SmithKline Beecham Pharmaceuticals

Avandia®
(rosiglitazone maleate)

Food & Drug Administration

Center for Drug Evaluation and Research

Endocrinologic and Metabolic Drugs Advisory Committee

April 22, 1999

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

Avandia®- Key Messages

- **Potent antidiabetic PPARγ agonist**
- **Effective in mono and combination therapy**
- **Durable effect**
- **Well characterized safety profile**
  - no signal of hepatotoxicity
  - neutral effect on lipids
  - minimal cardiovascular / hemodynamic effects
- **Positive Risk / Benefit Assessment**

Avandia®
Preclinical Findings - Highlights

- **Rosiglitazone has greater pharmacological potency and a better hepatic safety profile than troglitazone**
- **Some preclinical findings are common to the thiazolidinediones**
- **Preclinical studies predicted efficacy and safety in clinical trials**

PPARγ is a Key Molecular Target for Thiazolidinediones

- **Thiazolidinediones**
  - high affinity for ligand binding domain of PPARγ but not PPARα or PPARδ
  - activate PPARγ to regulate expression of genes encoding proteins involved in lipid and glucose metabolism

Rosiglitazone - Preclinical Efficacy

In rodent models of obesity, insulin resistance and/or Type 2 diabetes

- Increased insulin sensitivity in liver, skeletal muscle and adipose tissue
- Improved glycemic control without causing hypoglycemia
- Lowered plasma concentrations of free fatty acids and triglycerides
- Protected against pancreatic β-cell insulin depletion

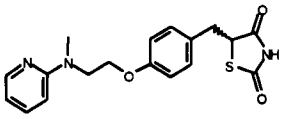
Preclinical Findings Common to Thiazolidinediones

- **Adipocyte hyperplasia**
  - subcutis, epididymal, bone marrow
- **Increased body weight**
- **Increased plasma volume and decreased hematocrit**
  - increased plasma volume was related to increased retention of sodium and water in association with increased regional blood flow (fat and s/c tissue) and lowered blood pressure
- **Cardiac hypertrophy**
  - related to increased cardiac preload

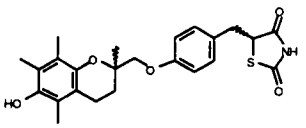
Preclinical Findings Common to Thiazolidinediones

- **Inhibition of ovarian steroidogenesis**
- **Fetal toxicity, but no teratogenicity**
- **Benign lipomas in rats**

Differences in Pharmacological Potency



Rosiglitazone

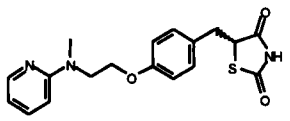


Troglitazone

	Rosiglitazone	Troglitazone
Human PPARγ binding IC_{50} (nM ± SEM)	41 ± 18	7970 ± 580
Clinical dose (mg)	4 - 8	400 - 600

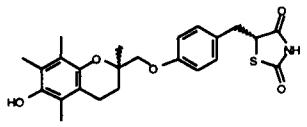
- Binding affinity/agonist potency at PPARγ are highly correlated with antidiabetic potency

Differences in Hepatic Safety Profile



Rosiglitazone

- ALT increase in dogs only
- No effect on LDH release from rat hepatocytes (100 uM)



Troglitazone

- ALT increase in rats, dogs, monkey and man
- Increased LDH release from rat hepatocytes (EC25 = 40 uM)

Differences in Metabolism and Disposition

	Rosiglitazone	Troglitazone
Volume of Distribution	0.1 to 0.2 L/kg	10.5 to 26.5 L/kg
Half-life in man	4 hours	16 to 34 hours
Enterohepatic recirculation	None	Marked
Liver/plasma ^{14}C ratio in rats	≤ 1	~15
CYP 3A4 induction	Clinically insignificant	Clinically significant
Primary route of ^{14}C excretion in man	kidney	liver

Efficacy and Safety Predictions from Preclinical Studies

- **Potential clinical benefits**
  - Improved glycemic control and insulin sensitivity
  - Decreased concentration of free fatty acids in plasma
  - Favorable drug interaction profile
  - Improved hepatic safety
- **Potential safety issues for clinical trials**
  - Cardiovascular / hemodynamic effects
  - Reduced Hematocrit
  - Increased body weight

