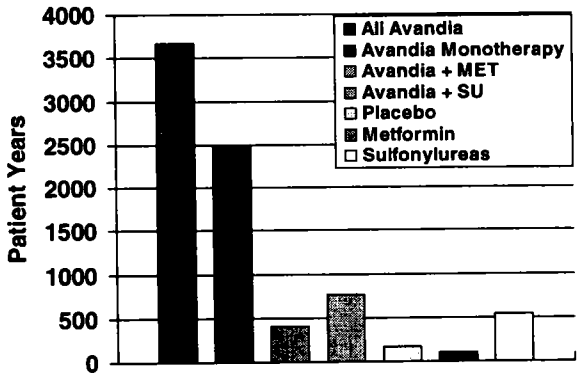


Avandia® Safety Database Phase 2/3 Clinical Program



120 Day Safety Update

Avandia® Safety Database- Patient Years of Treatment



120 Day Safety Update

Characteristics of the Safety Populations

- **63 - 65% Male**
- **Mean Age: 59**
- **81 - 85% Caucasian**
- **68 - 78% Baseline BMI >27kg/m^2**
- **Mean duration of diabetes was:**
  - 5.7 yrs - Avandia® monotherapy
  - 7.5 yrs - Avandia® + metformin
  - 8.7 yrs - Avandia® + sulfonylureas

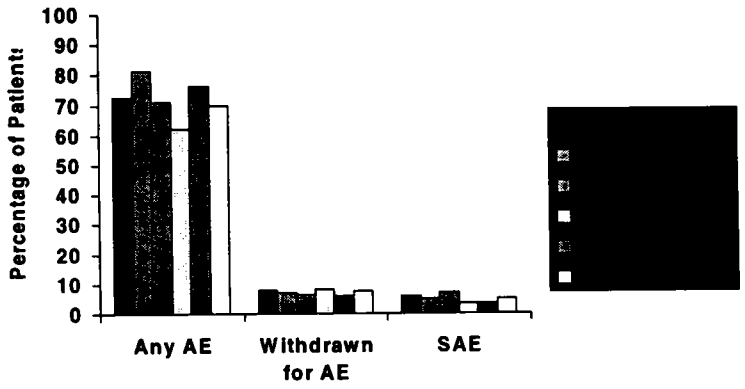
Clinical Characteristics of the Safety Population

- **Co-existing conditions**
  - Hypertension 40-45%
  - Hyperlipidemia 18-32%
  - Ischemic Heart Disease 3-9%
  - Peripheral Neuropathy 7-15%
- **Specific exclusions**
  - NYHA III/IV angina/CHF
  - Uncontrolled hypertension
  - Clinically significant renal or hepatic disease

Frequency of Concomitant Medication Use in the Study Population

- ACE inhibitors 20-30%
- Diuretics 11-16%
- β blockers 11-15%
- Ca^{++} channel blockers 10-14%
- Lipid lowering agents 17-28%

Percent of Patients with One or More Adverse Event Report



Double-blind and open label (NDA)

Most Frequent Adverse Events in Double-blind Trials - Avandia® Monotherapy

Adverse Events	Avandia® Mono n=2526 %	Placebo n=601 %	MET n=225 %	SU n=626 %
URTI	9.9	8.7	8.9	7.3
Injury	7.6	4.3	7.6	6.1
Headache	5.9	5.0	8.9	5.4
Back pain	4.0	3.8	4.0	5.0
Hyperglycemia	3.9	5.7	4.4	8.1
UTI	3.8	3.0	3.1	4.2
Fatigue	3.6	5.0	4.0	1.9
Hypercholesterolemia	3.4	0.5	1.3	1.3
Sinusitis	3.2	4.5	5.3	3.0
Infection viral	3.2	4.0	3.6	3.8

>3% incidence

SB

Avandia®

Most Frequent Adverse Events in Double-blind Trials - Avandia® in Combination with Sulfonylureas

Adverse Events	Avandia® + SU n=726 %	SU n=626 %
URTI	8.4	7.3
Injury	5.8	6.1
Hyperglycemia	5.2	8.1
Hypoglycemia	4.8	5.9
Headache	4.4	5.4
Infection viral	4.4	3.8
UTI	4.3	4.2
Pain	3.7	2.6
Dizziness	3.6	3.0
Hypercholesterolemia	3.6	1.3
Sinusitis	3.4	3.0
Arthralgia	3.4	3.0
Back pain	3.2	5.0

>3% incidence

SB

Avandia®

Most Frequent Adverse Events in Double-blind Trials - Avandia® in Combination with Metformin

Adverse Events	Avandia® +MET n=338 %	MET n=225 %
URTI	16.0	8.9
Diarrhea	12.7	15.6
Injury	8.0	7.6
Anemia	7.1	2.2
Headache	6.5	8.9
Sinusitis	6.2	5.3
Fatigue	5.9	4.0
Infection viral	5.0	3.6
Arthralgia	5.0	2.2
Back pain	5.0	4.0
Nausea	4.1	3.1
Pain	4.1	4.0

