CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-700

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL LABELING REVIEW

NDA/Serial Number:	21-700
Drug Name:	Avandaryl (rosiglitazone maleate and glimepiride)
	3 dosages: 4mg rosi+1mg glim; 4mg rosi+2mg glim; 4mg rosi+4mg glim
Indication(s):	Treatment of Type 2 Diabetes
Applicant:	GlaxoSmithKline
Date(s):	Submitted 10/31/03
	Review Completed 8//04
	PDUFA Goal 8/31/04
Review Priority:	Standard
Biometrics Division:	Division of Biometrics 2 (HFD-715)
Statistical Reviewer:	Joy Mele, M.S.
Concurring Reviewers:	Todd Sahlroot, Ph.D.
Medical Division:	Division of Metabolic and Endocrine Drug Products (HFD-510)
Clinical Team:	Joanna K. Zawadzki, M.D. (Clinical Reviewer)
	David Orloff, M.D. (Division Director)
Project Manager:	Lina Aljuburi

Keywords: Labeling, Clinical Studies

Table of Contents

1. Introduction

Avandaryl is a fixed–dose combination tablet of Avandia (rosiglitazone maleate) and Amaryl (glimepiride). The proposed indication is as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes who are already treated with a combination of [redacted] and sulfonylurea or who are not adequately controlled on a [redacted] or sulfonylurea alone. The applicant is planning to market 3 doses of the combination product: 4mg rosi+1mg glim; 4mg rosi+2mg glim; 4mg rosi+4mg glim.

The use of Avandia plus sulfonylureas (SU) was approved in April, 2000 and Avandia has labeling for this combination. The applicant is seeking approval of Avandyrl based on pharmacokinetic studies. Also, the applicant has proposed to include the clinical study results from the original Avandia application in the Avandyrl label and the results from two additional clinical studies. The primary goal of this review is to determine if the two additional studies provide useful information for the Avandaryl labeling.

2. Background

At a pre-NDA meeting in June 2003, the applicant and the FDA Division of Metabolic and Endocrine Drug Products agreed that four pharmacokinetic studies (a single-dose bio-equivalence study, an interaction study, a dose-proportionality study and a food effect study) would be sufficient to bridge to the clinical studies which supported the approval of the combination of rosiglitazone and SU's and, therefore, would form the basis for the approval of Avandaryl.

The approval of the combination of Avandia plus SU's was based on the first three studies summarized in Table 1 (see Appendices 5.1 and 5.2 for schematics of the trial designs). The last two studies were submitted as part of the Avandaryl NDA. The applicant is proposing including results for all five studies in labeling.

Table 1. Controlled Clinical Trials

Study (Sites)	Design	Treatment (# randomized)	Duration of Treatment
Studies previously reviewed and in Avandia and Avandaryl labels			
096 (33 USA)	Add-on to glyburide	Glyburide ≤10mg/day (115) RSG 2 mg daily + GLY (116) RSG 4 mg daily + GLY (116)	26 weeks
015 (54 European)	Add-on to sulfonylureas	Sulfonylureas (198) RSG 1 mg twice daily + SU (205) RSG 2 mg twice daily + SU (190)	26 weeks
079 (41 USA)	Combination versus components	Glyburide 10 mg twice daily (115) RSG 2 mg twice daily (116) RSG 2 mg twice daily + GLY (116)	26 weeks
Studies NOT previously reviewed and in Avandaryl label			
234 (32 Germany)	Add-on to glimepiride	Glim+ Pla (57) Glim+RSG 4 mg daily (56) Glim+RSG 8 mg daily (59)	26 weeks
135 (48 US and Canada)	Add-on to glipizide	Glip+Pla (111) Glip+RSG 4 mg BID (116)	2 years

Table 2 shows the doses of the various sulfonylureas used in the clinical trials with the rosiglitazone doses; these can be compared against the proposed Avandyrl doses in the first row of the table.

