CLINICAL REVIEW

Application Type	NDA (new drug application) pediatric supplement
Submission Number	**NDA 21-071 S-015** (b) (4)
Submission Code	N-000
Letter Date	September 30, 2004
PDUFA Goal Date	3/31/05
Reviewer Name	Joanna K. Zawadzki M.D.
Review Completion Date	4/15/05
Established Name	rosiglitazone maleate (subsequently referred to as rosiglitazone)
Trade Name	*Avandia* ®(GlaxoSmithKline)Tablets
Therapeutic Class	Hypoglycemic Agent (3031450)
Applicant	GlaxoSmithKline
Priority Designation	P
Formulation	rosiglitazone maleate 2, 4, 8 mg
Dosing Regimen	once daily or twice daily (rosiglitazone 2 and 4 mg twice daily regimen was used in this study)
[redacted] (b) (4)	
Intended Population	Children (ages 10-17) with type 2 diabetes mellitus
Relevant NDA(s)	**NDA 21-071** (rosiglitazone maleate [BRL-049653-C] *Avandia* ®,GlaxoSmithKline) approved 5/25/99
Relevant IND(s)	**IND 43,468**
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Table of Contents

1 EXECUTIVE SUMMARY 4

1.1 RECOMMENDATION ON REGULATORY ACTION 4

1.2 SUMMARY OF CLINICAL FINDINGS 4
1.2.1 Brief Overview of Clinical Program 4
1.2.2 Efficacy 5
1.2.3 Safety 7
1.2.4 Overall Assessment ..... **Error! Bookmark not defined.**

2 INTRODUCTION AND BACKGROUND 9

2.1 PRODUCT INFORMATION 9
2.2 PEDIATRIC TYPE 2 DIABETES MELLITUS DIAGNOSIS AND TREATMENT ..... **ERROR! BOOKMARK NOT DEFINED.**
2.3 AVAILABILITY OF PROPOSED ACTIVE INGREDIENT IN THE UNITED STATES 13
2.4 IMPORTANT ISSUES WITH PHARMACOLOGICALLY RELATED PRODUCTS 13
2.5 PRESUBMISSION REGULATORY ACTIVITY 13

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES 14

3.1 CMC (AND PRODUCT MICROBIOLOGY, IF APPLICABLE) ..... **ERROR! BOOKMARK NOT DEFINED.**
3.2 ANIMAL PHARMACOLOGY/TOXICOLOGY 14

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY 15

4.1 SOURCES OF CLINICAL DATA 15
4.2 TABLES OF CLINICAL STUDIES 15
4.3 REVIEW STRATEGY 15
4.4 DATA QUALITY AND INTEGRITY 16
4.5 COMPLIANCE WITH GOOD CLINICAL PRACTICES 16
4.6 FINANCIAL DISCLOSURES 16

5 CLINICAL PHARMACOLOGY 17

5.1 BACKGROUND ADULT PHARMACOKINETICS 17
5.2 PEDIATRIC POPULATION PHARMACOKINETICS 17

6 INTEGRATED REVIEW OF EFFICACY 19

6.1 (b) (4) 19
6.1.1 Methods 21
6.1.2 General Discussion of Endpoints 21
6.1.3 Study Design 21
6.1.4 Efficacy Findings 27
6.1.5 Efficacy Conclusions 29

7 INTEGRATED REVIEW OF SAFETY 30

7.1 METHODS AND FINDINGS 30
7.1.1 Deaths 31
7.1.2 Other Serious Adverse Events 31
7.1.3 Dropouts and Other Significant Adverse Events 31
7.1.4 Other Search Strategies ..... **Error! Bookmark not defined.**
7.1.5 Common Adverse Events 32

7.1.6 Assessment of Effect on Growth 35

7.1.7 Overdose Experience 35
7.1.8 Postmarketing Experience....36

8 ADDITIONAL CLINICAL ISSUES 36

9 OVERALL ASSESSMENT....38

9.1 CONCLUSIONS 38
9.2 RECOMMENDATION ON REGULATORY ACTION 38
9.3 LABELING REVIEW 39

10 APPENDICES....40

10.1 LINE-BY-LINE LABELING REVIEW....40

REFERENCES 41

1 EXECUTIVE SUMMARY

Recommendation on Regulatory Action

GlaxoSmithKline has submitted data from a multicenter, randomized, active-controlled clinical study (Study BRL-049653/207, subsequently referred to as Study 207) to support FDA's granting of Pediatric Exclusivity, (b) (4) for use of rosiglitazone (AVANDIA®), a peroxisome proliferator activated receptor gamma agonist, of the thiazolidinedione class, in children with type 2 diabetes mellitus (b) (4) Pediatric Exclusivity was granted in December 2004. (b) (4) Data from this study that address efficacy as well as safety should be included in the prescribing information to be available to clinicians. The label revisions are under discussion with the sponsor.

Summary of Clinical Findings

1.1.1 Brief Overview of Clinical Program

The FDA issued a Written Request to assess the safety and efficacy of rosiglitazone (*Avandia*®, GlaxoSmithKline), a thiazolidinedione approved for the treatment of adult Type 2 diabetes mellitus on 5/25/199 (b) (4) In response to the Written Request, the sponsor conducted Study 207, a 24-week, randomized, double-blind, active-controlled clinical trial in children ages 8-17 years with Type 2 diabetes mellitus, and a population pharmacokinetic study with sparse sampling technique in a subset of the population randomized to rosiglitazone.

After screening and a 4-week placebo run-in with diet counseling, patients were randomized to 2 mg twice daily of rosiglitazone (n=99) or to 500 mg twice daily of the control drug metformin (n=101), which had been approved for pediatric use. At 8 weeks, the dose of the medication was doubled in about half of both treatment groups based on fasting plasma glucose (FPG) concentration greater than 126 mg/dl.

The study protocol named the within-group change from baseline as the primary efficacy endpoint, and a non-inferiority comparison of change in HbA1c from baseline as the secondary

efficacy comparison. The study was not adequately powered to rule out a difference in the HbA1c effects between the two treatments (favoring metformin) of 0.4% HbA1c units, defined prospectively as defining a clinically meaningful difference.
Initial inclusion criteria included patients who presented with HbA1c values between 7.1 and 10%, who were not adequately controlled on diet and exercise alone and who had not been treated pharmacologically for Type 2 diabetes mellitus, and who did not have type 1 diabetes mellitus, as demonstrated by stimulated c-peptide concentration > 1.5 ng/dl and negative GAD and 1CA512 autoantibodies. The sponsor lowered the HbA1c criterion to 6.5% as national diabetes guidelines with more intensive glycemic control were proposed and difficulties with enrollment were encountered. The screening HbA1c value was used as the randomization criterion. Thus 32 patients (16%) were randomized to pharmacologic treatment though the baseline HbA1c was less than 6.5%, a value below which pharmacologic treatment for Type 2 diabetes mellitus is usually not indicated. About one-half of the randomized patients (n=90) had been previously treated pharmacologically and had prior pharmacologic therapy for diabetes discontinued at screening.

The sponsor planned to screen 383 patients; 208 entered the run-in, and 200 were randomized at 59 centers in Canada (4), USA (33), Mexico (6), Brazil (3), Singapore (2), Hong Kong (2), Malaysia (3), Thailand (1), Hungary (1), Italy (1), Slovenia (1) , and the Netherlands (1). About 10% of the patients in each treatment group discontinued because of lack of efficacy, about 5% in each treatment group discontinued because of adverse events (and about half of these also demonstrated lack of efficacy), and 80 (81%) and 73 (72%) completed treatment with rosiglitazone and metformin, respectively. The randomized treatment groups were comparable at baseline in respect to mean age (14 years [age was reported in years, not months]), gender (2/3 were female) [the groups were stratified by gender], race (34% Hispanic, 28% Black, 22% white, 12% Asian, and 4% East Indian), weight (about 90 kg), body mass index (BMI) (33 kg/m^2), duration of diabetes (mean was 1 year) and prior diabetes therapy (55% diet only, monotherapy 38%, and combination therapy 8%). Most of the previously treated patients had taken metformin.

At baseline more of the patients in the metformin treatment group took additional medications (79% vs. 71%). The differences were most apparent in the following drug categories: nervous system (including analgesic and psychotropic medications: 27% vs. 16%, and 8% vs. 2%, respectively), respiratory system (27% vs. 13%), systemic hormonal therapy (including steroids and thyroid hormones; 7% vs. 3%). Even though most of the randomized patients met the adult World Health Organization (WHO) criterion for obesity (BMI > 30 kg/m^2), a history of obesity was listed only for about 18% of the patients. Sixteen percent of the patients had acanthosis nigricans. Family history, Tanner staging of puberty, menstrual history, and evaluation of height velocity standardized for age and gender were not included in the study report.

1.1.2 Efficacy

A summary of the sponsor's efficacy analyses for fasting plasma glucose and HbA1c of the total randomized population and the naïve subgroup is outlined in the table below. As expected, fasting plasma glucose (FPG) decreased in patients naïve to diabetes medication (n=104) and

increased in patients withdrawn from prior medication (usually metformin) (n=90) during the run-in period. The sponsor did not include efficacy data for the subgroup of randomized previously treated patients in the NDA submission. Since it takes about three months for the change in HbA1c, the primary efficacy variable, to reflect a steady state, the changes in glycemia from screening to baseline are better reflected in the secondary efficacy variable, FPG.

Summary Table of Efficacy at 24 Weeks (Intent to treat, LOCF**)**
for all randomized pediatric patients and subgroup of naïve patients.
Data Sources: Sponsor's tables 11, 12, 19, 20

	Randomized Patients		Naïve Patients	
	metformin	rosiglitazone	metformin	rosiglitazone
N	98	96	50	54
FPG (mg/dl)				
Screening (mean, SD)	160 (57)	156 (58)	157 (50)	158 (53)
Baseline (mean, SD)	183 (76)	169 (68)	158 (63)	156 (58)
Change from baseline (mean,SD)	-23 (61)	-6 (56)	-17 (56)	-7.6 (45)
95% CI	-35.1, -10.4	-17.1, 5.6	-33.1, -1.2	-19.9, 4.8
p-value	0.0004	0.3183	0.0352	0.2239
Treatment difference (rosiglitazone – metformin)		12		8
95% CI for the difference		-3.3, 27.0		-10.6, 26.9
p-value		0.1249		0.3931
% patients with ≥ 30 mg/dl decrease from baseline	36.7%	22.9%	34.0%	22.2%
N	98	97	50	55
HbA1c (%)				
Screening (mean, SD)	8.1 (1.3)	8.2 (1.4)	8.2 (1.4)	8.3 (1.5)
Baseline (mean, SD)	8.2 (1.6)	7.9 (1.5)	7.8 (1.6)	7.8 (1.4)
Change from baseline (mean,SD)	-0.49 (1.65)	-0.14 (1.52)	-0.60 (1.59)	-0.32 (1.64)
95%CI	-0.82,-0.16	-0.45, 0.17	-1.05, -0.15	0.76, 0.12
p-value	0.0043	0.3629	0.0104	0.1552
Treatment difference (rosiglitazone – metformin)		0.28		0.25
95% CI for the		-0.16, 0.72		-0.37, 0.87

difference				
p-value		0.2047		0.4309
% patients with ≥ 0.7% decrease from baseline	51.0%	36.1%	54.0%	43.6%

The FDA considered the non-inferiority comparison as primar (b) (4) For the overall intent-to-treat population, at Week 24, the mean change from baseline in HbA1c was -0.14% with rosiglitazone and -0.49% with metformin, (95% CI for the difference, -0.16, 0.72). The upper bound of the confidence interval (0.72%) exceeded the proposed 0.4% change in HbA1c established as the criterion for inference of non-inferiority of rosiglitazone to metformin. Therefore, there were insufficient patients in this study to establish statistically whether these observed mean treatment effects were similar or different. The data were similar for the treatment-naïve subgroup. In both analyses, the total randomized population and the naïve subgroup, the changes from baseline in FPG and HbA1c in the rosiglitazone-treated group were small and not statistically significant. Rosiglitazone activity appeared to be less than previously observed in adult clinical trials.