> 4% Incidence

Analysis of AEs in Patient Sub-Groups

Avandia® was well tolerated

- across age, gender, BMI or race classifications
- with commonly co-administered medications
- in the presence of common co-existing medical conditions

Adverse Events Leading to Withdrawal

% of patients

	Avandia® Mono N=2902	PLA N=601	Avandia® +Met N=546	Met N=225	Avandia® +SU N=974	SU N=626
Any AE	7.8	8.2	7.0	5.8	6.3	7.7
Hyperglycemia/ Diabetes Aggravated	2.0	3.2	0.0	0.9	1.4	1.1
Elevated Lactate Levels	n/a	n/a	1.1	1.8	n/a	n/a
Diarrhea	0.1	0.2	1.1	1.3	0.3	0.0

SB

Avandia®

Summary of Serious Non-fatal Adverse Experiences

Events/100 pt yrs

	Avandia® Mono N=2902	PLA N=601	Avandia® +MET N=546	MET N=225	Avandia®+ SU N=974	SU N=626
Any SAE	10.1	12.4	9.9	8.2	12.1	8.8
Cardiovascular SAE	3.3	5.3	4.0	6.1	3.3	1.4
Injury	0.8	0.6	1.1	0.0	0.4	0.7
Withdrawn for SAE	3.5	6.5	2.6	3.1	2.7	4.7

SB

Avandia®

Reported Deaths

	N	n	Events/ 100 pt yrs	(95% C.I.)
Avandia®	4598	28	0.76	(0.51-1.10)
Sulfonylureas	845	2	0.37	(0.04-1.33)
Placebo	601	1	0.59	(0.01-3.25)
Metformin	225	0	0	(und-3.96)

Double-blind and open label 120 Day Update

Adverse Event Summary

- Avandia® is safe when administered alone or in combination with Met or SU
- Total daily doses of 4mg and 8mg are safe and well tolerated
- Overall frequencies of AEs, serious AEs and withdrawals are similar for Avandia® and comparators
- Overall AE profile was similar across patient subgroups

Areas of Interest
Based on Preclinical Findings

- Hemodynamic / Cardiovascular
- Hematology
- Weight

Areas of Interest
Based on Preclinical Findings

- Hemodynamic / Cardiovascular
- Hematology
- Weight

Hemodynamic/Cardiovascular Effects

- Plasma volume expansion was associated with cardiac hypertrophy in Avandia treated animals
- Echocardiography studies were conducted in non-hypertensive patients with Type 2 Diabetes
- Evaluated cardiac adverse events
- Evaluated adverse events of edema

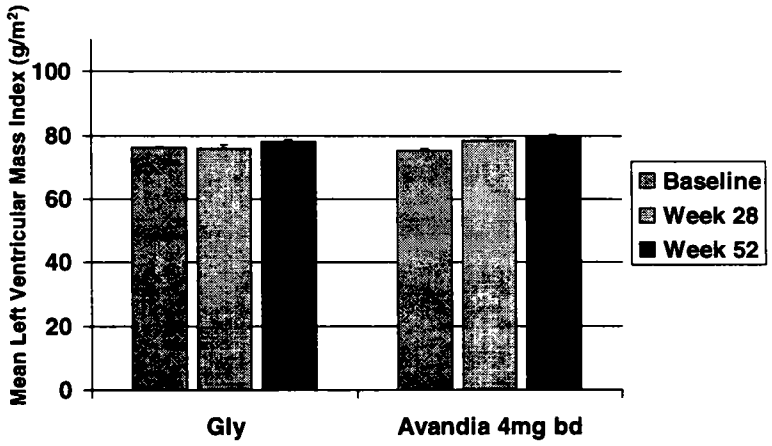
Echocardiography Study- 080

- Randomized, 2 year open-label, glyburide-controlled study
- Patients excluded
  - NYHA Class III/IV angina/CHF
  - Treatment with ACE inhibitors, β blockers or Ca^{++} channel blockers
  - SBP >160 mm Hg or DBP >100 mmHg

Echocardiography Study- 080

- Echocardiograms were taken at baseline, 12 weeks, 28 weeks, 52 weeks
- All echocardiograms read in a blinded fashion by central reader
- Change in LVMI from baseline to week 52 compared to assess 'non-inferiority' of Avandia® to glyburide with respect to effect on LVMI
- Criterion for withdrawal: increase in LV mass of >60g

