

## **Areas of Interest Based on Preclinical Findings**

- **Hemodynamic / Cardiovascular**
- **Hematology**
- **Weight**

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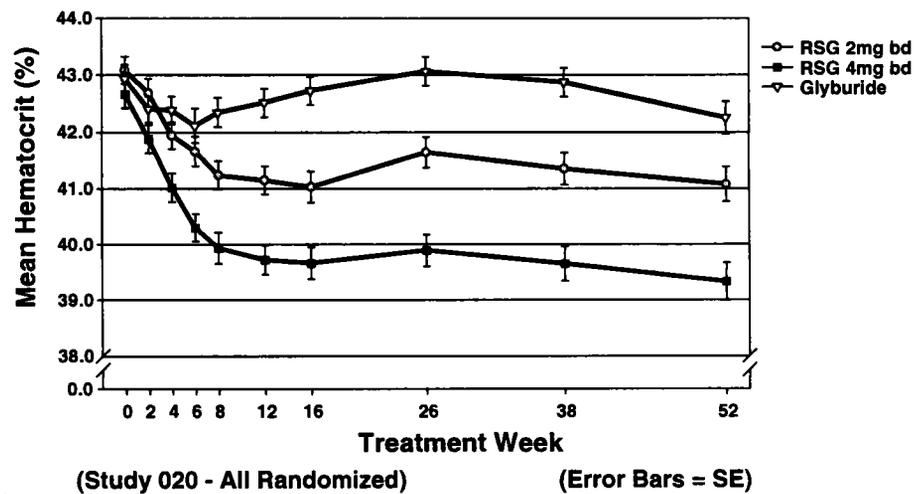
## **Hematology**

- **In preclinical studies repeated administration of Avandia® produced decreases in hemoglobin and hematocrit**
- **In healthy volunteers Avandia® produced no change in red blood cell mass**
- **In patients with Type 2 diabetes Avandia® produced dose dependent reductions in hemoglobin and hematocrit:**
  - Hb decreased ~ 1gm/dL with 8mg/day
  - Hct decreased 3-5 percentage points with 8mg/day

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## 020: Mean Hematocrit Over Time



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## Anemia Adverse Events

- Anemia was reported in 1.9% of patients on Avandia® monotherapy vs 0.7% of patients on placebo.
- In combination of Avandia® with metformin, anemia was reported in 7.1% of patients vs 2.2% of patients treated with metformin alone.
- Little change in other blood cell types

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## Criteria for Hemoglobin and Hematocrit Assessment

- Hemoglobin >2g below the lower limit of the age and gender specific reference range
- Hematocrit > 5 percentage points below the lower limit of the age and gender specific reference range

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## Percentage of Patients Below Threshold Values for Hemoglobin or Hematocrit

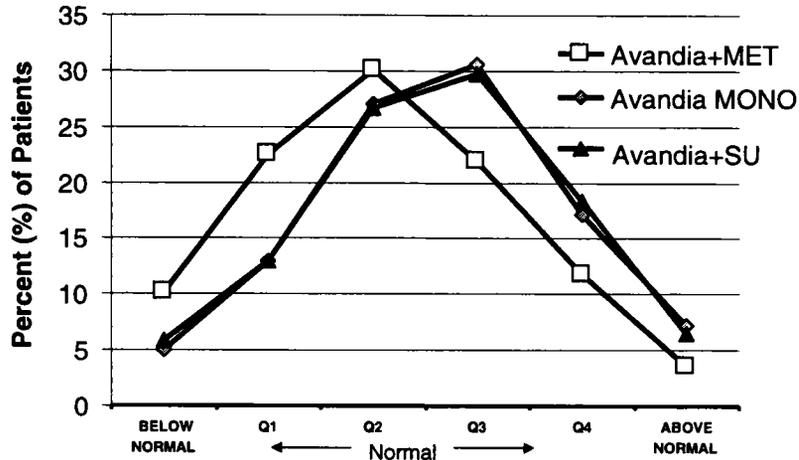
	Hemoglobin	Hematocrit
Avandia® Mono	1.6	2.4
Met	1.8	2.3
SU	0.8	1.0
Avandia® +MET	4.2	6.2
Avandia® +SU	1.4	3.0
PLA	0.4	0.4