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Avandia®
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Efficacy Profile

Anthony S. Rebuck, MD
Vice President and Director
Pulmonary and Diabetes Therapeutic Unit

Avandia® Data Presentation

Monotherapy

- as an adjunct to diet and exercise to lower blood glucose in patients with type 2 diabetes mellitus

Combination with Metformin

- concomitantly with metformin when diet and metformin alone do not result in adequate glycemic control

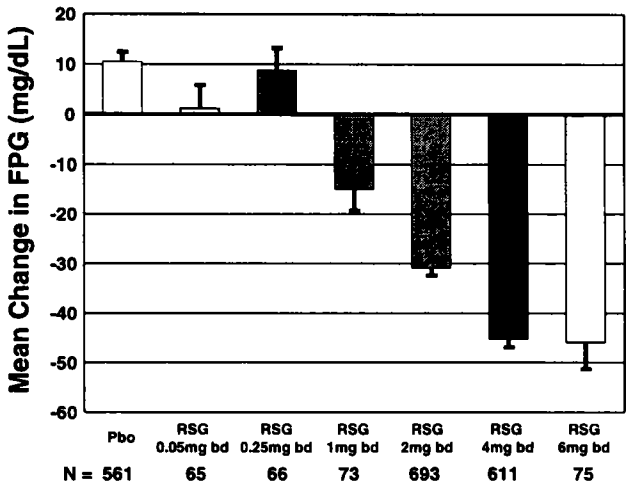
Avandia® Phase 2/3 Clinical Program

	Monotherapy N = 3417	Combination with Metformin N = 645	Combination with Sulfonylurea N = 1216
8 - 12 weeks	**006, 090, 098** (0.1 - 12 mg)		
26 weeks	**011, 024** (4 - 8 mg)	**093, 094** (4 - 8 mg)	**015, 079, 096** (2 - 4 mg)
52 weeks	**020** (4 - 8 mg)		
104 weeks	**080, 097** **009, 084, 091, 105** (8 mg)	**113** (8 mg)	**009, 112** (4 mg)

Dose-response of Avandia® in Monotherapy

Change from Baseline in FPG at Week 8

(Pooled Monotherapy Data)



(ISE - ITT, LOCF)

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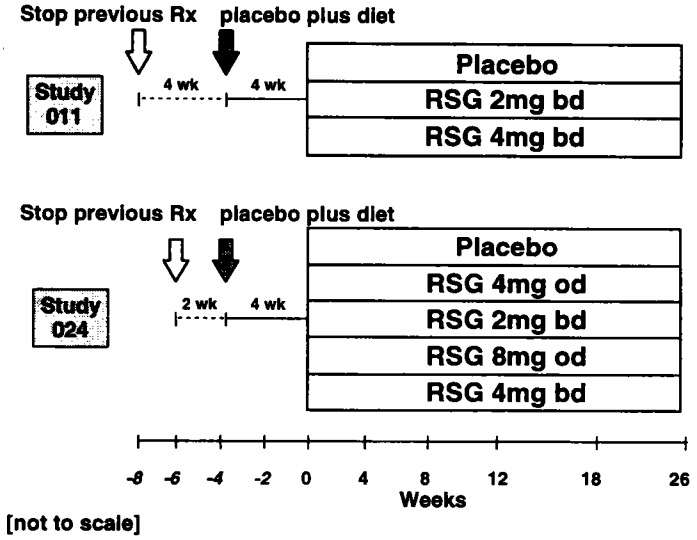
Avandia® – Monotherapy

Monotherapy Study Design



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011: Baseline Demographic Characteristics

Baseline Characteristics, n (%)	Treatment Group		
	Placebo (N = 158)	RSG 2mg bd (N = 166)	RSG 4mg bd (N = 169)
Age (years)			
Mean ± SD	59 ± 10.9	60 ± 9.8	61 ± 9.5
Gender			
Males	104 (66)	107 (65)	113 (67)
Females	54 (34)	59 (36)	56 (33)
Baseline BMI (kg/m²)			
Mean ± SD	30 ± 4.1	30 ± 4.1	29 ± 3.9
Race			
White	117 (74)	125 (75)	124 (73)
Black	13 (8)	14 (8)	16 (10)
Other	28 (18)	27 (16)	29 (17)