Additional analyses by the sponsor of evaluable patients and non-parametric analyses and additional analyses by the FDA statistician of the naïve subgroup with baseline HbA1c>6.5% (i.e., excluding about 16% of the randomized patient population) also did not establish that the effects of the two treatments were statistically comparable. The FDA statistician's descriptive analysis (based on mean data) suggested that in the small subset of patients with HbA1c ≤ 6.5% at baseline, there was no change in HbA1c from baseline at 24 weeks in the metformin group (n=16) and perhaps a slight worsening (i.e., increase in HbA1c) in the rosiglitazone group (n=20) . Note that there was no placebo control in this study. Both groups benefited (HbA1c decreased) if baseline HbA1c was > 6.5 and ≤ 10% (n=72 metformin, n=68 rosiglitazone). When baseline HbA1c > 10%, the metformin group (n=13) improved (HbA1c was lower at 24 weeks), while the rosiglitazone group (n=11) worsened (HbA1c was higher at 24 weeks). There was much variability in the high HbA1c baseline group, and the n was relatively small.

1.1.3 Safety

No deaths were reported. There was one serious adverse event reported in the rosiglitazone group listed as the preferred term "hyperglycemia", which was actually mild diabetic ketoacidosis (glucose 292 mg/dl, 2+ ketonuria) that required insulin rescue. Six serious adverse events were listed in the metformin group, including three that were listed under the preferred terms "drug ineffective," "diabetic ketoacidosis," and "diabetes mellitus inadequate control." Glucose concentrations were in the high 200's and 300's in these three patients, and all three required insulin rescue, though one of them was reported as completing the study. The other three preferred terms were suicidal ideation, status asthmaticus, and menorrhagia, and none of these three patients required insulin rescue. A total of 6 patients (6%) in the rosiglitazone group and 7 (7%) patients withdrew from the study because of an adverse event. In the rosiglitazone

group, 5 of these had uncontrolled diabetes of whom 3 received insulin rescue. One patient presented with bronchitis and gastroenteritis, facial and hand edema, and rectal hemorrhage. In those discontinuing metformin due to an adverse event, two had hypoglycemia, one had diarrhea and nausea, two had uncontrolled diabetes and required insulin rescue, and two presented with slightly elevated baseline alanine aminotransferase that increased to about 3X ULN during the study.

Adverse events associated with rosiglitazone treatment in adults include weight gain, anemia, increases in lipid parameters, edema, congestive heart failure, and other cardiovascular adverse events. Fatal hepatic events that were associated with troglitazone, another thiazolidinedione, and resulted in its withdrawal from the market, have been seen only rarely in association with rosiglitazone based on postmarketing reports.

Significantly more weight gain was seen for pediatric patients treated with rosiglitazone (mean +2.7 kg) than with metformin (mean –0.3 kg), a difference consistent with the known effects of these drugs in adults. About 54% of rosiglitazone-treated patients and 30% of metformin-treated patients gained 2 kg or more on study. About 1/3 of rosiglitazone-treated patients gained 5 kg or more, and none of the metformin-treated patients gained more than 5 kg. Of note, height was apparently not measured precisely in this study, as about 11% of the children had a height decrease of ≥ 1 cm, and about 40% had no change or a decrease at 24 weeks. Thus, analyses of changes in body mass index (perhaps more appropriate than weight for assessments of changes in adiposity related to rosiglitazone therapy in growing children) were not possible. Observed changes in hemoglobin were smaller than those observed in adult studies. Variability in the lipid measurements and the small sample size contributed to poor estimates of change in the lipids. Only one episode of edema was reported in the rosiglitazone treatment group, and there were no other adverse cardiovascular events reported, as expected in this young population. Gastrointestinal events were more commonly reported in the metformin treatment group (24% vs. 14%). There were two reports of transaminase elevation 3X the upper limit of normal in the metformin group, but none were reported in the rosiglitazone treatment group.

Hypoglycemia is rarely reported with either rosiglitazone or metformin. There were no reports of hypoglycemia with rosiglitazone and two with metformin. Diabetic ketoacidosis is rarely reported in adult studies of rosiglitazone and metformin. Five patients in the rosiglitazone treatment group and three patients in the metformin treatment group had mild diabetic ketoacidosis (serum glucose about 300 mg/dl, 2+ ketonuria) and/or required insulin rescue.

1.1.4 Overall Assessment

(b) (4)

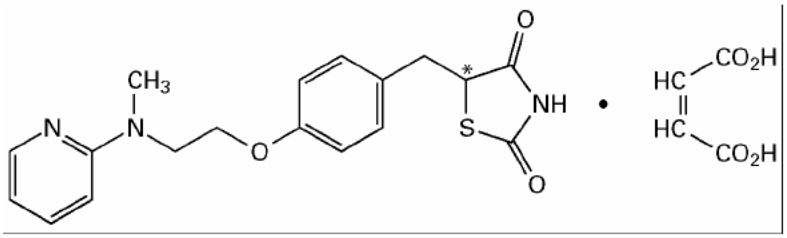
The pediatric efficacy and safety findings are summarized in the prescribing information.

2 INTRODUCTION AND BACKGROUND

Product Information

Rosiglitazone maleate (AVANDIA®, GlaxoSmithKline), subsequently referred to as rosiglitazone, is a peroxisome proliferator activated receptor (PPAR) gamma agonist, of the thiazolidinedione class, that was approved for the treatment of adult type 2 diabetes mellitus on 5/25/1999. PPARs are members of the nuclear hormone receptor superfamily of transcription factors, which also includes vitamin D, retinoic acid and thyroid hormone receptors. PPARs bind to promoter/enhancer elements in responsive genes to modulate gene expression in target tissues in a cell-, developmental-, and sex-specific manner. (SA Kliewer et al, Nature 1992) PPAR gamma is a subtype of this receptor that is expressed primarily in adipose tissue and the immune system. (O. Braissant et al, Endocrinology 1996) Activation of PPAR gamma by thiazolidinediones, such as rosiglitazone, reduces hyperglycemia by producing adipose tissue proliferation and increasing glucose transport across the cell membranes, leading to a decrease in HbA1c.

Chemically, rosiglitazone maleate is (±)-5-[[4-[2-(methyl-2-pyridinylamino) ethoxy]phenyl]methyl]-2,4-thiazolidinedione, (*Z*)-2-butenedioate (1:1) with a molecular weight of 473.52 (357.44 free base). The molecular formula is $C_{18}H_{19}N_3O_3S \bullet C_4H_4O_4$. The structural formula of rosiglitazone is indicated below.



In adults, rosiglitazone is modestly effective as monotherapy and more effective in combination with insulin, metformin, and sulfonylurea.

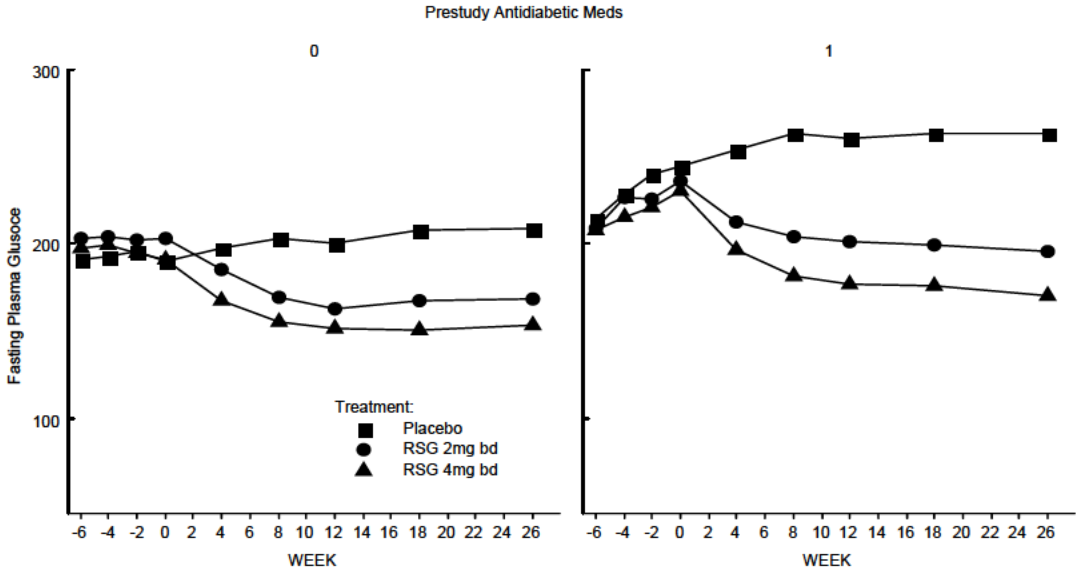
Table Change in FPG and HbA1c in 24-week Adult Monotherapy Clinical Studies

Source: Avandia ® Prescribing Information

	Placebo	AVANDIA		AVANDIA	
		4 mg once daily	2 mg twice daily	8 mg once daily	4 mg twice daily
N	173	180	186	181	187
FPG (mg/dL)					
Baseline (mean)	225	229	225	228	228
Change from baseline (mean)	8	-25	-35	-42	-55
Difference from placebo (adjusted mean)	–	-31*	-43*	-49*	-62*
% of Patients with ≥ 30 mg/dL decrease from baseline	19%	45%	54%	58%	70%
HbA1c (%)					
Baseline (mean)	8.9	8.9	8.9	8.9	9.0
Change from baseline (mean)	0.8	0.0	-0.1	-0.3	-0.7
Difference from placebo (adjusted mean)	–	-0.8*	-0.9*	-1.1*	-1.5*
% of Patients with ≥0.7% decrease from baseline	9%	28%	29%	39%	54%

Adult pharmacologically-naive patients respond more to rosiglitazone than do previously treated patients, as is indicated in the figure below from the original FDA statistical review of rosiglitazone.

Figure 6. Study 011 Mean FPG (LOCF) for naïve patients (0) and patients previously treated with anti-diabetic medications (1)



Pediatric Type 2 Diabetes Mellitus Diagnosis and Therapy

Type 2 diabetes mellitus (T2dm), previously also known as non-insulin dependent diabetes and adult-onset diabetes, has usually been considered an adult disease. Type 1 diabetes mellitus, previously known as insulin-dependent diabetes mellitus or juvenile diabetes, on the other hand, has often been considered a pediatric disease, because most cases are diagnosed in childhood. In the general US population, it is estimated that there are about 16 million people with diabetes and that about 90-95% have Type 2 diabetes mellitus, while 5-10% have type 1 diabetes mellitus.