Table 2. Sulfonylurea and rosiglitazone doses studied in the clinical trials

	SU	SU Dose	Rosiglitazone Dose (daily dose)
Proposed Avandaryl doses	**glimepiride**	**1 mg 2 mg 4 mg**	**4 mg 4 mg 4 mg**
Clinical Studies			
096	glyburide	Max 10 mg	2 mg 4 mg
015	glibenclamide gliclazide glipizide	Med 15 Max 30 Med 160 Max 480 Med 15 Max 60	2 mg 4 mg
079	glyburide	20 mg	4 mg
234	**glimepiride**	**3 mg**	**4 mg 8 mg**
135	glipizide	Start 20 mg Max 40	Start 4 Max 8

None of the studies used the dosing combinations being proposed for avandaryl. Therefore, there is no clinical trial data for the to-be-marketed doses of avandaryl. Only one study, Study 234, used the sulfonylurea (glimepiride) contained in Avandaryl; this study is reviewed in the following section of this review.

The HbA1c and FPG results for the four 26-week and one 2-year add-on studies of rosiglitazone and a sulfonylurea are summarized in Table 3. All trials showed a statistically significant decrease in HbA1c for the combination over sulfonylurea monotherapy with patients usually worsening on monotherapy.

Table 3. HbA1c and FPG results for four 26-week clinical trials and one 2-year study of rosiglitazone added to sulfonylureas

	Sample Size	HbA1c Mean (%)		FPG Mean (mg/dL)	
		Baseline	Change	Baseline	Change
Study 015 Avandia 2 mg BID+SU Sulfonylurea (SU)	 183 192	 9.2 9.2	 **-0.9*** +0.2	 205 207	 **-38*** +6
Study 096 Avandia 4 mg OD+Glyburide Glyburide	 116 115	 9.1 8.9	 **-0.3*** +0.6	 214 209	 **-25*** +23
Study 079 Avandia 2 mg BID+Glyburide Glyburide	 98 99	 9.2 9.2	 **-0.5*** +0.9	 222 220	 **-34*** +24
Study 234 Avandia 4 mg OD+Glimepiride Glimepiride	 56 57	 8.2 7.9	 **-0.63*** -0.08	 189 176	 **-26** +2
Study 135 (2-year study) Avandia 4 mg OD+Glipizide Glipizide	 115 110	 7.6 7.4	 **-0.65*** +0.13	 149 149	 **-25*** +14

* Results are statistically significantly different from the control at $p<0.05$.

The results for Studies 234 and 135, are presented in Section 2.1 and 2.2 below.

2.1 Study 234

Study 234 was a 26-week double-blind, placebo-controlled, randomized study. At screening, patients were removed from any pre-existing anti-diabetic medication and placed on open-label glimepiride and titrated to a maximum dose of 3 mg over a maximum of 4 weeks. Patients titrated to the maximum dose were eligible to continue into a single-blind run-in taking 3 mg of glimepiride and placebo-rosiglitazone. After 4 weeks, patients satisfying the entry criteria were randomized to placebo, rosiglitazone 4 mg or rosiglitazone 8 mg as add-on to glimepiride 3 mg; all once a day dosing. See Appendix 5.2 for a schematic of the study design.

Entry criteria included the following:

- Took oral anti-diabetic medication "within >3 months prior to screening" (Section 5.3.1 of study report)
- HbA1c≥7% at screening
- 126 mg/dL ≤FPG≤270 mg/dL at Week –2
- No anti-diabetic combination therapy within 3 months of screening
- No history of chronic use of insulin

During the 26-week double blind treatment, the dose of glimepiride could be reduced to 2 mg at the discretion of the investigator; the rosiglitazone dose was not changed. Visits were scheduled every 4 weeks up to Week 20 and then at Week 26.

A total of 241 patients were screened, 174 were randomized (**58**:GLI+PLA; **57**:GLI+ROSI 4 mg and **57**:GLI+ROSI 8 mg) and 93% completed the study. Two patients in the GLI+PLA group and no patients in the ROSI groups dropped due to lack of efficacy. At the end of treatment, 5% of the patients randomized to GLI+PLA and GLI+ROSI 4 mg were on the 2 mg dose of GLI while 8.6% of the patients on GLI+ROSI 8 mg had lowered their dose to 2 mg.

The mean age of patients was 63 years (range of 43 to 79); 47% were females; and the median duration of diabetes was 6 years. The most commonly taken anti-diabetic drugs used prior to randomization were glibenclamide and glimepiride.

The applicant reported a statistically significant treatment effect for each combination versus the GLI monotherapy arm (Table 4, ANCOVA results). The HbA1c lowering for the GLI+ROSI 8 mg was significantly greater than the lowering seen for GLI+ROSI 4 mg ($p<0.004$). The 4 mg combination has about half the effect of the 8 mg combination. The results for completers are also more strongly in favor of the high dose combination ($p<0.0001$ compared to GLI) than the low dose combination ($p=0.0556$ compared to GLI). The applicant's per protocol analysis of 4 mg group versus GLI-placebo yielded a non-significant p-value of 0.12.