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## Patient Distribution by Baseline Hematocrit

107



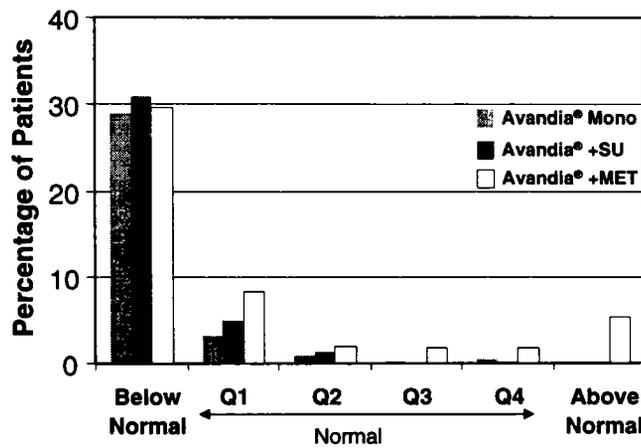
Double-blind and open label (NDA)

SU

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## Percentage of Patients with On-therapy Threshold Values of Hematocrit by Baseline Hematocrit

108



Double blind and open label studies (NDA)

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## Summary: Hematology

- Dose dependent reductions in hemoglobin and hematocrit within first 90 days
- Increased duration of exposure produced little further decrease in hemoglobin or hematocrit
- Increased frequencies of low Hb and Hct in patients on Avandia® + Met appear to be related to low baseline values

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## Weight

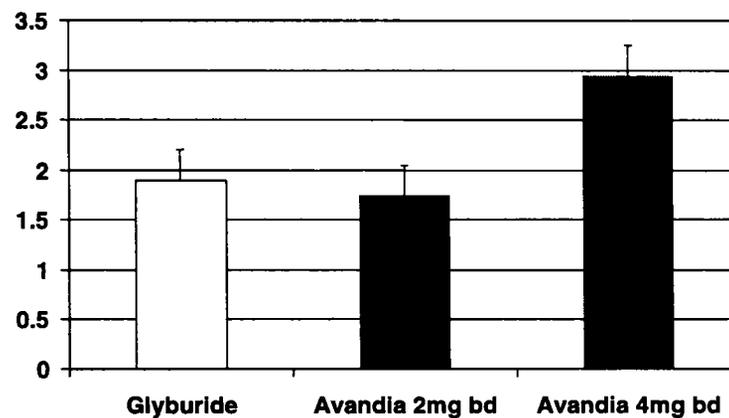
- Weight gain has been observed in pre-clinical models
- Weight gain was observed in patients treated with Avandia, consistent with improvement in glycemic control

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## Weight

Mean Change (kg) from Baseline to Week 52



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Study 020

Error bars= S.E.

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## Weight Conclusions

**Weight gain 2-3 kg during first 6 to 12 months in Avandia®-treated patients**

- Improved glycemic control
- LDL/HDL ratio preserved
- FFA decreased
- Reduction in diastolic BP



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## Area of Special Interest Liver



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## Liver Safety

- Examined liver test values for all patients in the Phase 2/3 Program
- Evaluated all hepatic adverse events



## Study Entry Criteria & Monitoring

- Patients included with liver enzyme elevation up to 2.5x ULRR\*
- No specific screening to exclude patients with liver disease
- Liver test and AEs monitored at each visit:
  - ◆ every 4 weeks for 3 months
  - ◆ every 6 weeks for 2 months
  - ◆ every 3 months thereafter
- No specific liver test criteria for withdrawal

\*ULRR- upper limit reference range



## ALT Levels > 3x ULRR in the Avandia® Clinical Program

All Avandia®	Placebo	SU or Metformin
13/4421 (0.29%)	1/561 (0.18%)	5/1041 (0.48%)
0.35 cases per 100 pt yr exposure (3673 pt yr)	0.59 cases per 100 pt yr exposure (169.5 pt yr)	0.78 cases per 100 pt yr exposure (640 pt yr)

n (%) pts with ALT >3x ULRR during clinical trials program based on 120 day safety update