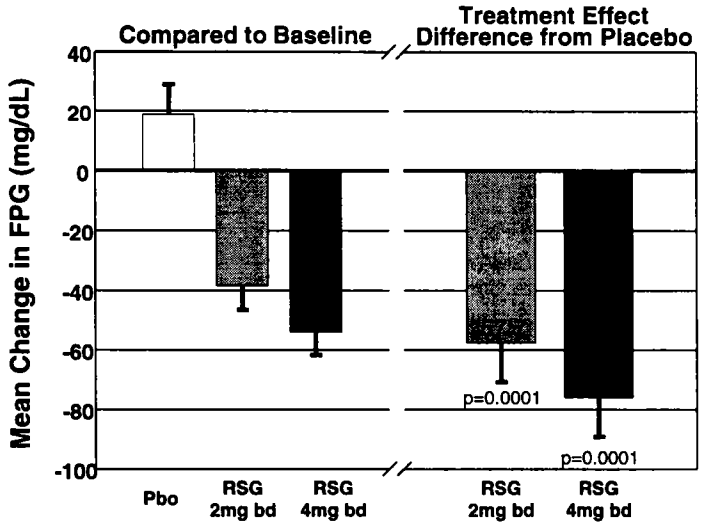
(Study 011 - ITT Population)

011: Baseline Metabolic Characteristics

Baseline Characteristics, n (%)	Treatment Group		
	Placebo (N = 158)	RSG 2mg bd (N = 166)	RSG 4mg bd (N = 169)
Baseline FPG (mg/dL)			
Mean ± SD	229 ± 59.5	227 ± 61.6	220 ± 63.7
Baseline HbA1c (%)			
Mean ± SD	9.0 ± 1.66	9.0 ± 1.52	8.8 ± 1.56
Duration of Diabetes (years)			
Mean ± SD	4.6 ± 4.80	4.8 ± 5.83	5.4 ± 6.03
Previous Therapy			
Diet Only	45 (29)	44 (27)	45 (27)
Single Agent	101 (64)	114 (69)	111 (66)
Combination	12 (8)	8 (5)	13 (8)

(Study 011 - ITT Population)

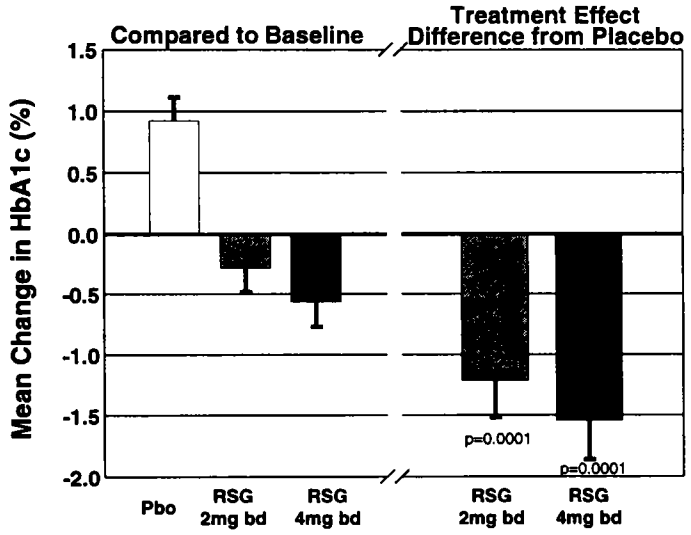
011: FPG at Week 26



(Study 011 - ITT, LOCF) (Error Bars = 95% CI)