Type 2 diabetes is a chronic, progressive disease, associated with a slightly decreased lifespan. Often, in adults, the metabolic abnormalities present "silently" and the diagnosis is made when the patient presents with chronic microvascular complications, such as retinopathy (which may be clinically evident after about 7 years of diabetes duration, nephropathy, neuropthy (e.g., distal sensory motor neuropathy or impotence) or macrovascular complications, including cardiovascular and cerebrovascular events. Treatment with diet, weight loss, exercise, oral antidiabetic agents, or insulin improves glycemia but rarely results in remission of diabetes mellitus. Since the Written Request for rosiglitazone was issued in 2000, the approach to the management of Type 2 diabetes mellitus has continued to evolve and intensify. Whereas the American Diabetes Association recommends a HbA1c goal of 7%, the American Association of Clinical Endocrinologists have recommended a more stringent HbA1c goal of 6.5% or less (American College of Endocrinology [ACE] Diabetes Mellitus Consensus Conference, August 2001). It is known that a decrease of glycemia towards normal is associated with a decrease in the risk of chronic complications.

In the past two to three decades, type 2 diabetes mellitus has also been emerging as a diagnosis in children and adolescents, and some have referred to it as a "new epidemic." (Rosenbloom 1999, Kaufman 2002). As in adults, type 2 diabetes mellitus is commonly associated with obesity, and thought to be due to a combination of impairment of insulin action with resulting increased insulin resistance, and insulin secretion. The prevalence of diabetes in a representative sample of the US population in children in the NHANESIII survey (1988-1994) was estimated at 4.1 per 1000, or about 0.4% of the pediatric population had diabetes mellitus, including both type 1 and type 2 diabetes mellitus (ADA 2000). Since that survey, published pediatric case series have indicated that progressively more cases of pediatric Type 2 diabetes mellitus are being diagnosed. In case series from the 1990s, the percentage of Type 2 diabetes mellitus among new cases of pediatric diabetes ranged from 8 to 45%. The incidence of adolescent type 2 diabetes mellitus in greater Cincinnati increased tenfold between 1982 and 1994, from 0.7 to 7.2 new cases per year per 100,000 (Pinhas-Hamiel et al, 1996).

Risk factors for type 2 diabetes mellitus in children appear to be similar to those in adults, including obesity, family history, diet, sedentary lifestyle, and intrauterine exposure to diabetes. In addition, puberty, per se, has been shown to be associated with increased insulin resistance in children with and without type 1 diabetes (Amiel et al 1986). Increased growth hormone secretion during puberty may contribute to the increase in insulin resistance. Populations most at risk include African Americans, Hispanics, American Indians and Asian Americans. The increased prevalence of pediatric Type 2 diabetes mellitus has also been reported globally, particularly in Asia and more recently also in Europe.

As in the adult population, the prevalence of obesity in the pediatric population has been increasing dramatically in the past three decades (Ogden 2002). In national United States health surveys, overweight in children ages 2 to 19 years is defined as at or above the 95% of body mass index (bmi) (calculated as the weight in kg divided by the square of the height in meters) for age . The percentage of overweight children ages 6-11 rose from about 4% before 1975, to 6.5% (1975-1980 survey), 11.3% (1988-1994), and 15.3% (1999-2000). Similarly the percentage of overweight in children ages 12-19 rose from about 5% before 1980 to 10.5% (1988-1994) and 15.5% (1999-2000). In the 12-19 age group, 11.2% had a BMI $\geq$ 30, the World Health Organization (WHO) and National Institute of Health Lung and Blood Institute (NHLBI) definition of obesity in the adult population. The 5% increase in overweight between the last two surveys was due to an increase in overweight in African American and Mexican American adolescents.

In view of the association of increasing trends of obesity and type 2 diabetes mellitus in both the pediatric and adult populations, prevention may be the best approach. Lifestyle modifications, including diet and daily exercise, were more effective in preventing type 2 diabetes mellitus than was treatment with metformin,. Both decreased the incidence of type 2 diabetes mellitus in comparison to the placebo group. The incidence of diabetes was 4.8, 7.8, and 11 cases per 100 person-years in the lifestyle, metformin, and placebo groups, respectively, after an average followup of 2.8 years. (Diabetes Prevention Program Research Group, NEJM 2002).

Reviews of pediatric Type 2 diabetes mellitus list the treatments that have been available for adult type 2 diabetes mellitus, including diet, oral antidiabetic agents, and insulin. In the ADA Consensus Statement on Type 2 Diabetes in Children and Adolescents (ADA 2000), the goal of successful treatment with diet and exercise includes near normalization of glycemia (FPG < 126 mg/dl and HbA1c < 7%) and "cessation of excessive weight gain with normal linear growth". . The consensus report states that only about 10% of adult patients with type 2 diabetes mellitus can be successfully treated with diet. This reviewer did not identify any clinical trials of diet and weight loss in pediatric type 2 diabetes mellitus. This consensus statement recommends the use of metformin in children because of its glucose lowering efficacy, low risk of hypoglycemia, weight stability or weight loss, and decrease in LDL and triglyceride levels. In a placebo-controlled 16-week clinical trial in 82 children ages 10-17, there was a placebo-subtracted mean decrease from baseline in fasting plasma glucose of 64 mg/dl ($p<0.0001$). Metformin is the only oral agent to date approved by the FDA for pediatric Type 2 diabetes mellitus (12/15/2000). The use of insulin for the treatment of Type 2 diabetes mellitus is limited by the required injections, the risk of hypoglycemia, and the associated weight gain. No prior clinical trial of thiazolidinedione treatment in children has been completed.

Availability of Proposed Active Ingredient in the United States

Rosiglitazone has been marketed in the US since May 1999.

Important Issues With Pharmacologically Related Products

Rosiglitazone is a PPAR gamma agonist. Most other PPARs including the other approved thiazolidinedione pioglitazone and most PPARs in development have both PPAR alpha and gamma activity. Pre-clinical carcinogenicity has been a concern with the dual PPAR alpha gamma agonists, and that may limit the evaluation of these drugs in children.

Presubmission Regulatory Activity

Relevant regulatory activity is summarized in the table below:

Date	Regulatory Activity
1997	Section 111 of the FDA Modernization Act (21 USC 355a) provides an additional 6 months of market exclusivity if pediatric studies are completed in response to a written request and the prescribed timeframe.
4/1/1999	"Pediatric Rule" (21 C.F.R. 314.55) Assessment of safety and efficacy in pediatric patients required in applications subject to the rule unless the requirement was waived or deferred.
5/25/1999	Approval letter for rosiglitazone (*Avandia®)* required submission of pediatric drug development plan within 120 days and granted deferral for submission of required pediatric assessment until 12/2/2000.
9/21/1999	GSK (formerly SmithKlineBeecham) submitted Proposed Pediatric Study

	Request – including proposed pediatric development plan for award of pediatric exclusivity and pediatric assessment. Placebo-controlled monotherapy study was proposed.
2/1/2000	FDA/Division of Metabolic and Endocrine Drug Products (DMEDP) issued Written Request for pediatric study with metformin as active control. GSK counter-proposed combination or second-line study in a teleconference, but ultimately active control monotherapy trial was agreed upon. Submission date was specified as 4/30/2002.
12/15/2000	Pediatric use of metformin (*Glucophage®,* Bristol Myers Squibb*)* approved by FDA.
1/4/2002	Best Pharmaceuticals for Children Act (BPCA) re-authorized exclusivity incentive program.
5/24/2002	Written Request, Amendment #1 issued by FDA in response to sponsor's request Submission date was revised to 9/30/2003.
7/3/2002	Written Request was re-issued under BPCA.
10/2002	Pediatric rule was invalidated by a federal district court decision.
12/3/2003	Pediatric Research Equity Act (PREA) restored requirement of pediatric assessments, essentially as FDA had promulgated in 1999.
12/15/2003	Written Request, Amendment #2 issued by FDA in response to sponsor's request. Submission date was revised to 9/30/2004.
9/30/2004	Study report for Study 207 (pediatric study) was submitted (NDA 21-071 S15 (b) (4)) by GSK.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

CMC

No new chemistry data was submitted.

Animal Pharmacology/Toxicology

Please see FDA pharmacology reviewer's summary and discussion.

Briefly, the sponsor submitted a study report for Protocol G99143 "Oral Toxicity Study in Juvenile Rats," which evaluated the toxicity of BRL- 49653- C (Rosiglitazone, Avandia) when given orally once daily for up to 10 weeks to juvenile male and female rats. The sponsor selected doses of 0.2, 2.0 and 40 mg/kg/day juvenile rats. Exposure multiples at the high dose of 40 mg/kg/day were greater than 60 times clinical exposures with the MRHD of 4 mg, bid. The toxicology findings in juvenile rats were found to be qualitatively similar to findings in adult rats. (b) (4)

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

Sources of Clinical Data

This submission was submitted electronically in the common technical document (CTD) format and was available in the Electronic Document Room at \\CDSESUB1\N21071\S_015\2004-09-30.
Datasets were available at \\Cdsesub1\n21071\S_015\2004-09-30\crt and were accessed using JMP. Case report forms (CRF) and narratives were provided for patients with serious adverse events and for patients who withdrew secondary to adverse events.

Table of Clinical Studies

The following table is adapted from the FDA statistician's review.

Study (# of centers) (dates conducted)	**Design**	**Treatment groups (N)**	**Duration of treatment**
BRL-049653/207 59 centers North and South America, Asia and Europe 3/19/2001 – 4/13/2004	Double blind randomized parallel active-control Naive and previously treated patients	Rosiglitazone 2 mg BID (99) Metformin 500 mg BID (101)	4- week placebo run-in 24 week treatment period

A population pharmacokinetic study with sparse sampling technique was conducted in a subset of the population randomized to rosiglitazone (n=96 patients, 33 males and 63 females).

Review Strategy

The sponsor's study report was reviewed, and efficacy and some safety analyses were discussed and reviewed with the FDA statisticians. This review posed complex statistical issues, and discussion with the statistical team was invaluable. Preclinical and clinical pharmacology data were also discussed with the primary FDA reviewers and their divisions. Narratives and Case Report Forms were reviewed for all the patients with serious adverse events and all patients who withdrew because of adverse events. Relevant adverse events, chemistry, and efficacy data were also reviewed in the data sets using JMP.

Data Quality and Integrity

Much of the data that related to growth in children and details of diabetes care was not carefully assessed. Some of the clinical data, e.g., measurement of height, was not carefully ascertained, as it was noted that 10% of the children actually lost ≥ 1cm in height and and 40% did not show any increase in height. Family history, Tanner staging of puberty, menstrual history, and evaluation of height velocity standardized for age and gender were not included in the submission. Age and duration of diabetes was reported only in years, and not in months. There was no specific information included about the diet, exercise program, dietary and exercise adherence, or patient self-monitoring of blood glucose.