Patients exposed to Avandia® alone in a primary study, Avandia®+metformin or SU in extension studies are counted only once in the all Avandia® denominators

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## Patients withdrawn due to ALT Levels >3x ULRR

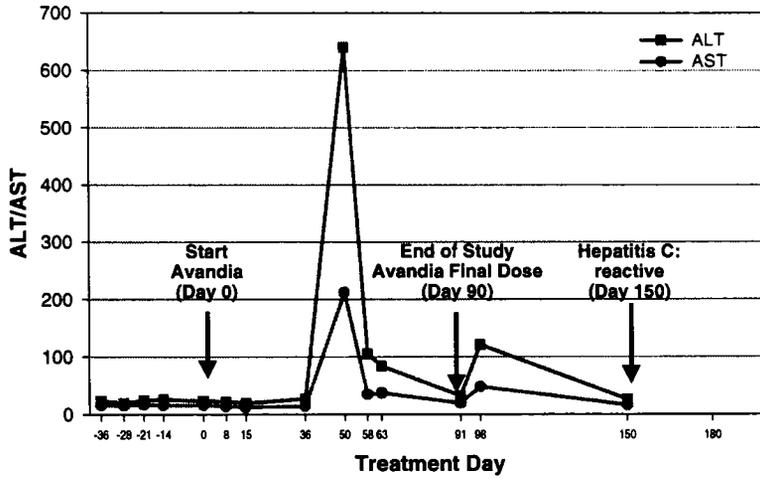
ALT (IU/ L)	All Avandia®		Placebo		SU or Metformin	
	n	WD	n	WD	n	WD
>3 to ≤ 5x ULRR	8	2	1	0	3	0
>5 to ≤ 8x ULRR	4	2	0	0	2	1
> 8x ULRR	1*	0	0	0	0	0

\* Transient elevation; subsequent diagnosis of Hepatitis C

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### 006.003.00359 Avandia® 1mg bd

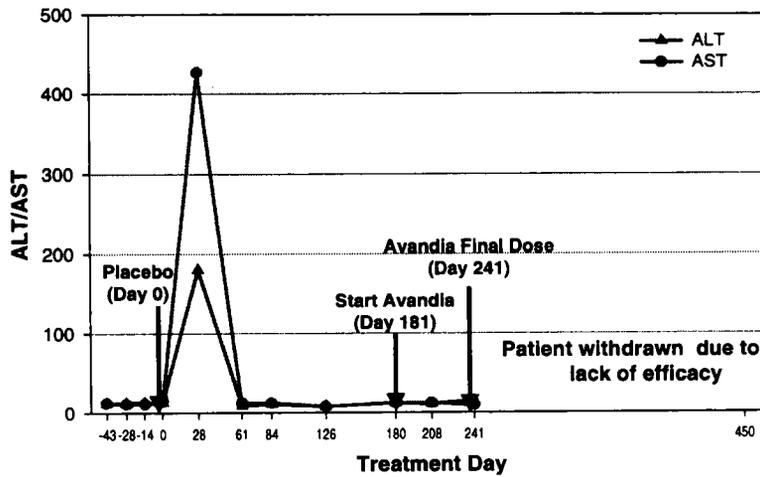


Completed Study as planned

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### 024.030.02644 - 105.022.60241 Placebo / Avandia® 8mg od



Patient withdrawn due to lack of efficacy

Med History: 0 units alcohol/week  
cholelithiasis  
cholecystectomy

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## Two Patients with Jaundice

**44 year old male**

(cholestatic jaundice secondary to biliary obstruction)

**53 year old male**

(enterococcal sepsis)



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## Liver - Summary

- **No signal of Avandia-related hepatocellular injury**
- **No patients had liver failure**
- **No liver related deaths (excluding metastatic neoplasm)**



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## Avandia®

### Conclusions: Safety Profile

- 4598 Avandia® treated patients, 3673 patient years exposure
- Favorable safety profile - few patients withdrawn due to AEs
- No signal of hepatotoxicity related to Avandia®
- Events associated with Avandia® therapy:
  - edema, anemia, and weight gain
  - frequencies are low and not dose limiting
- Cardiovascular safety comparable to placebo and active comparators