Table 4. Study 234 HbA1c change from baseline (LOCF)

	GLI+PLA	GLI+ROSI 4 mg	GLI+ROSI 8 mg
N	54	53	57
Baseline Mean (SD)	7.9 (1.4)	8.2 (1.4)	8.1 (1.5)
Mean change(SD)	-0.02 (1.1)	-0.64 (1.3)	-1.27 (1.5)
LS Mean change	-0.08	-0.63	-1.17

p-value vs. GLI		0.03	0.0001

The applicant reported non-significant FPG results for the 4 mg dose group (p=0.088) and significant results for the 8 mg group (p<0.0001).

The results for females were stronger than for males (see Appendix 5.3) particularly for the 4 mg combination where essentially no treatment effect is seen for males.

Overall the results for the 8 mg combination dose are stronger and more robust than the results for the 4 mg combination, particularly for males. Since the 4 mg combination is close to the proposed Avandaryl doses, the limited efficacy is concerning. However, it is noteworthy that the 4 mg combination is statistically significantly more effective in lowering HbA1c than GLI alone in patients inadequately treated with GLI 3 mg with a sample size of only about 50 patients in each treatment group.

2.2 Study 135

Study 135 was a long-term study designed to determine if the combination of rosiglitazone plus glipizide delays or prevents deterioration in glycemic control compared to glipizide treatment alone. Eligible patients entered a 4-week run-in period of glipizide 10 mg BID alone and then, were randomized to either glipizide monotherapy or glipizide and rosiglitazone 4 mg once a day. The treatment period was 2 years with a total of 16 visits (see Appendix 5.2 for the design schematic). Patients with an FPG of 180 mg/dL or greater had their doses titrated to maximum doses of rosiglitazone 4 mg BID or glipizide 20 mg BID (see Appendix 5.4 for details regarding titration). If at maximal doses, FPG remains at or above 180 mg/dL, a patient was withdrawn from glipizide and given insulin treatment; these patients were considered treatment failures. Time to treatment failure was the primary endpoint for this trial.

To enter this trial, patients with Type 2 diabetes mellitus needed to meet the following criteria:

- prior to screening, on sulfonylurea monotherapy for at least 3 months and taking ¼ to ½ of the maximum recommended sulfonylurea dose for at least 2 months;
- at least 60 years old;
- 126≤FPG≤250 at screening;
- 126≤FPG≤179 at Week –2 (Visit 3);
- no treatment with a thiazolidinedione within 3 months of screening

A total of 357 were screened, 227 were randomized (111 to glipizide monotherapy and 116 to combination therapy). Fifty-seven (51%) monotherapy patients and 90 (78%) combination therapy patients completed 2 years on study. The reasons for withdrawal are shown below.

Table 5. Study 135 Reasons for withdrawal

	Glipizide (n=111)	RSG+Glipizide (n=116)
Adverse event	8 (7%)	13 (11%)
Lack of Efficacy	32 (29%)	3 (3%)
Protocol deviation	7 (6%)	4 (3%)
Other	7 (6%)	6 (5%)

Patients considered treatment failures, could withdraw from the study or stop glipizide treatment and initiate insulin treatment.

The average age of patients was 68 years old (range of 59-89); 73% were male and 91% were Caucasian. About 14% of the patients were intolerant or contraindicated for metformin use (this was originally an entry criteria but was changed due to difficulties in recruitment).

The applicant reported limited data on the doses taken in the study stating only in the study report that 59 completers on combination therapy remained on their initial dose and 13 combination patients and 53 monotherapy patients were titrated to the maximum dose. This reviewer determined the last dose all patients were on at the time that they either completed the full study or discontinued from the study (this dosing data was ascertained from a dataset called DOSE provided by the applicant). The majority of the patients (69%) on the combination therapy were not titrated above their starting dose while half of the patients on monotherapy were titrated to higher doses of glipiride (most to the maximum dose of 40 mg).