Avandia®

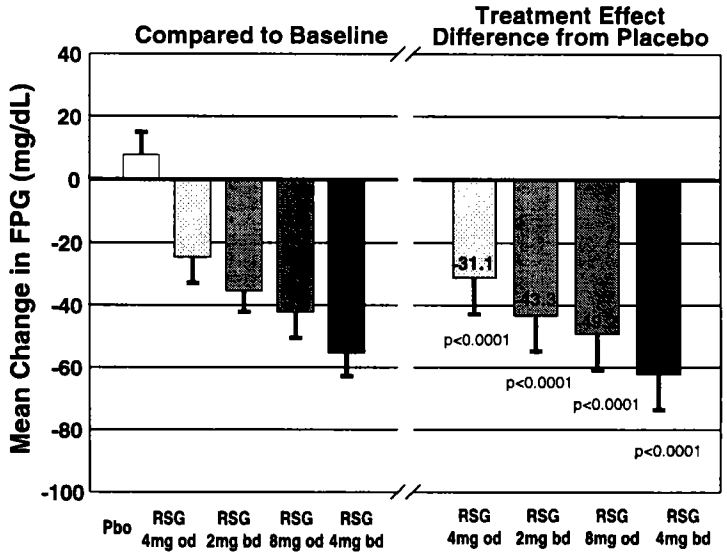
011: HbA1c at Week 26



(Study 011 - ITT, LOCF) (Error Bars = 95% CI)

Avandia®

024: FPG at Week 26

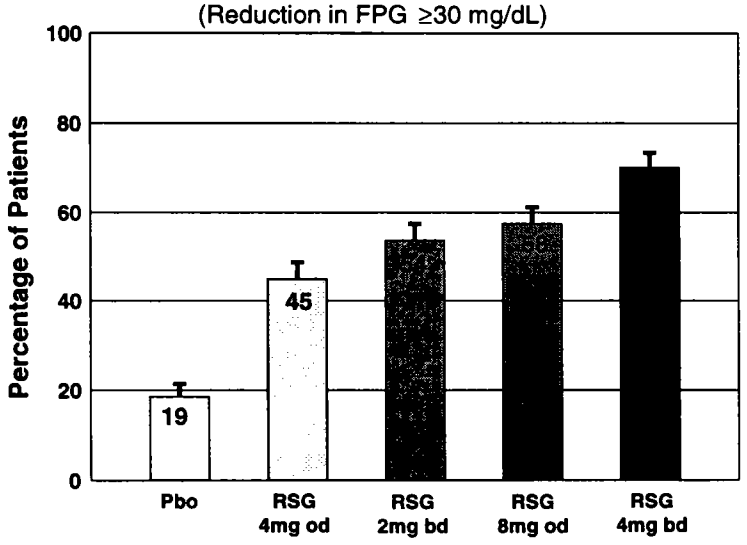


(Study 024 - ITT, LOCF) (Error Bars = 95% CI)

Avandia®

024: FPG Responders

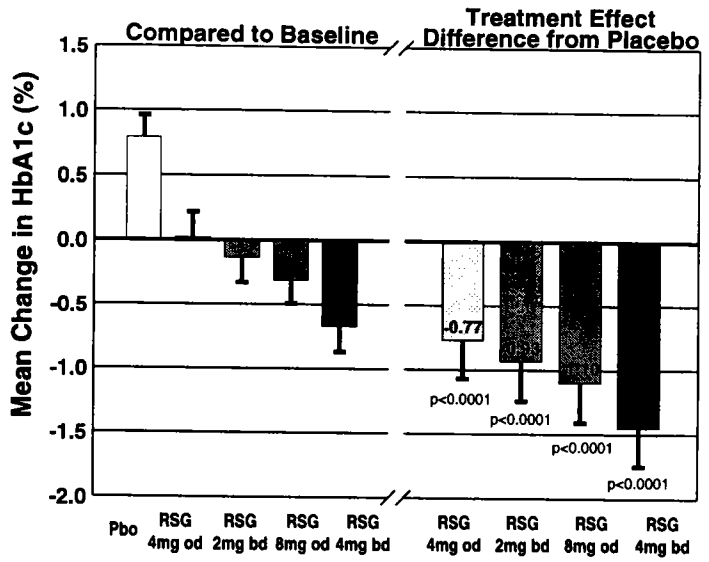
(Reduction in FPG ≥30 mg/dL)



(Study 024 - ITT, LOCF) (Error Bars = SE)