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## 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

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*SmithKline Beecham Pharmaceuticals*

**Avandia®**  
(rosiglitazone maleate)

## **Risk / Benefit Assessment**

**Dr. Douglas Greene**

**Professor, Internal Medicine; Director, Michigan  
Diabetes Research Center, University of Michigan**



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## **Avandia®: 5 Main Points**

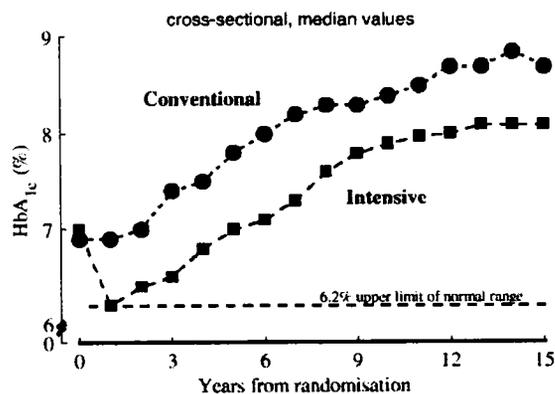
- 1) Type 2 Diabetes: an unmet therapeutic challenge**
- 2) Avandia®: a potent PPAR $\gamma$ -agonist.**
- 3) Clinically significant, dose-ordered, durable glycemic control alone or with Metformin**
- 4) No evidence of hepatotoxicity**
- 5) Good overall cardiovascular risk profile**

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## Type 2 Diabetes: Lessons from UKPDS\*

- Unmet Therapeutic Challenge
- Progressive Metabolic Derangement



\*UK Prospective Diabetes Study (UKPDS) Group (1998). *Lancet* 352:837-53.

## **Type 2 Diabetes: Lessons from UKPDS**

- **Chronic Micro & Macro-vascular Complications**
- **Glucose Control Improves Outcomes**

<b>Risk Reduction 1% <math>\Delta</math> HbA1c</b>	
<b>Any Diabetes Endpoint:</b>	<b>21%</b>
<b>Diabetes-related Death:</b>	<b>21%</b>
<b>Myocardial Infarction:</b>	<b>14%</b>
<b>PVD Amputation/Death:</b>	<b>43%</b>
<b>Microvascular Endpoint:</b>	<b>37%</b>

(all  $p < 0.0001$ )

## **Avandia®: 5 Main Points**

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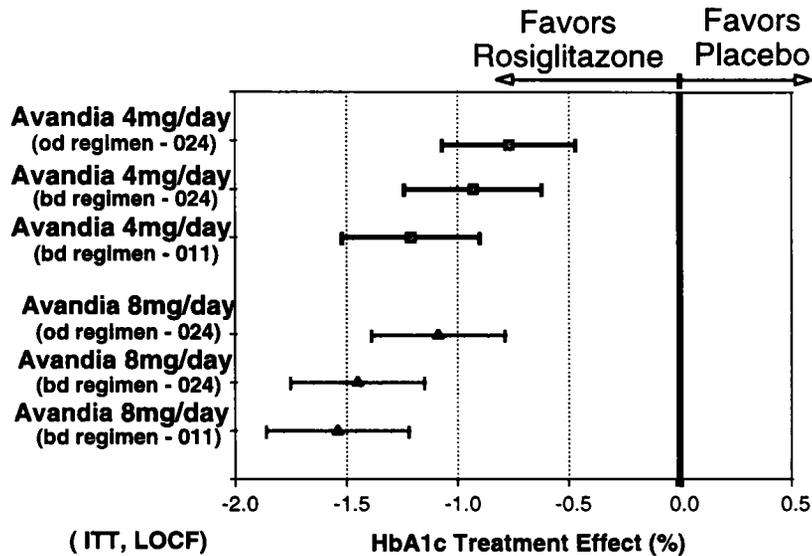
## **Avandia®: Insulin Sensitizer in Preclinical Studies**