Some of the data had not been carefully checked prior to submission. For example, the CRF for patient 207.039.88450 was located under investigator 028 rather than under investigator 039. The duration of diabetes for one patient was listed as 14 years (highly unlikely for Type 2 diabetes mellitus in a 15 year old) rather than 4 years, as subsequently corrected by the sponsor in response to FDA query.

No Division of Scientific Investigation (DSI) inspection was requested.

Compliance with Good Clinical Practices

Informed consent was obtained from parents or guardians, and assent was obtained from the children. However, the informed consent did not stress the importance of hygienic measures (e.g., diet, exercise, weight maintenance or weight loss).

Financial Disclosures

In compliance with the Final Rule on Fianancial Disclosure by Clinical Investigators (published 2/2/98 (63 FR 5233; revised 12/31/98 (63 FR 72171), the financial certification disclosure, OMB Form No. 0910-0396, is signed by David Wheadon, MD, Senior Vice President, US Regulatory Affairs, GlaxoSmithKline, and paragraph (1) and is checked, as the sponsor of the submitted studies, certifying that there were no financial agreements between the sponsor and the investigators where compensation was linked to study outcome (as defined in 21 CFR 54.2(a)), and that no clinical investigator reported any proprietary interest in this product or significant equity in the sponsor (as defined in 21 CFR 54.2(b)) in Study 207. A reference to lists of investigators is made.

(b) (6)

The sponsor provided two lists of investigators, List A, a list of investigators with no disclosable financial interests/arrangements (65 principal and 221 subinvestigators) and List B, a list of investigators from whom required information could not be obtained..(56 investigators). In the list with no disclosable financial interests/arrangements, List (A) Supporting Item of Form FDA 3454, a principal investigator is included at each of the 63 centers. The Guidance on Financial Disclosure defines the clinical investigator as the person(s) taking responsibility for the study at a given site.

List B is prefaced by the following statement: "Based on information available internally, none of the clinical investigators listed below had disclosable interests of the type described in 21 CFR 54.2(a) (compensation potentially affected by the outcome of the study). In addition, based on whatever information may have been obtained at the threshold from some or all of the listed clinical investigators, no one listed had a disclosable interest of the type described in 21 CFR 54.2(b) (significant equity interest in the study sponsor) or 21 CFR 54.2(c) (proprietary interest in the tested product.) ."

Since the principal investigators have provided disclosure, and since the sponsor has provided some information for the investigators with the missing information, it is unlikely that this lack of disclosure would have significantly biased the results of the study, particularly since there are only a small number of patients at each site..

5 CLINICAL PHARMACOLOGY

Background Adult Pharmacokinetics

This background information was presented by the clinical pharmacology reviewer at the Clinical Pharmacology Office Level Briefing (3/15/05).

Pharmacological effects:
- Highly selective and potent agonist for the PPARg.
- Improves glycemic control by improving insulin sensitivity.

Pharmacokinetics:
- Cmax and AUC increase in a dose-proportional manner over the therapeutic dose range.
- Elimination half-life is 3-4h.
- Absolute bioavailability is 99%.
- No effect of food on exposure, but there was a 28% decrease in Cmax.
- Approximately 99.8% bound to plasma proteins, primarily albumin.
- Predominantly metabolized by CYP2C8 and CYP2C9 (minor pathway).

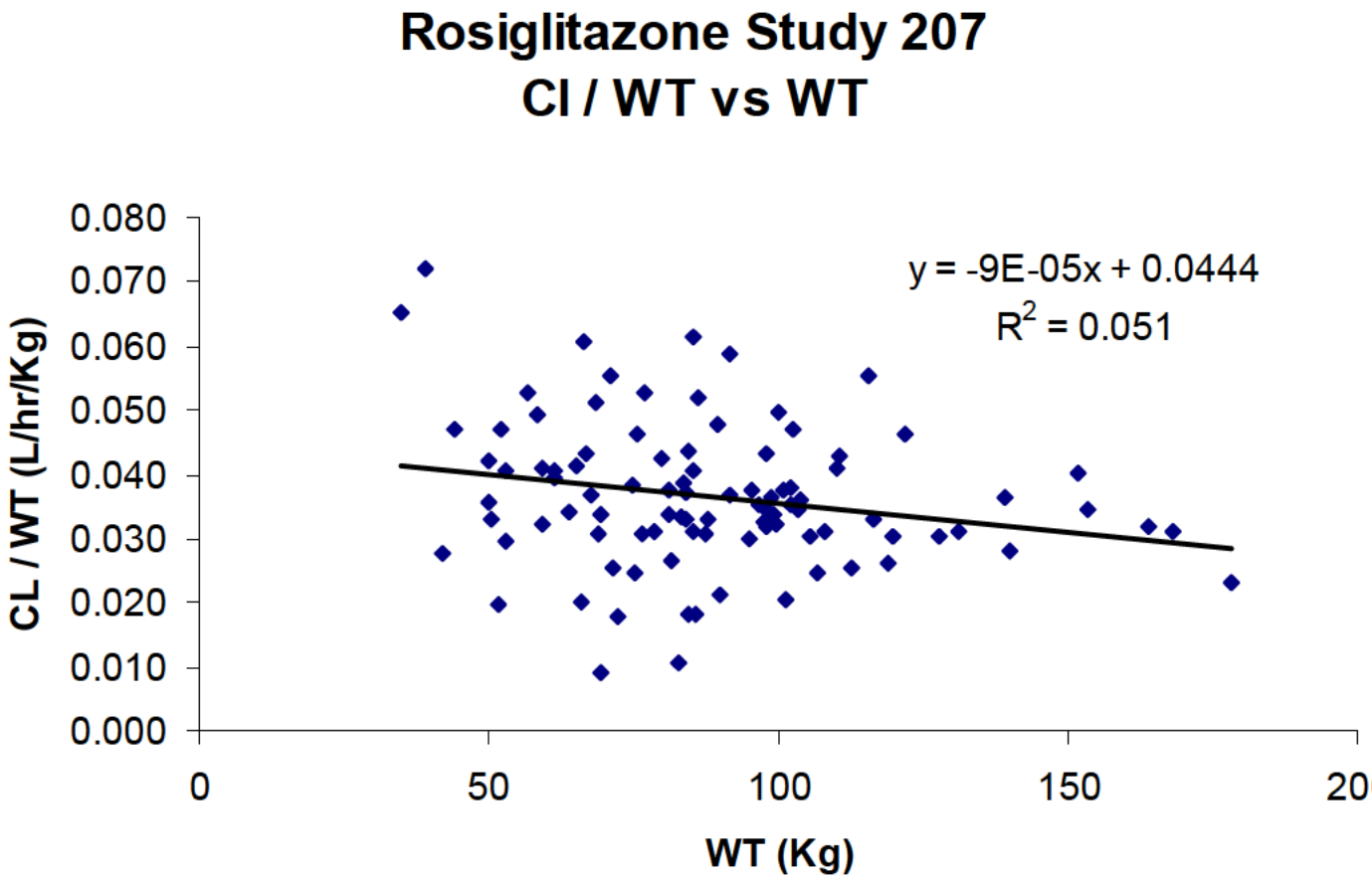
Population Pharmacokinetics in Adult Patients:
- One-compartment linear model with first order absorption model described the data.
- PK not influenced by age, race, smoking, or alcohol consumption.
- CL/F and V/F were shown to increase with increases in body weight.
- Rosiglitazone clearance was shown to be about 15% lower in females than males.

Pediatric Population Pharmacokinetics

Please see clinical pharmacology review for the full review and discussion. The summary of the population pharmacokinetic study is included below.

A population pharmacokinetic approach was used to determine the pharmacokinetics of rosiglitazone maleate in the pediatric population. The population pharmacokinetic (PK) study was a subset of the clinical study (Study BRL-49653/207) "A 24-week randomized, double-blind, activecontrolled, multi-center study to evaluate the safety and efficacy of rosiglitazone when administered to pediatric patients (age 10-17) with type-2 diabetes." In adults, the usual starting dose of rosiglitazone is 4 mg administered either as a single dose QD or in divided doses twice daily for monotherapy as well as in combination therapy. The maximum recommended dose is 8 mg daily. Rosiglitazone was initiated at 2 mg twice daily and then increased to 4 mg twice daily in pediatric patients with fasting plasma glucose > 126 mg/dl after 8 weeks post randomization. Blood samples were withdrawn from each subject before the dose and after the dose at 15-30 min (Week 4), 45-60 min (Week 4), 3-5 h (Week 16), 6-10 h (Week 24).

The population PK of rosiglitazone was described by a one-compartment model with first order absorption. Following oral administration of a single dose of rosiglitazone 2 or 4 mg in pediatric population, rosiglitazone was rapidly absorbed with Tmax of 1.5 h. Typical population PK parameters (95% CI) were 3.15 (2.1, 4.87) L/hr, 13.5 (9.11, 22.8) L and 2.05 (1.54, 3.04) hr-1 for oral clearance (CL/F), volume of distribution (V/F) and the oral absorption rate constant (Ka), respectively. These points and interval estimates of CL/F and V/F were consistent with the typical parameter estimates from a prior adult population analysis (CL/F=2.4 L/hr and V/F=17.6 L). Modest negative correlations of CL with age and weight were observed. The decreased clearance with higher body weight may explain the greater efficacy of rosiglitazone in heavier patients.



For pediatric patients, predicted average steady-state exposures over a 24-h interval were 1520 ng*hr/ml and 3040 ng*hr/ml for dosing regimens of 2 mg twice daily and 4 mg twice daily respectively. These exposures were similar to exposure estimates reported for adults at equivalent doses.

6 INTEGRATED REVIEW OF EFFICACY

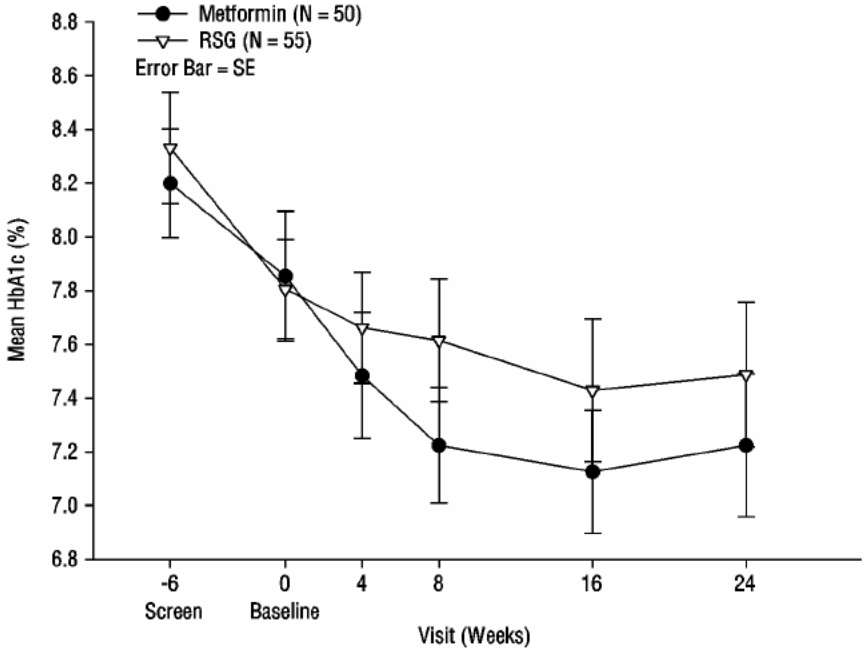
(b) (4)