Table 6. Final doses for all randomized patients computed from the Applicant's dataset DOSE

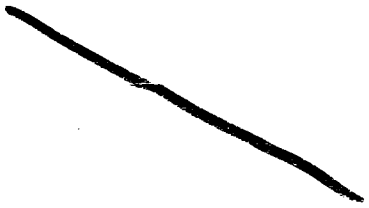
Final Dose	GLIP+PLA (n=110)	GLIP+ROSI 4 mg OD (n=115)
Glip 20 mg+Rosi 4mg OD (or Pla)	35 (35%)	78 (69%)
Glip 20 mg+Rosi 4mg BID (or Pla)	14 (14%)	19 (17%)
Glip 30 mg+Rosi 4mg BID (or Pla)	10 (10%)	9 (8%)
Glip 40 mg+Rosi 4mg BID (or Pla)	40 (40%)	7 (6%)

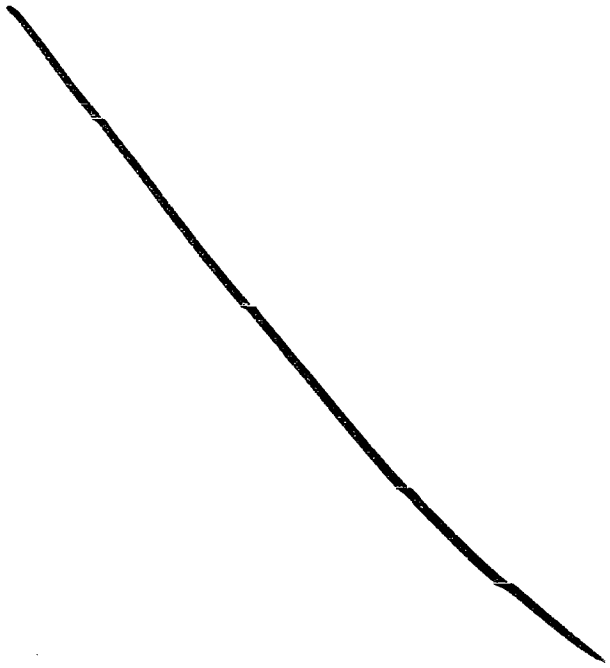
Only 2 patients (2%) on combination therapy were treatment failures while 27 patients (29%) on monotherapy glipizide were failures (log rank test $p<0.0001$). Eleven (11) of the 27 treatment failures on monotherapy, stopped glipizide and switched to insulin.

Both the FPG and HbA1c change from baseline results showed significant treatment effects at both Week 26 and endpoint. Also the results for patients who stayed on the initial doses of combination therapy (rosiglitazone 4 mg and glipizide 10 mg daily) had results comparable to patients titrated to higher doses. So the results at endpoint shown in Table 3 of this review are representative of the results at both Week 26 and endpoint and for patients titrated and not titrated.

3. Labeling comments for the Clinical Studies Section

CLINICAL STUDIES





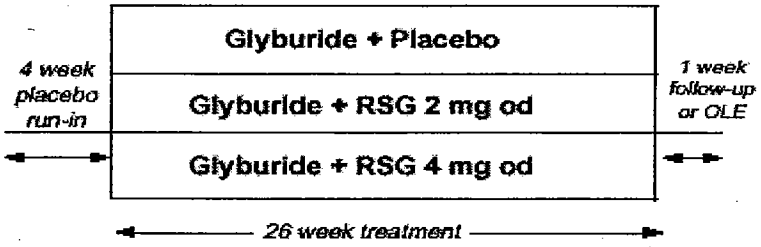
4. Recommendations

The FDA medical division has agreed to accept PK studies in lieu of clinical trials for the approval of avandaryl. Therefore the purpose of this review was to critique the clinical trials section of the avandaryl labeling. Recommendations regarding the labeling are made in Section 3 of this review. These recommendations will be discussed with the medical reviewer, Dr. Zawadzki.