- **Potent PPAR $\gamma$  agonist**
- **Modifies gene expression/adipose cell differentiation**
- **Reduces serum insulin, glucose and free fatty acids in diabetic animals**
- **Protects against pancreatic  $\beta$ -cell insulin depletion**
- **Suggests insulin sensitizing action**

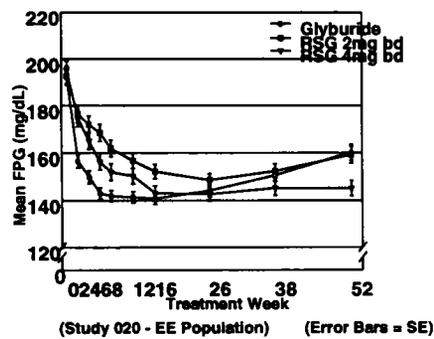
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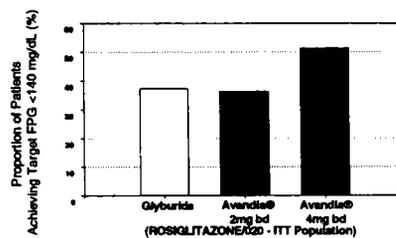
## HbA1c - Treatment Effect (95% CI) Monotherapy



## Hypoglycemic Effect is Durable and Clinically Significant

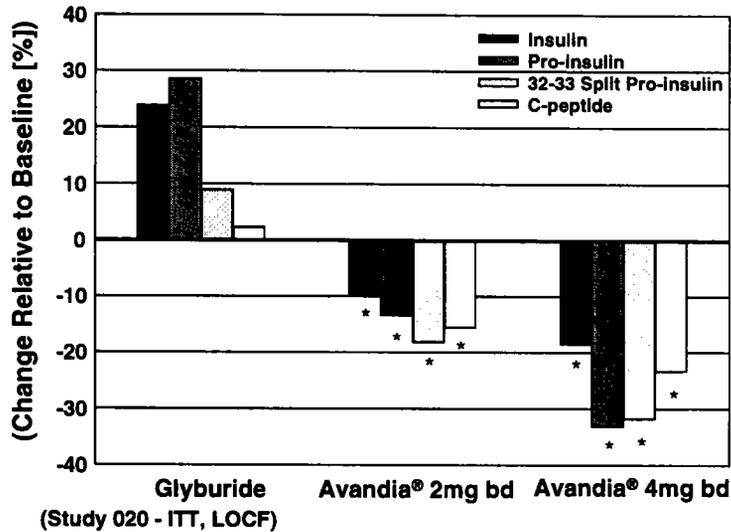


**Durability of hypoglycemic action vs sulfonylurea**

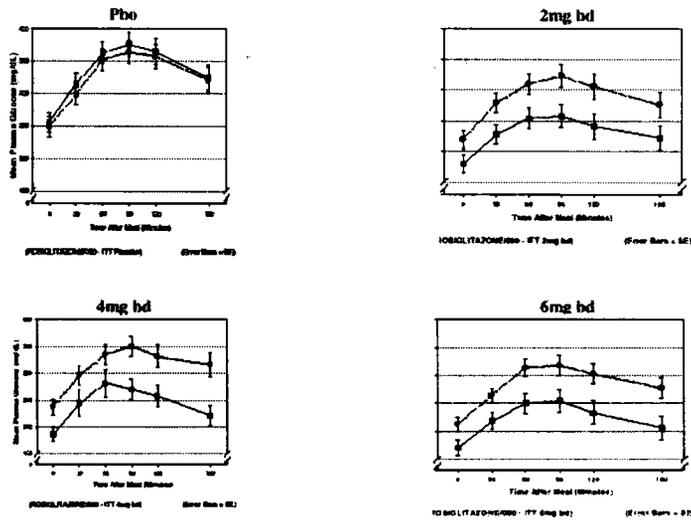


**Percent achieving FPG <140 mg/dl**

## Avandia®: Insulin Sensitizer in Man



## Avandia®: Insulin Sensitizer in Man



**Lowers Post-meal Plasma Glucose Excursions**

## **Avandia®: 5 Main Points**

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## **No Evidence of Hepatotoxicity**

### **After 3600 patient-years of experience:**

- No cases of drug related jaundice, liver failure or death.
  - 0.35 cases per 100 patient years with ALT  $\geq$ 3x ULRR for Avandia®
  - 0.59 cases per 100 patient years with ALT  $\geq$ 3x ULRR for placebo
  - 0.78 cases per 100 patient years with ALT  $\geq$ 3x ULRR for active comparators
- Structural, metabolic profile and potency differences may explain distinction from troglitazone.