In addition, the sponsor has included the following data in the ***PRECAUTIONS/*Pediatric Use** Section of the prescribing information:

Pediatric Use: (b) (4)

Adverse events observed in this study are described in ADVERSE REACTIONS, (b) (4)

Figure 3. Mean HbA1c Over Time in a 24-Week Study of AVANDIA and Metformin in Pediatric Patients — Drug-Naïve Subgroup



(b) (4)

[redacted]

6.1.1 Methods

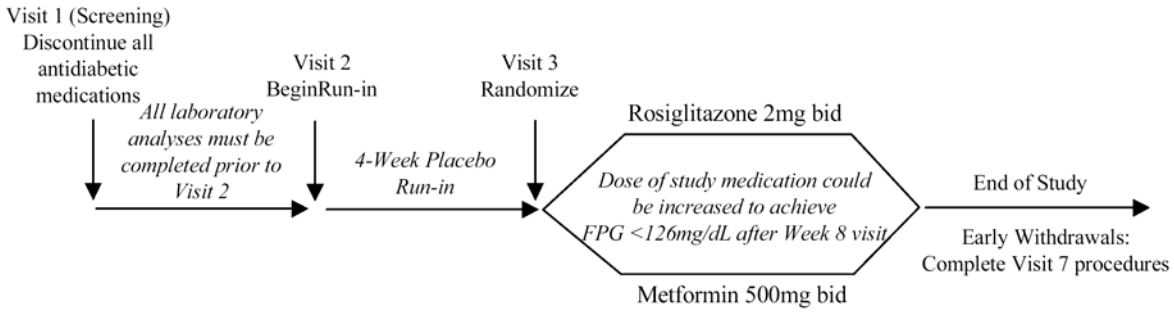
6.1.2 General Discussion of Endpoints

The study protocol named the within-group change from baseline as the primary efficacy endpoint, and a non-inferiority comparison of change in HbA1c from baseline as the secondary efficacy comparison. The study was not adequately powered to rule out a difference in the HbA1c effects between the two treatments (favoring metformin) of 0.4% HbA1c units, defined prospectively as a clinically meaningful difference. The FDA considered the non-inferiority comparison as primary (b) (4) [redacted]

6.1.3 Study Design

The following figure outlines the study design and is from the sponsor's submission.

Figure 1 Study Design Schematic



After screening and a 4-week placebo run-in with diet counseling, patients were randomized to 2 mg twice daily of rosiglitazone (n=99) or to 500 mg twice daily of the control drug metformin (n=101), which had been approved for pediatric use. At 8 weeks, the dose of the medication was doubled in about half of both treatment groups as the fasting plasma glucose (FPG) exceeded 126 mg/dl. In 17 of the metformin-treated patients (18%) and 9 of the rosiglitazone-treated patients (10%), the dose of the drug was not increased at week 8, and in 15 of the metformin-treated patients (16%) and 10 of the rosiglitazone-treated patients (11%), the dose of the drug was not increased at week 16 even though FPG exceeded 126 mg/dl at those timepoints. Thus more patients in the rosiglitazone group than in the metformin group were treated with the appropriate increased dose.

The sponsor's table below outlines the assessments in the study.

Table 1 Schedule of Assessments

	SCREENING PERIOD	RUN-IN/WASHOUT PERIOD			TREATMENT PERIOD					
Visit No.	1	2	2a	3	3a	4	4a	5	6	7[1]
Weeks (Relative to Baseline Visit 3)	Screening	-4	-2	0 (Baseline)	+2	+4	+6	+8	+16	+24
Signed Informed Consent	X									
Inclusion/Exclusion	X	X		X						
Physical Exam[2] and Vital Signs	X	X		X		X		X	X	X
History[3] and concomitant medications	X	X		X		X		X	X	X
Baseline Signs/Symptoms; Adverse Experiences		X	X	X	X	X	X	X	X	X
Body Weight and Height[4]	X	X		X		X		X	X	X
LABS: C-peptide; GAD65 and ICA512 autoantibodies	X									
LABS: Fasting blood specimens (safety and efficacy)[5,6,7]	X	X[7]		X		X		X	X	X
LABS: Fasting urine specimen[5]	X			X		X		X	X	X
LABS: Serum βHCG[8]	X									X
LABS: Pharmacokinetic samples[9]						X		X	X	X
Test Meal Challenge	X									
ECG (standard 12-lead)	X									
Study Drug Compliance				X		X		X	X	X
Diabetic Diet Instruction or Reinforcement[10]		X		X		X		X	X	
Dispense Study Medication and dosing instruction[11]		X		X		X		X	X	
Check blood glucose using glucose meter test only			X		X		X			

1. All procedures listed at Visit 7 must have been performed at any time the subject was discontinued from the Treatment Period.
2. Complete physical exam including vital signs at Visit 1 and Visit 7; Brief physical exam and vital signs at all other visits.
3. Complete medical history during screening, and interim history at all subsequent visits. Record concomitant medications and/or changes.
4. Subjects were to be discontinued if variation in body weight ≥10% from Screening at Visit 3. Height and weight were measured at all study visits (except Visit 2).
5. See Section 5.6.3.4 for a listing of safety and efficacy labs performed at study visits.
6. If ALT was >3x ULRR at any visit, repeat lab was scheduled. If repeat continued to show values >3x ULRR, subject was to be discontinued.
7. Only FPG was performed at Visit 2; no other laboratory assessments were to be done.
8. Serum βhCG was to be obtained at Visits 1 and 7 for all females of childbearing potential.
9. See Section 5.6.4 for overview of pharmacokinetic assessments.
10. Diabetic diet instruction was provided at Visit 2 and diabetic reinforcement was provided at all subsequent visits.
11. 4-Week supply at Visit 2, 3, 4; 8-week supply at Visit 5 and 6. Doses were to be increased from Level 1 to Level 2 at Visit 5 or any subsequent visit if FPG>126mg/dL.

All patients received glucose meters, but no requirement or review of glucose monitoring and/or diaries was discussed in the study report. There was no discussion of a specific diet or exercise

or weight loss plan in the protocol or study report. When the FDA requested "written records indicating that all patients received instructions in the principles of diet and exercise therapy," the sponsor responded "sites were instructed to utilize local standards of care with regard to diet and exercise instruction for patients in this study. The CRF contained prompts [*DIABETIC DIET FOR WEIGHT MAINTENANCE: Ask patient if they have complied with their specific dietary allowance. If 'No', encourage the patient to comply with the dietary allowance and stress the importance of this to the study.*] to the site personnel to ensure that patients had received proper nutritional instruction." Compliance with study medication was assessed by a count of the unused study medication and empty bottles.

Initial inclusion criteria included patients who presented with HbA1c values between 7.1 and 10%, who were not adequately controlled on diet and exercise alone and who had not been treated pharmacologically for Type 2 diabetes mellitus, and who did not have type 1 diabetes mellitus, as demonstrated by stimulated c-peptide concentration > 1.5 ng/dl and negative GAD and 1CA512 autoantibodies. The sponsor lowered the HbA1c criterion to 6.5% as national diabetes guidelines with more intensive glycemic control were proposed and difficulties with enrollment were encountered. The screening HbA1c value was used as the randomization criterion. Thus 32 patients (16%) were randomized to pharmacologic treatment though the baseline HbA1c was less than 6.5%, a value below which pharmacologic treatment for Type 2 diabetes mellitus is usually not indicated. About one-half of the randomized patients (n=90) had been previously treated pharmacologically and had prior pharmacologic therapy for diabetes discontinued at screening.

The amended eligibility criteria for the study are excerpted from the Case Report Form and are listed below. Patients were to be enrolled only if they met all the inclusion criteria and none of the exclusion criteria.

INCLUSION CRITERIA

1 Male or female patients 8 to 17 years of age~ inclusive, with Type 2 diabetes mellitus as defined by the American Diabetes Association (Appendix D). Female patients of childbearing potential who are sexually active must agree to using hormonal or barrier contraceptive methods.
2 Patients with no prior antidiabetic therapy, or who were previously treated by diet and exercise alone or by a single oral agent.
3 For patients with no prior treatment or treatment with diet and exercise alone: HbA1 c >6.5% at screening. For patients with prior oral agent monotherapy: HbAlc >6.5%, ≤ 10% at screening.
4 Fasting Plasma Glucose ≤ 270 mgldL at screening.
5 C-peptide ≥ 1 .5ng/dL following a test meal challenge at screening.
6 Negative assay for GAD65- and 1CA512-autoantibodies at screening.
7 Parent or legal guardian must give signed informed consent for patient to participate.
Patients who are legally regarded as emancipated minors may give signed informed consent for themselves to participate.
8 Patient must give assent to participate.

EXCLUSION CRITERIA

1 Pregnancy or lactation.
2 Any clinically significant abnormality identified in the screening (Visit 1) physical examination, laboratory tests or electrocardiogram which, in the judgment of the investigator, would preclude safe completion of the

study.

3 Use of any investigational drug within 30 days or 5 half-lives (whichever is longer) preceding the first dose of study medication.

4 Patients who have taken thiazolidinediones (rosiglitazone [Avandia®], pioglitazone [Actos®] or troglitazone [Rezulin']), or who have participated in clinical trials involving these compounds or any other known investigational thiazolidinediones or PPAR~agonists in the 3 months prior to screening.

5 Patients who have been on insulin therapy for 1 week or less within 1 month prior to screening or patients who have been on insulin therapy for longer than 1 week within 3 months prior to screening.

6 Patients with a documented history of significant hypersensitivity to thiazolidinediones or metformin.

7 Any contraindication to metformin, including renal disease or renal dysfunction as suggested by serum creatinine levels >1.0 mg/dL or abnormal creatinine clearance; congestive heart failure requiring pharmacologic treatment; planned or anticipated need for radiologic studies involving parenteral administration of iodinated contrast materials; or chronic acidosis.

8 Presence of clinically significant hepatic disease (ALT ≥ 2.5X ULRR).

9 Patient known to have maturity-onset diabetes of youth (MODY), severe insulin resistance syndromes (e.g. Kahn syndrome, HAIR-AN syndrome, leprechaunism, lipodystrophy syndrome), or structurally abnormal insulin (e.g. hyperproinsulinemia).

10 Change in weight ≥ 10% from Visit 1 to Visit 3.

11 Patients with significant anemia (hemoglobin less than 11 g/dL for males, 10 g/dL for females).

12 Patients with clinically significant hypertension (>160 mmHg systolic; >110mmHg diastolic) who are not receiving antihypertensive treatment.