Avandia®

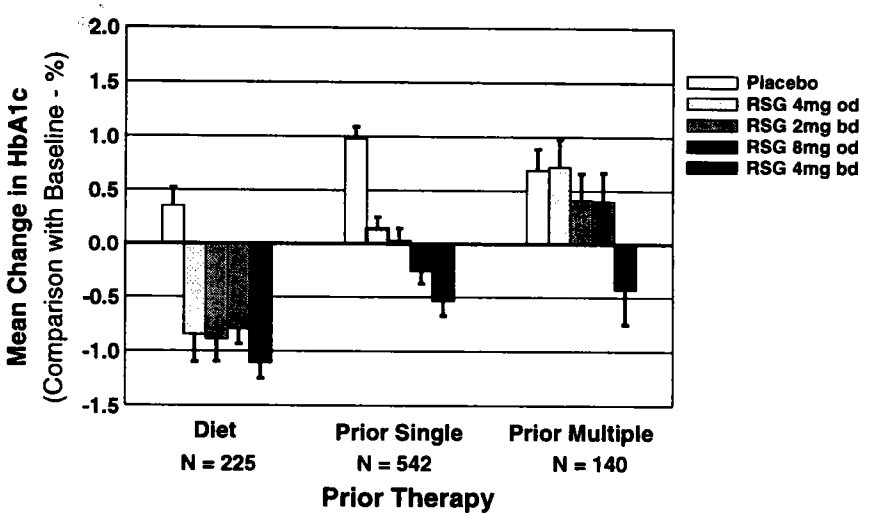
024: HbA1c at Week 26



(Study 024 - ITT, LOCF) (Error Bars = 95% CI)

Avandia®

024: HbA1c by Prior Therapy



(Study 024 - ITT, LOCF) (Error Bars = SE)

Avandia®

Monotherapy Summary

- Avandia® used as monotherapy is effective in improving glycemic control at doses of 4mg/day and 8mg/day, either once daily or in divided doses

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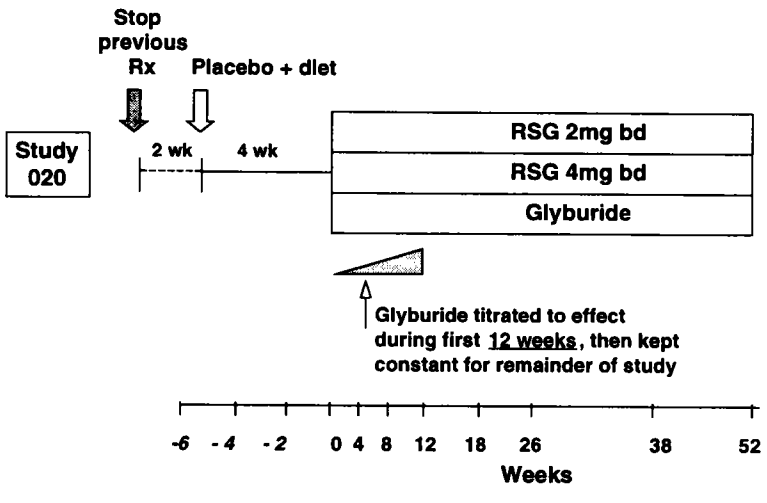
- Avandia® used as monotherapy is effective in improving glycemic control at doses of 4mg/day and 8mg/day, either once daily or in divided doses
- Recommended starting dose of Avandia® as monotherapy is 4mg/day