## **Avandia®: 5 Main Points**

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## **Cardiovascular Lipid Profile**

- Marked, sustained reduction in free fatty acids**
- Increase in LDL, HDL and total cholesterol**
- Neutral effect on LDL/HDL ratio, suggesting minimal long-term risk of increase in cardiovascular events**
- Triglyceride data are variable, with no decrease despite improved glycemic control and decreased free fatty acids.**

## **Hemodynamic Effects**

- **Modest plasma volume increase with slight fall in Hgb and Hct. Mild edema.**
- **Cardiographic studies show no effect on LVMI or ejection fraction.**
- **Trend towards decrease in diastolic blood pressure seen in trials.**

## **Avandia: Conclusion**

- **Type 2 Diabetes: An Unmet Therapeutic Challenge with Progressive Metabolic Deterioration and Macrovascular and Microvascular Complications.**
- **Avandia®: A Potent PPAR $\gamma$ -agonist with Dose-ordered Insulin Sensitizing Hypoglycemic Action**
- **Clinically Significant Durable Glycemic Control Alone or in Combination with Metformin**
- **No Evidence of Hepatotoxicity**
- **Good Overall Cardiovascular Risk Profile**

## Positive Risk / Benefit Assessment

- **Significant reductions in HbA1c shown**
  - UKPDS data shows risk reductions with 1%  $\Delta$  HbA1c
- **Safety profile well characterized**
- **Answers an unmet need in treating type 2 diabetes**

144

### **Avandia<sup>®</sup>**

#### **SmithKline Beecham Pharmaceuticals**

**David E. Wheadon, MD**

VP & Director, North American Regulatory Affairs

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Chairman, Research & Development, SmithKline Beecham Pharmaceuticals

#### **Summary**



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*SmithKline Beecham Pharmaceuticals*

**Avandia®**  
(rosiglitazone maleate)

**Summary**

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



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**Avandia® - Profile**

- Selective and Potent Agonist of PPAR $\gamma$
- Favorable Pharmacokinetic Profile
- Minimal Risk for Clinically Relevant Drug Interactions
- Effective and Safe
- Positive Risk/Benefit Assessment



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## **Avandia® - Efficacy**

### **Approximately 4100 Patients Evaluated**

- Efficacy demonstrated in all monotherapy studies including diet only, previous monotherapy, and previous multiple therapy subsets
- Efficacy demonstrated in combination with metformin
- Further improvement in glycemic control with addition of Avandia® to maximal metformin

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## **Avandia® - Efficacy**

### **Approximately 4100 Patients Evaluated**

- Durable effect - improvement in glycemic control is maintained
- Improvement in glycemic control associated with a reduction in endogenous insulin
- Flexible dosing regimen - once or twice daily administration

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## **Avandia® - Safety**

### **Approximately 5500 Patients Evaluated**

- Well characterized safety profile
- No signal of hepatotoxicity
- Low incidences of mild to moderate edema, decreased hemoglobin and hematocrit with few withdrawals

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## **Avandia® - Safety**

### **Approximately 5500 Patients Evaluated**

- Reduction in circulating FFA and otherwise risk neutral lipid profile
- Cardiovascular safety comparable to placebo and active comparators

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## **Avandia® Proposed Indications**

- As monotherapy as an adjunct to diet and exercise to lower blood glucose in patients with type 2 diabetes mellitus.
- Concomitantly with metformin when diet and metformin do not result in adequate glycemic control.

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## **Avandia® (rosiglitazone maleate)**

Food & Drug Administration  
Center for Drug Evaluation and Research  
Endocrinologic and Metabolic Drugs  
Advisory Committee

April 22, 1999

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