13 Presence of unstable or severe angina or coronary insufficiency.

14 Active alcohol or drug abuse within the last 6 months.

15 Inability or unwillingness to comply with requirements of the protocol.

The sponsor planned to screen 383 patients; 208 entered the run-in, and 200 were randomized at 59 centers in Canada (4), USA (33), Mexico (6), Brazil (3), Singapore (2), Hong Kong (2), Malaysia (3), Thailand (1), Hungary (1), Italy (1), Slovenia (1) , and the Netherlands (1). About 10% of the patients in each treatment group discontinued because of lack of efficacy, about 5% in each treatment group discontinued because of adverse events (and about half of these also demonstrated lack of efficacy), and 80 (81%) and 73 (72%) completed treatment with rosiglitazone and metformin, respectively. The randomized treatment groups were comparable at baseline in respect to mean age (14 years [age was reported in years, not months]), gender (2/3 were female) [the groups were stratified by gender], race (34% Hispanic, 28% Black, 22% white, 12% Asian, and 4% East Indian), weight (about 90 kg), body mass index (BMI) (33 kg/m^2), duration of diabetes (mean was 1 year) and prior diabetes therapy (55% diet only, monotherapy 38%, and combination therapy 8%). Most of the previously treated patients had taken metformin.

The following summary table of demographics is excerpted from the statistician's review:

Table: Demographics of Randomized Population
Source: FDA Statistician's Review

	Metformin (n=101)	Rosiglitazone (n=99)
Age Mean (SD) Range	 14 (2.3) 8-17	 14 (1.9) 10-17
Gender % female	 68%	 66%
Race		

White	24	21
Black	25	29
American Indian	1	0
Asian	10	14
Hispanic	35	33
East Ind.	6	2
Weight (kg)		
Mean (SD)	92 (33)	88 (28)
Range	42-221	36-178
Hx Obesity	19 (19%)	16 (16%)
BMI	34 (9.7)	33 (8.7)
Prior Therapy		
Diet only	52%	57%
Monotherapy	41%	35%
Comb. Therapy	8%	8%

The FDA statistician has also compared the baseline diabetes characteristics for the naïve and previously treated patients. As expected, the naïve patients have had a shorter known duration of diabetes. The sponsor recorded duration of diabetes in years. Thus, less than one year would be recorded as zero.

Table: Baseline Diabetes Demographics in Subgroups
Source: FDA statistician's Review

	Naïve Patients		Previously Treated Patients	
	Metformin (n=52)	Rosiglitazone (n=56)	Metformin (n=49)	Rosiglitazone (n=43)
Years with diabetes [1]				
Mean (SD)	0.4 (0.8)	0.3 (0.8)	1.8 (1.5)	2.0 (2.6)
Median	0	0	1	1
Range	0-3	0-4	0-6	0-7
HbA1c				
Screening				
Mean (SD)	8.2 (1.4)	8.3 (1.5)	7.9 (1.2)	7.9 (1.1)
Range	6.5-12.6	6.6-12	6.1-11.4	6.4-11.1
Baseline				
Mean (SD)	7.8 (1.7)	7.8 (1.4)	8.5 (1.5)	8.0 (1.6)
Range	5.3-12.4	5-11.1	5.6-12	6-11.4
Screen to Baseline				
Mean (SD)	-0.4 (0.9)	-0.5 (1.3)	+0.6 (1.2)	+0.04 (1.3)
Median	-0.25	-0.3	+0.6	-0.1
Range	-3.8-1.2	-4.1-2.4	-4.3-3.6	-2.6-4.2
FPG				
Screening				

Mean (SD)	156 (50)	159 (53)	164 (64)	156 (66)
Range	82-304	88-277	85-344	26-353
Prior to run-in				
Mean (SD)	153 (57)	162 (60)	192 (79)	179 (71)
Range	73-337	81-309	86-386	84-329
Baseline				
Mean (SD)	156 (63)	157 (60)	208 (80)	189 (78)
Range	74-343	76-346	74-353	92-344

At baseline more of the patients in the metformin treatment group took additional medications (79% vs. 71%). The differences were most apparent in the following drug categories: nervous system (including analgesic and psychotropic medications: 27% vs. 16%, and 8% vs. 2%, respectively), respiratory system (27% vs. 13%), systemic hormonal therapy (including steroids and thyroid hormones; 7% vs. 3%). Even though most of the randomized patients met the adult World Health Organization (WHO) criterion for obesity (BMI > 30 kg/m^2), a history of obesity was listed only for about 18% of the patients. Sixteen percent of the patients had acanthosis nigricans. Family history, Tanner staging of puberty, menstrual history, and evaluation of height velocity standardized for age and gender were not included in the study report. Stimulated C-peptide data was an inclusion criterion if post-Sustacal stimulated C-peptide ≥ 1.5 ng/dl. Since there are duplications of the results in the data sets for C-peptide in the CRT, a request to the sponsor for the stimulated C-peptide data has been made. The baseline and stimulated C-peptide data are not discussed in the sponsor's report.

Table: Protocol Violations
Source: Sponsor's Submission

Violation	metformin n=101	rosiglitazone n=99
Subjects who violated any of the criteria	55 (54.5)	55 (55.6)
Prior use of combination antidiabetic therapy	6 (5.9)	6 (6.1)
Screening HbA1c≤6.5% (Drug-Naïve subjects)	1 (1.0)	0
Screening HbA1c≤6.5% or >10% (subjects with prior agent	2 (2.0)	1 (1.0)
monotherapy) C-peptide <1.5ng/dL after Sustical challenge	1 (1.0)	2 (2.0)
Positive for GAD65 and ICA512 autoantibodies at Screening I	0	0
nsulin therapy within 1 month prior to Screening	1 (1.0)	0
Screening FPG >270mg/dL	4 (4.0)	4 (4.0)
Use of prohibited antidiabetic medication:		
During Screening date +3 days to first study medication	6 (5.9)	7 (7.1)
During 4-Week, Run-in Period	3 (3.0)	3 (3.0)
During double-blind treatment period	1 (1.0)	1 (1.0
FPG>126mg/dL on or after Week 8 but not uptitrated	14 (13.9)	9 (9.1)
No Visit 7 value for primary efficacy variable	20 (19.8)	19 (19.2)
Double-blind treatment exposure <156 days	23 (22.8)	20 (20.2)
Subjects who took <80% or >120% of study medication overall	16 (15.8)	19 (19.2

6.1.4 Efficacy Findings

Please see also statistician's review and discussion of efficacy.

A summary of the sponsor's efficacy analyses for fasting plasma glucose and HbA1c of the total randomized population and the naïve subgroup is outlined in the table below. As expected, fasting plasma glucose (FPG) decreased in patients naïve to diabetes medication (n=104) and increased in patients withdrawn from prior medication (usually metformin) (n=90) during the run-in period. The sponsor did not include efficacy data for the subgroup of randomized previously treated patients in the NDA submission. Since it takes about three months for the change in HbA1c, the primary efficacy variable, to reflect a steady state, the changes in glycemia from screening to baseline are better reflected in the secondary efficacy variable, FPG.

Summary Table of Efficacy at 24 Weeks (Intent to treat, LOCF**)**
for all randomized pediatric patients and subgroup of naïve patients.
Data Sources: Sponsor's tables 11, 12, 19, 20

	Randomized Patients		Naïve Patients	
	metformin	rosiglitazone	metformin	rosiglitazone
N	98	96	50	54
FPG (mg/dl)				
Screening (mean, SD)	160 (57)	156 (58)	157 (50)	158 (53)
Baseline (mean, SD)	183 (76)	169 (68)	158 (63)	156 (58)
Change from baseline (mean,SD)	-23 (61)	-6 (56)	-17 (56)	-7.6 (45)
95% CI	-35.1, -10.4	-17.1, 5.6	-33.1, -1.2	-19.9, 4.8
p-value	0.0004	0.3183	0.0352	0.2239
Treatment difference (rosiglitazone – metformin)		12		8
95% CI for the difference		-3.3, 27.0		-10.6, 26.9
p-value		0.1249		0.3931
% patients with $\geq$ 30 mg/dl decrease from baseline	36.7%	22.9%	34.0%	22.2%
N	98	97	50	55
HbA1c (%)				
Screening (mean, SD)	8.1 (1.3)	8.2 (1.4)	8.2 (1.4)	8.3 (1.5)
Baseline (mean, SD)	8.2 (1.6)	7.9 (1.5)	7.8 (1.6)	7.8 (1.4)
Change from baseline	-0.49 (1.65)	-0.14 (1.52)	-0.60 (1.59)	-0.32 (1.64)

(mean,SD)				
95%CI	-0.82,-0.16	-0.45, 0.17	-1.05, -0.15	0.76, 0.12
p-value	0.0043	0.3629	0.0104	0.1552
Treatment difference (rosiglitazone – metformin)		0.28		0.25
95% CI for the difference		-0.16, 0.72		-0.37, 0.87
p-value		0.2047		0.4309
% patients with ≥ 0.7% decrease from baseline	51.0%	36.1%	54.0%	43.6%

The FDA considered the non-inferiority comparison as primar (b) (4) For the overall intent-to-treat population, at Week 24, the mean change from baseline in HbA1c was -0.14% with rosiglitazone and -0.49% with metformin, (95% CI for the difference, -0.16, 0.72). The upper bound of the confidence interval (0.72%) exceeded the proposed 0.4% change in HbA1c established as the criterion for inference of non-inferiority of rosiglitazone to metformin. Therefore, there were insufficient patients in this study to establish statistically whether these observed mean treatment effects were similar or different. The data were similar for the treatment-naïve subgroup. In both analyses, the total randomized population and the naïve subgroup, the changes from baseline in FPG and HbA1c in the rosiglitazone-treated group were small and not statistically significant. The change in FPG from baseline for the randomized population was -6 mg/dl, and the change in HbA1c was 0.14% (p=N.S.). Rosiglitazone activity appeared to be less than previously observed in adult clinical trials. In comparison, the change in FPG from baseline for the metformin randomized population was -23 mg/dl, and the change in HbA1c was -0.49% (p=0.0004 and p=0.0043, respectively).

Additional analyses by the sponsor of evaluable patients and non-parametric analyses and additional analyses by the FDA statistician of the naïve subgroup with baseline HbA1c>6.5% (i.e., excluding about 16% of the randomized patient population) also did not establish that the effects of the two treatments were statistically comparable.

Table: **Efficacy in Subgroups with baseline HbA1c > 6.5%**
Source: Data are summarized from FDA statistician's review.

	Naive		Prior therapy	
	metformin	rosiglitazone	metformin	rosiglitazone
N	41	46	44	33
HbA1c (%)				
Baseline (mean, SD)	8.3 (1.5)	8.2 (1.2)	8.8 (1.4)	8.5 (1.4)
Change from baseline (mean,SD)	-0.58	-0.43	-0.19	+0.27
Treatment		+0.15		+0.46

difference (rosiglitazone – metformin)				
95% CI for the difference		-0.54,+0.84		-0.28,+1.20

The FDA statistician's descriptive analysis (based on mean data) suggested that in the small subset of patients with HbA1c $\leq$ 6.5% at baseline, there was no change in HbA1c from baseline at 24 weeks in the metformin group (n=16) and perhaps a slight worsening (i.e., increase in HbA1c) in the rosiglitazone group (n=20) . Note that there was no placebo control in this study. Both groups benefited (HbA1c decreased) if baseline HbA1c was > 6.5 and ≤ 10% (n=72 metformin, n=68 rosiglitazone). When baseline HbA1c > 10%, the metformin group (n=13) improved (HbA1c was lower at 24 weeks), while the rosiglitazone group (n=11) worsened (HbA1c was higher at 24 weeks). There was much variability in the high HbA1c baseline group, and the n was relatively small.