Mean LVMI at Baseline, Week 28 and Week 52



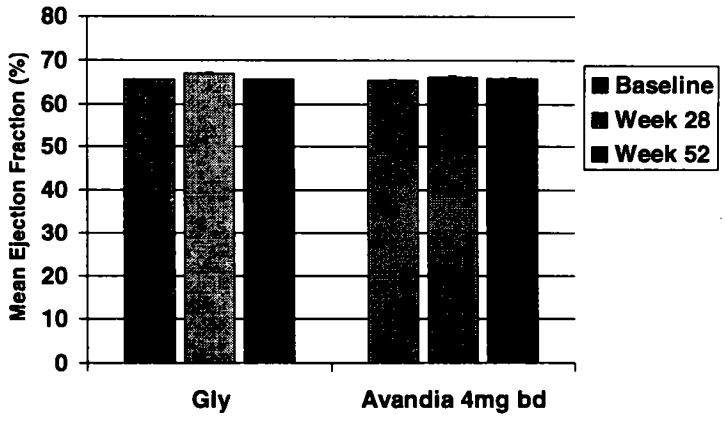
	Gly	Avandia 4mg bd
N=	71	72
N=	71	72
N=	63	58

Avandia®/080 - All randomized [observed case] patients) (Error Bars= SE)

Echocardiography Results

- Changes in LVMI similar to glyburide; met criterion for non-inferiority
- No patient met withdrawal criterion for increase in LV mass
- No patients shifted from a low or normal LVMI at baseline to a LVMI above the reference range at any time on-therapy

Mean Ejection Fraction at Baseline, Week 28 and Week 52

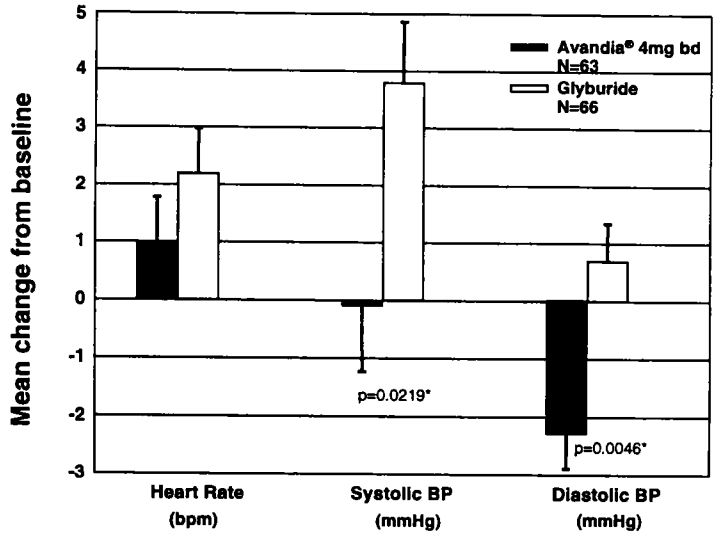


	Gly	Avandia 4mg bd
N=	68	72
N=	68	72
N=	60	58

(Avandia®/080 - All randomized [observed case] patients) (Error Bars= SE)

Change in Mean 24 Hour Ambulatory Blood Pressure- 080

(Baseline to Week 52 - All Randomized [OC] Population)



* Comparison with Glyburide

Error bars= S.E.

Avandia®

Cardiovascular Serious Adverse Experiences -

	Rate per 100 pt yrs			
	All Avandia®	PLA	MET	SU
	2492.8	169.5	98.1	362.8
Ischemic Heart Disease	2.6	1.8	3.1	1.1
Cardiac Rhythm/ Conduction Abn.	0.5	0.6	2.0	0.3
Heart Failure	0.4	0.6	0.0	0.6
Cerebrovascular Disorder	0.2	1.8	1.0	0.3
Hypertension	<0.1	0.6	0.0	0.0
Total	3.4	5.3	6.1	1.4

Double blind and open label studies (NDA)

Avandia®

Deaths Attributed to Cardiac Events

	N	n	Events/ 100pt yrs	(95% C.I.)
Avandia®	4598	14	0.38	(0.21-0.64)
Placebo	601	1	0.59	(0.01-3.28)
Sulfonylureas	845	1	0.18	(0.00-1.03)
Metformin	225	0	0	(und-3.67)

Double blind and open label studies (120 Day Update)

Cardiac Mortality Comparison to Other Clinical Trials and Observational Studies

	pt yrs	n	Events/ 100pt yrs	(95% C.I.)
Avandia®	3673	14	0.38	0.21-0.64
Comparators	810	2	0.25	0.03-0.89
Repaglinide	1228	6	0.50	0.18-1.06
Glyburide	417	1	0.24	0.01-1.34
UKPDS	42778	295	0.69	0.61-0.77

Frequency of Edema in Double-blind Studies

	N	%	withdrawal	SAE
RSG Mono	2526	4.8	1	0
RSG + Met	338	4.4	1	0
RSG + SU	726	3.0	0	0
PLA	601	1.3	1	0
Met	225	2.2	0	0
SU	626	1.0	0	0

Hemodynamic / Cardiovascular Conclusions

- **52 week echocardiography study with Avandia® 4 mg bd**
  - no adverse effects on cardiac structure or function
  - statistically significant decrease in diastolic BP with no change in systolic BP
- **Frequency of cardiac adverse events with Avandia® was similar to comparators**
- **Death attributed to cardiac events occurred at a rate similar to rates in other studies**
- **Mild to moderate edema occurred in few patients in dose ordered fashion**