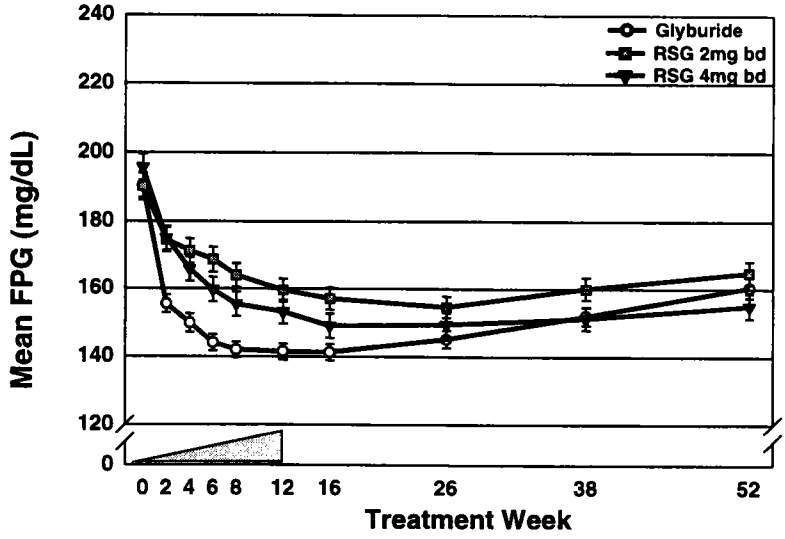
Avandia® – Durability of Effect

020: Study Design
Double-blind, double-dummy



[not to scale]

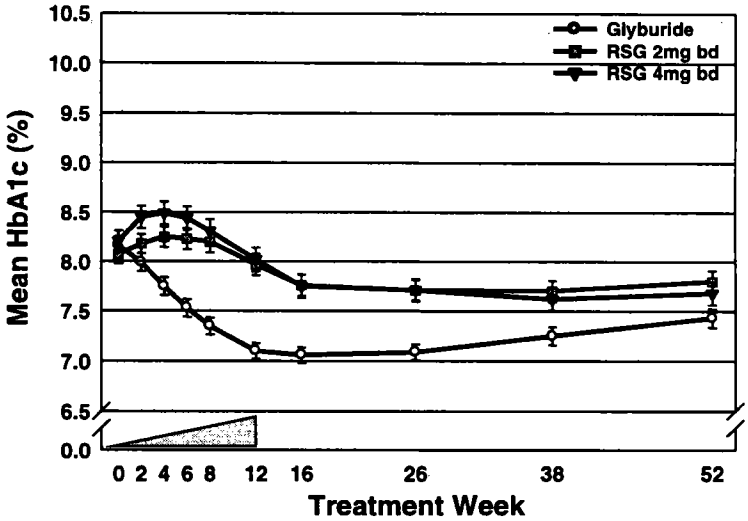
020: FPG Over Time



(Study 020 - ITT, LOCF) (Error Bars = SE)

Avandia®

020: HbA1c Over Time



(Study 020 - ITT, LOCF) (Error Bars = SE)

Avandia®

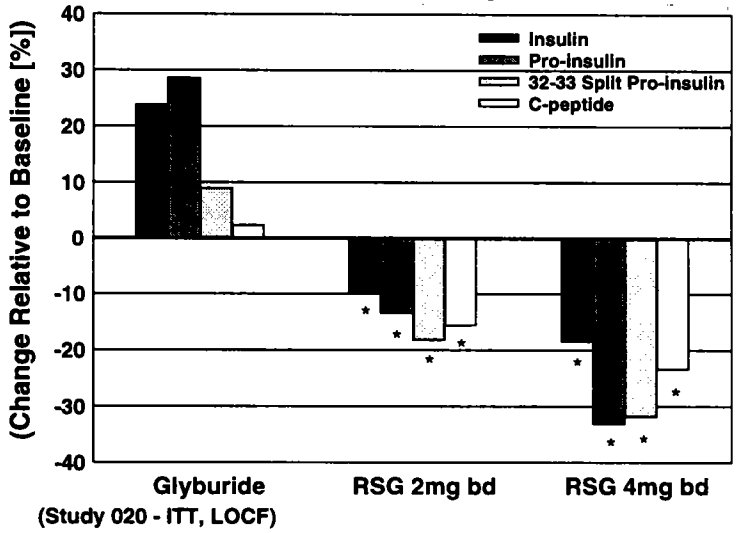
020: Hypoglycemia

	Treatment Group		
	Glyburide (N=207)	RSG 2mg bd (N=200)	RSG 4mg bd (N=191)
AE of hypoglycemia, n (%)	25* (12.1)	1** (0.5)	3** (1.6)
Withdrawal due to AE of hypoglycemia, n (%)	6 (2.9)	0 (0.0)	1 (0.5)