6.1.5 Efficacy Conclusions

(b) (4)

In the adult monotherapy studies, which comprised approximately – pharmacologically naïve and ---previously pharmacologically treated patients, rosiglitazone has modest glucose lowering activity in naïve patients and no significant glucose lowering activity in patients previously treated with other antidiabetic agents, as noted in the statistical review of the initial NDA. This observation is reflected in the label by the recommendation not to take patients off prior sulfonylurea therapy but rather to add rosiglitazone. Less glucose lowering activity is observed in the pediatric study because of the smaller n and comparison to an active control. In addition, compliance with hygienic measures (diet and exercise) may be less in the pediatric population (as has been suggested in the literature) and insulin resistance may be augmented by higher levels of growth hormone.

7 INTEGRATED REVIEW OF SAFETY

Methods and Findings

7.1.1.1 Patient Disposition

The sponsor planned to screen 383 patients and randomize 215 patients to obtain a total of 150 completers (as requested in the FDA Written Request). A total of 208 patients were enrolled at 59 centers in North America (66%), South America (22%), Asia (13%) and Europe (3%) and 200 were randomized. About 77% of the patients completed the study with more than 90% of the patients completing 10 weeks of treatment.

Table 3.1.1 Patient Disposition
Source: FDA Statistician's Review

	Metformin	Rosiglitazone	Total
Entered Run-in			208
Randomized	101	99	200
Wk 4 Wk 8 Wk 16	98 (97%) 93 (92%) 84 (83%)	97 (98%) 91 (92%) 87 (88%)	
Week 24 Completers	73 (72%)	80 (81%)	153 (77%)
ITT	98 (97%)	97 (98%)	195 (98%)

Lack of efficacy was the primary reason for dropout and represented about 10% of the patients in each treatment group. Narratives and case report forms were not provided for these patients. However, several of the patients who presented with uncontrolled diabetes also had lack of efficacy marked in the CRFs and subsequently changed. The FDA statistician has noted that lack of efficacy was usually noted after 3 months of treatment, while uncontrolled diabetes as an adverse event occurred in the first three months of treatment.

Table 3.1.2. Reasons for discontinuation
Source: FDA Statistician's Review

	Metformin (n=101)	Rosiglitazone (n=99)
Adverse Event	5	4
Lack of Efficacy	9	9
Protocol Violation	5	3
Lost-to-Followup	5	2
Other	4	1

7.1.2 Deaths

No deaths were reported in this study.

7.1.3 Other Serious Adverse Events

There was one serious adverse event reported in the rosiglitazone group listed as the preferred term "hyperglycemia", which was actually mild diabetic ketoacidosis (glucose 292 mg/dl, 2+ ketonuria) that required insulin rescue (See Table DKA below, Patient 207.026.88293).The investigator states that this finding is "not related", but it does reflect lack of efficacy of the drug. Six serious adverse events were listed in the metformin group, including three that were listed under the preferred terms "drug ineffective," "diabetic ketoacidosis," and "diabetes mellitus inadequate control." Glucose concentrations were in the high 200's and 300's in these three patients, and all three required insulin rescue, though one of them was reported as completing the study. The other three preferred terms were suicidal ideation, status asthmaticus, and menorrhagia, and none of these three patients required insulin rescue.

Table 36 Randomized Subjects with On-Therapy Serious Non-Fatal Adverse Events

Treatment Subject ID	Age (y)	Gender (M/F)	Serious AE (Preferred term)	Day of onset	Duration (days)	Intensity	Relationship	Action	Corrective Therapy	Withdrawn
RSG										
207.026.88293	12	M	Hyperglycemia	110	9	Severe	Not Related	Drug stopped	Yes	Yes
MET										
207.026.88295	17	M	Suicidal ideation	156	7	Severe	Not Related	None	Yes	No
207.039.88450	16	F	Drug ineffective	108	14	Moderate	Unlikely	Drug stopped	Yes	Yes
207.049.88399	17	M	Status asthmaticus	143	3	Moderate	Not Related	None	Yes	No
207.049.88626	15	M	Diabetic ketoacidosis	171	4	Moderate	Unlikely	None	Yes	No
207.053.88589	15	F	Diabetes mellitus inadequate control	56	2	Moderate	Unlikely	None	Yes	Yes
207.206.89299	17	F	Menorrhagia	21	5	Moderate	Suspected	None	Yes	No

Data Source: Attachment 3, Appendix D.L6.
Days since start of study drug.
Abbreviations: F=female, M=male, y=year(s).

7.1.4 Dropouts and Other Significant Adverse Events

A total of 6 patients (6%) in the rosiglitazone group and 7 (7%) patients withdrew from the study because of an adverse event. In the rosiglitazone group, 5 of these had uncontrolled diabetes of whom 3 received insulin rescue. One patient presented with bronchitis and gastroenteritis, facial and hand edema, and rectal hemorrhage. In those discontinuing metformin due to an adverse event, two had hypoglycemia, one had diarrhea and nausea, two had uncontrolled diabetes and required insulin rescue, and two presented with slightly elevated baseline alanine aminotransferase that increased to about 3X ULN during the study.

Table 37 On-Therapy Withdrawals from Study Medication Due to an Adverse Event

Treatment Subject ID	Age (y)	Gender (M/F)	AE leading to withdrawal (Preferred term)	Day of Onset[1]	Day of withdrawal[1]	Intensity	Relationship
RSG							
207.013.88382	15	F	Hyperglycemia	3	4	Severe	Not related
207.018.88659[2]	17	F	Diabetes mellitus	120	121	Mild	Not related
207.021.88287	15	M	Ketonuria	35	47	Mild	Not related
207.026.88293[2]	12	M	Hyperglycemia	110	115	Severe	Not Related
207.028.88561	16	F	Nocturia	25	32	Moderate	Suspected
			Polydipsia	25	32	Moderate	Suspected
			Polyuria	25	32	Moderate	Suspected
207.049.88627	17	F	Abdominal tenderness	39	44	Mild	Unlikely
			Swelling face	39	44	Mild	Unlikely
			Edema peripheral	39	44	Mild	Unlikely
			Rectal hemorrhage	39	44	Moderate	Unlikely
MET							
207.013.88395	8	F	Hypoglycemia	43	56	Mild	Probable
207.013.88666	9	F	Decreased appetite	0	15	Mild	Probable
			Hypoglycemia Lethargy	14	15	Moderate	Probable
			Somnolence	0	15	Moderate	Probable
207.028.88562	15	F	Diarrhea	7	21	Severe	Suspected
			Nausea	7	21	Moderate	Suspected
207.039.88450[2]	16	F	Drug ineffective	108	119	Moderate	Unlikely
207.053.88589[2]	15	F	Diabetes mellitus inadequate control	56	56	Moderate	Unlikely
207.501.23633	14	F	Alanine aminotransferase increased	118	118	Mild	Suspected
207.501.23637	16	F	Alanine aminotransferase increased	57	64	Mild	Suspected

Data Source: Attachment 3, Appendix D.L2.; Attachment 3, Appendix D.L4.
Abbreviations: F=female, M=male, y=year(s).
1. Days since start of study drug.
2. The primary reason for withdrawal was identified by the investigator as lack of efficacy (see Table 4).

7.1.5 Common Adverse Events

Adverse events associated with rosiglitazone treatment in adults include weight gain, anemia, increases in lipid parameters, edema, congestive heart failure, and other cardiovascular adverse events. Fatal hepatic events that were associated with troglitazone, another thiazolidinedione, and resulted in its withdrawal from the market, have been seen only rarely in association with rosiglitazone based on postmarketing reports.

Significantly more weight gain was seen for pediatric patients treated with rosiglitazone (mean +2.7 kg) than with metformin (mean –0.3 kg), a difference consistent with the known effects of these drugs in adults. About 54% of rosiglitazone-treated patients and 30% of metformin-treated patients gained 2 kg or more on study. About 1/3 of rosiglitazone-treated patients gained 5 kg or more, and none of the metformin-treated patients gained more than 5 kg. Of note, height was apparently not measured precisely in this study, as about 11% of the children had a height decrease of ≥ 1 cm, and about 40% had no change or a decrease at 24 weeks. Thus, analyses of changes in body mass index (perhaps more appropriate than weight for assessments of changes in adiposity related to rosiglitazone therapy in growing children) were not possible. Observed changes in hemoglobin were smaller than those observed in adult studies. Variability in the lipid measurements and the small sample size contributed to poor estimates of change in the lipids. Only one episode of edema was reported in the rosiglitazone treatment group, and there were no other adverse cardiovascular events reported, as expected in this young population.

Gastrointestinal events were more commonly reported in the metformin treatment group (24% vs. 14%) as expected

Table 38 Relevant Gastrointestinal Adverse Events

Gastrointestinal Adverse Event	MET N=101	RSG N=99	Total N=200
Any gastrointestinal AE	24 (23.8)	14 (14.1)	38 (19.0)
Nausea	11 (10.9)	4 (4.0)	15 (7.5)
Vomiting	9 (8.9)	3 (3.0)	12 (6.0)
Abdominal pain[1]	7 (6.9)	3 (3.0)	10 (5.0)
Diarrhea	13 (12.9)	1 (1.0)	14 (7.0)
Abdominal tenderness	0	1 (1.0)	1 (0.5)
Abdominal discomfort	0	1 (1.0)	1 (0.5)
Epigastric discomfort	1 (1.0)	0	1 (0.5)

Data Source: Section 15, Table 15.2.4.

1. Abdominal pain includes preferred terms of abdominal pain and abdominal pain upper.

There were two reports of transaminase elevation 3X the upper limit of normal in the metformin group, but none were reported in the rosiglitazone treatment group.

Hypoglycemia is rarely reported with either rosiglitazone or metformin. There were no reports of hypoglycemia with rosiglitazone and two with metformin. Though no home glucose records were included, a progressive decrease in the glycemia with metformin treatment in both patients, with a decrease in HbA1c from 8 to 5.5% was consistent with the reported symptomatology.

Diabetic ketoacidosis is rarely reported in adult studies of rosiglitazone and metformin. Five patients in the rosiglitazone treatment group and three patients in the metformin treatment group had mild diabetic ketoacidosis (serum glucose about 300 mg/dl, 2+ ketonuria) and/or required insulin rescue.

TABLE: **Patient Presentations with Mild Diabetic Ketoacidosis and/or Required Insulin Rescue**
Data Sources: Tables 36 and 37, Narratives, Case Report Forms, Electronic Data Sets (accessed using JMP) – compiled by Clinical Reviewer.