* 44 events in 25 patients

** 5 events in 4 patients

020: Endogenous Insulin Parameters - Change from Baseline at Week 52 Expressed as a Percentage of Baseline



(Study 020 - ITT, LOCF)

* statistically significant ($p<0.0001$) as compared to glyburide

Monotherapy Summary

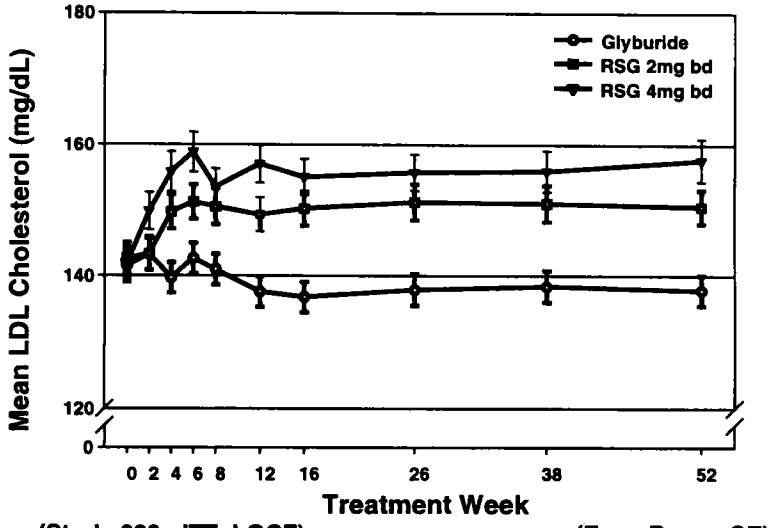
- Avandia® has a durable effect for up to 12 months

Monotherapy Summary

- 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

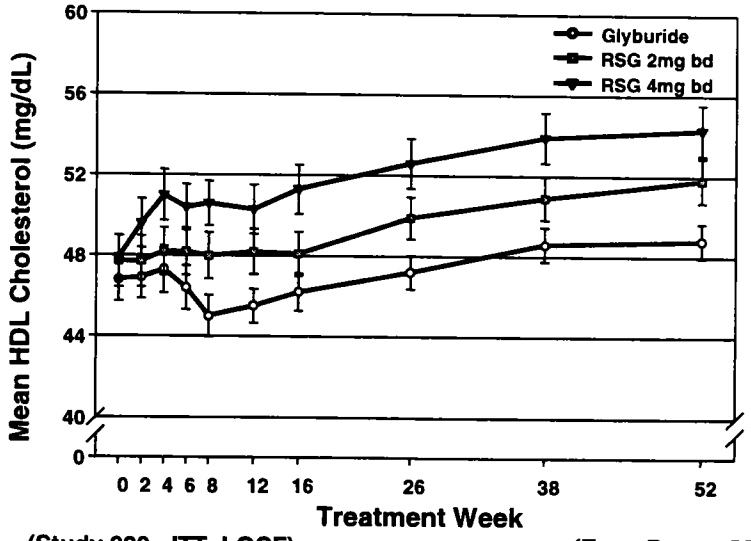
Avandia® - Lipid Effects

020: LDL-C Over Time



(Study 020 - ITT, LOCF) (Error Bars = SE)

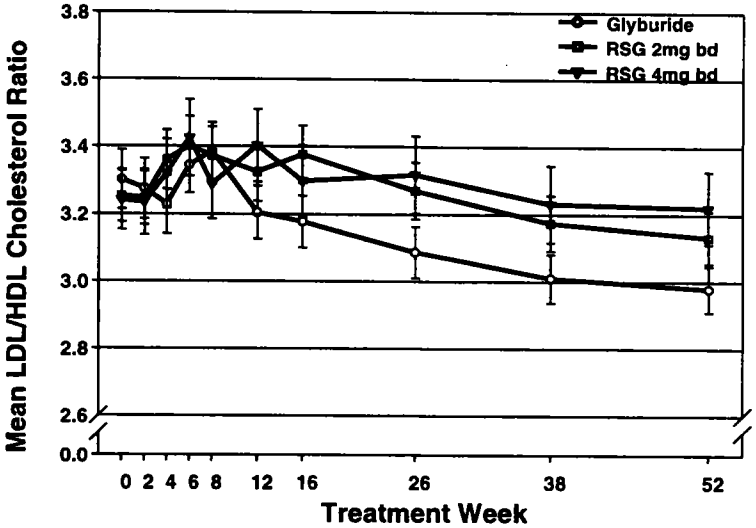
020: HDL-C Over Time



(Study 020 - ITT, LOCF) (Error Bars = SE)

Avandia®

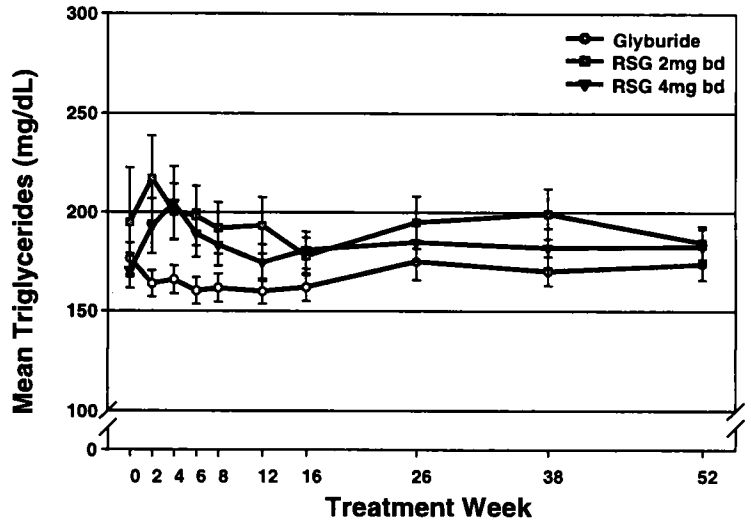
020: LDL-C/HDL-C Over Time



(Study 020 - ITT, LOCF) (Error Bars = SE)

Avandia®

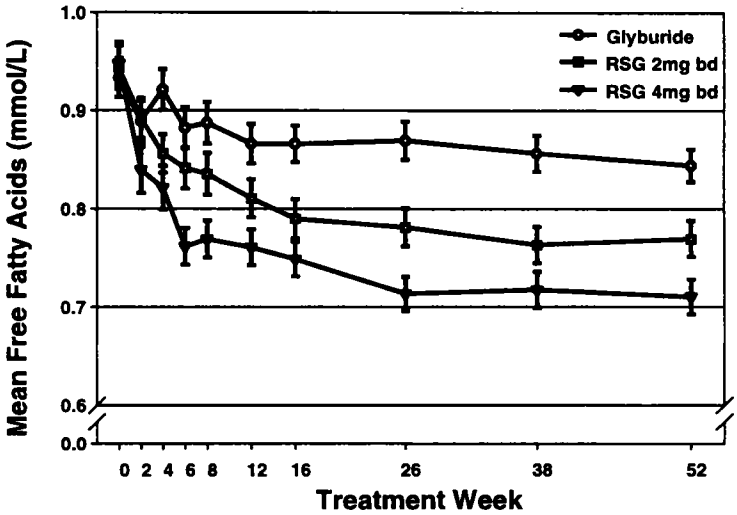
020: Triglycerides Over Time



(Study 020 - ITT, LOCF) (Error Bars = SE)

Avandia®

020: Free Fatty Acids Over Time



(Study 020 - ITT, LOCF) (Error Bars = SE)

Avandia®

Monotherapy Summary

Lipids

- small increases in LDL and HDL cholesterol

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- small increases in LDL and HDL cholesterol
- preserves the LDL/HDL cholesterol ratio

Monotherapy Summary

Lipids

- small increases in LDL and HDL cholesterol
- preserves the LDL/HDL cholesterol ratio
- neutral effect on triglyceride levels

Monotherapy Summary

Lipids

- small increases in LDL and HDL cholesterol
- preserves the LDL/HDL cholesterol ratio
- neutral effect on triglyceride levels
- sustained reduction in free fatty acids

Avandia® – Combination with Metformin

094 and 093: Eligible Patients