PtID	Age Race Gender	DM duration Prior therapy Other history	Study Day	serum glucose (mg/dl)	HbA1c (%)	Urinary ketones	Rescue	Completed study Withdrawal day
ROSIGLITAZONE (total daily dose)								
207.013.88382 (2 mg bid) no run-in	15 B F	< 1 year Amaryl 1mg (1 dose only) urinary infection at enrollment	3	187	8.8		Yes – Insulin	No day 4
207.018.88659 (2 mg bid)	17 W F	2 years Insulin	120	295	9.6		Yes – Insulin	No day 121
207.021.88287 (2 mg bid)	15 B M	3 years Insulin 2 yrs	35 42	328	12.4	2+ 3+	Yes – Metformin 1000 mg	No day 47

		Met 2gm 1 yr					bid	
207.026.88293 (4 mg bid)	12 B M	< 1 year diet	110	292	10.8	2+	Yes – insulin	No day 115
207.028.88561 (2 mg bid)	16 HISP F	2 years diet upper respiratory infection - day 25	25		11.1		Yes – insulin	No day 32
METFORMIN (total daily dose)								
207.039.88450 (500 mg bid)	16 B F	1 year Pioglitazone 30 mg qd (3 months)	108	308	9.7	trace	Yes – insulin	No day 119
207.049.88626* (500 mg bid)	15 B M	1 year diet	171	376	11.8	2+	Yes – insulin	Yes
207.053.88589 (500 mg bid)	15 B F	3 yr Metformin 850 tid (3 years)	56 (polys wt loss)	277	13.6	2+	Yes – insulin	No day 56

*This case is the only case of DKA identified by the sponsor.
Normal values: glucose (70 -109 mg/dl) ; HbA1c < 6.5%

(b) (4)

Since treatment was ineffective in about 10% of the population, actually a greater percentage may have presented with mild diabetic ketoacidosis or required insulin rescue.

Table 8. Adverse Events Reported by ≥5% of Patients in a Double-Blind, Active-Controlled, Clinical Trial With AVANDIA or Metformin as Monotherapy in Pediatric Patients
Source: Proposed Prescribing Information

Preferred Term	AVANDIA N = 99	Metformin N = 101
	%	%
Headache	17.2	13.9
Influenza	7.1	5.9
Upper Respiratory Tract Infection	6.1	5.9
Cough	6.1	5.0
Hyperglycemia	8.1	6.9
Dizziness	5.1	2.0
Back Pain	5.1	1.0
Nausea	4.0	10.9
Hypoglycemia	4.0	5.0
Nasopharyngitis	3.0	11.9
Vomiting	3.0	8.9
Abdominal Pain	3.0	6.9
Pharyngolaryngeal pain	2.0	5.0
Diarrhea	1.0	12.9
Sinusitis	1.0	5.0
Dysmennorhea	0	6.9

The major difference between the two groups reflects the greater gastrointestinal adverse events in children treated with metformin.

7.1.6 Assessment of Effect on Growth

Of note, height was apparently not measured precisely in this study, as about 11% of the children had a height decrease of ≥ 1 cm, and about 40% had no change or a decrease at 24 weeks. Thus, analyses of changes in body mass index (perhaps more appropriate than weight for assessments of changes in adiposity related to rosiglitazone therapy in growing children) were not possible.

7.1.7 Overdose Experience

The sponsor has submitted a report requesting US child resistant packaging requirements for rosiglitazone patient samples because more than 700 reports of possible accidental ingestion in children under age 6 has been reported.

7.1.8 Postmarketing Experience

The sponsor reported three serious adverse events in the postmarketing pediatric database prior to 5/24/2004.

Report A0327739A describes a fatal hemorrhagic pancreatitis in a 17 year old female (weight 91 kg, height 67 in, BMI 31.8 kg/m^2) with type 2 diabetes mellitus and hypertriglyceridemia (600-700 mg/dl) who was simultaneously treated with rosiglitazone and desogestrel/ethinylestradiol.

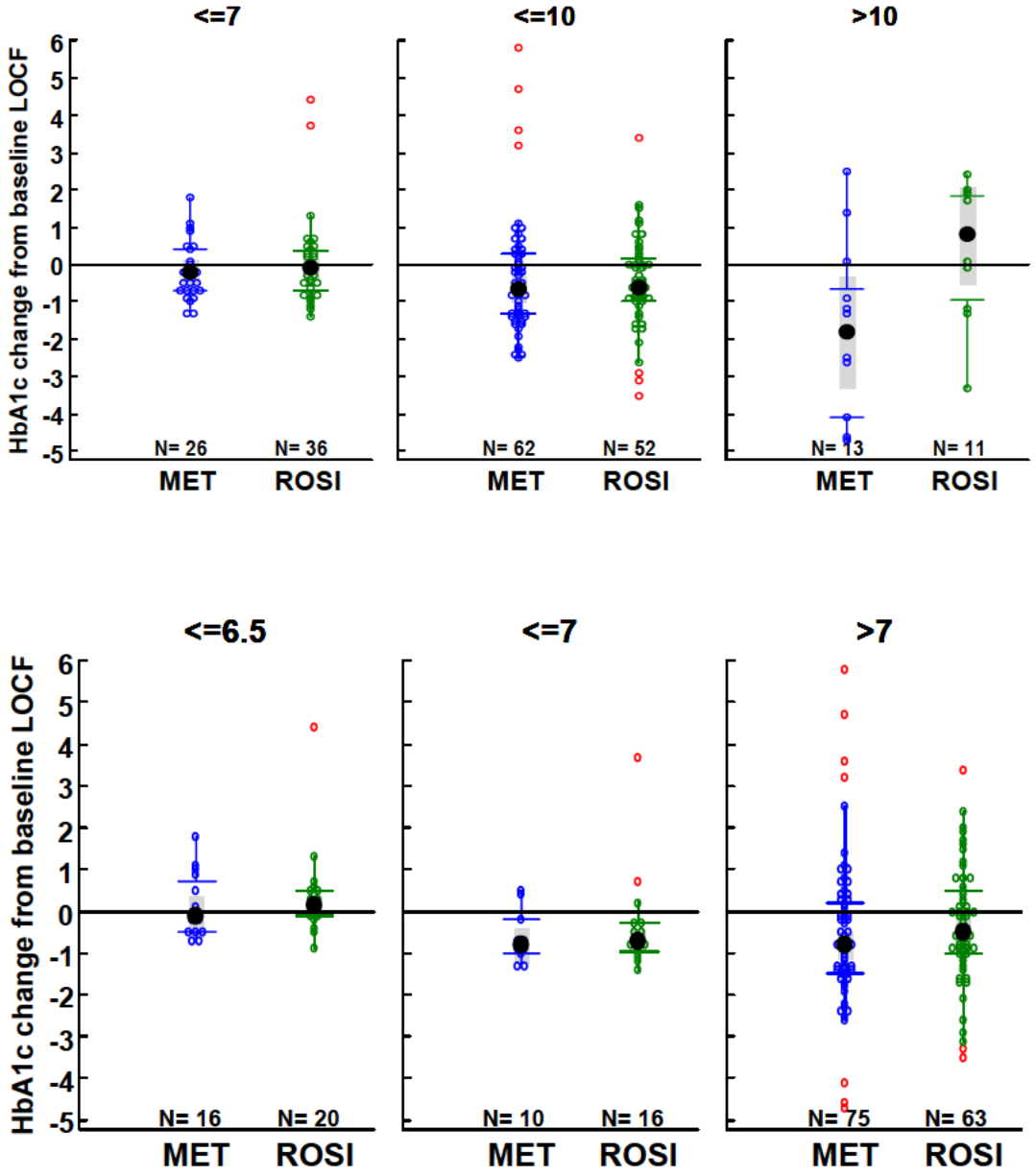
Report A0342315A describes an 11year old male with Type 2 diabetes mellitus (weight 47.5 kg, height 138 cm) with persistent elevated alanine transaminase (ALT) (109 U/L), hepatomegaly, and 10 lb weight gain after 10 months of rosiglitazone therapy. ALT remained elevated (189 U/L) two months after rosiglitazone was stopped and hepatitis viral serologies and monospot were reported to be negative.

Report A0504050A describes an 18 year old female who was hospitalized with ovarian cysts one month after starting rosigltiazone for severe insulin resistance. "According to the mother of the patient, two weeks after initiating rosiglitazone (8 mg) the patient began to experience back pain, headache, weight gain, low blood sugar (40 units not provided), inability to think, behavioral changes, confusion, nervousness, restless sleep, and onset of monthly menses. Treatment with rosiglitazone maleate was continued. The events were unresolved.

Search of the post-marketing database on 3/23/2005 by the FDA Office of Safety did not reveal any additional serious adverse events in the pediatric population.

8 ADDITIONAL CLINICAL ISSUES

The Written Request had initially requested enrollment of patients with HbA1c between 7.1 and 10%. The FDA statistician has plotted the data by baseline HbA1c. In the absence of a placebo group, it appears that the greatest effect of both treatments was within this HbA1c range. It is possible that there may be a slight benefit in the 6.5 to 7% range, but this small benefit would need to be balanced with the possible adverse events, particularly weight gain, which may then result in progressive insulin resistance.



An imbalance at randomization, with a sicker patient population randomized to metformin, may have contributed to a lower efficacy of treatment in the metformin group. Evaluation of stimulated C-peptide data may further clarify the response of the treatment groups.

The sponsor enrolled an insufficient n to address the endpoints, as is often noted in pediatric trials, where enrollment may be difficult. The exploratory statistical subgroup analyses create hypotheses, but these hypotheses are not supported by data from this clinical study. Particularly, since pediatric type 2 diabetes mellitus is a chronic and progressive disease, the risk benefit standard for therapy has to be at least as rigorous as it is for adult therapy.

The possible adverse events associated with rosiglitazone treatment, particularly the weight gain and the development of diabetic ketoacidosis and requirement for insulin rescue, particularly in the setting of an infection or non-compliance, emphasize that an intensive and diligent approach is essential in the treatment of pediatric type 2 diabetes mellitus. The more modest glycemic results in the pediatric population may reflect the smaller population, the increased insulin resistance, and possibly decreased compliance with medications, diet, exercise. The results of this pediatric study emphasize the need for an intensive preventive regimen in the treatment of pediatric type 2 diabetes mellitus. Prevention of overweight and obesity, an intensive regimen, and any delay in the onset of diabetes in this population will have a beneficial effect in mitigating chronic complications of diabetes mellitus in this young population.

9 OVERALL ASSESSMENT

Conclusions

(b) (4)

The pediatric efficacy and safety findings are summarized in the prescribing information.

Recommendation on Regulatory Action

GlaxoSmithKline has submitted data from a multicenter, randomized, active-controlled clinical study (Study BRL-049653/207, subsequently referred to as Study 207) to support FDA's granting of Pediatric Exclusivity, (b) (4) for use of rosiglitazone (AVANDIA®), a peroxisome proliferator activated receptor gamma agonist, of the thiazolidinedione class, in children with type 2 diabetes mellitus (b) (4)

(b) (4)

Pediatric Exclusivity was granted in December 2004.

Data from this study that address efficacy as well as safety should be included in the prescribing information to be available to clinicians. The label revisions are under discussion with the sponsor.

Labeling Review

Please see attached red-lined version of prescribing information, dated 4/11/05. The conclusion from this study, (b) (4) is included in the prescribing information. As noted on the PI, the changes in this label should be made to the recently altered 2/28/05 prescribing information.

10 APPENDICES

Line-by-Line Labeling Review

APPEARS THIS WAY ON ORIGINAL

REFERENCES

The following references in the sponsor's submission were reviewed.

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24 Page(s) of Draft Labeling has been Withheld in Full as B4 (CCI/TS) immediately following this page

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