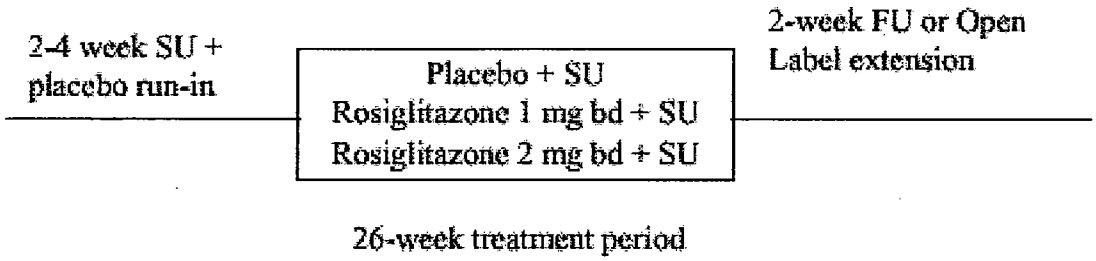
5. Appendices

5.1 Study designs for studies previously reviewed for Avandia

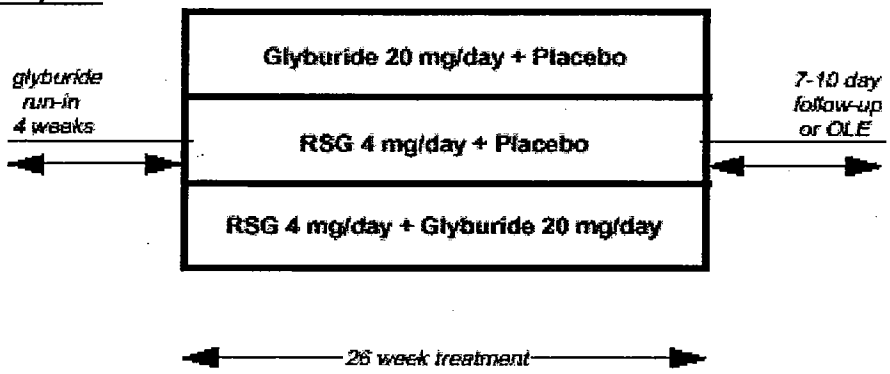
Study 096



Study 015



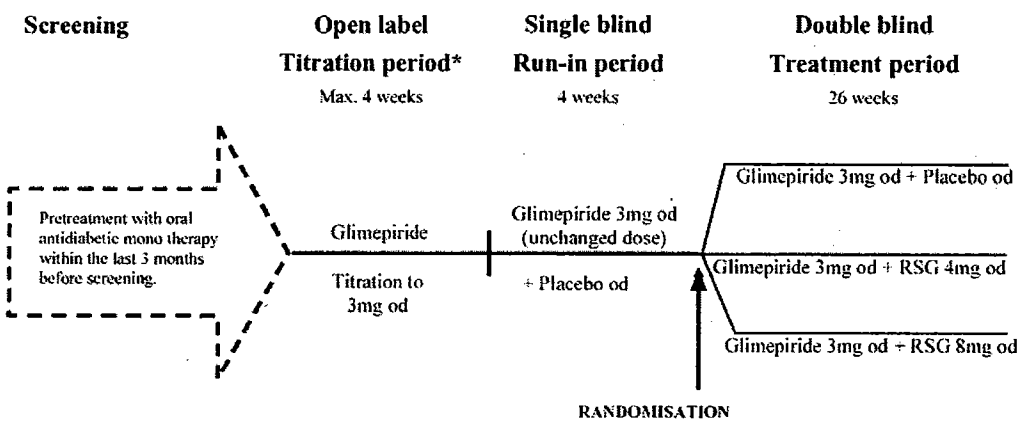
Study 079



5.2 Study designs for studies submitted for Avandyrl

Study 234

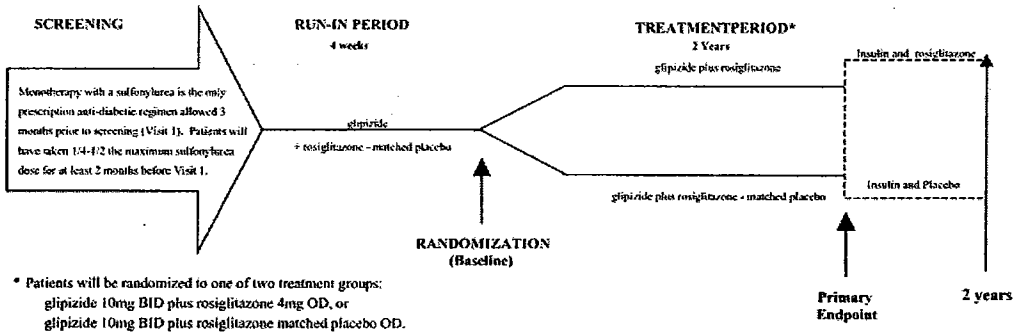
Figure 1 Study design



* In patients already treated with 3mg Glimepiride the open label titration period was not required.

Study 135

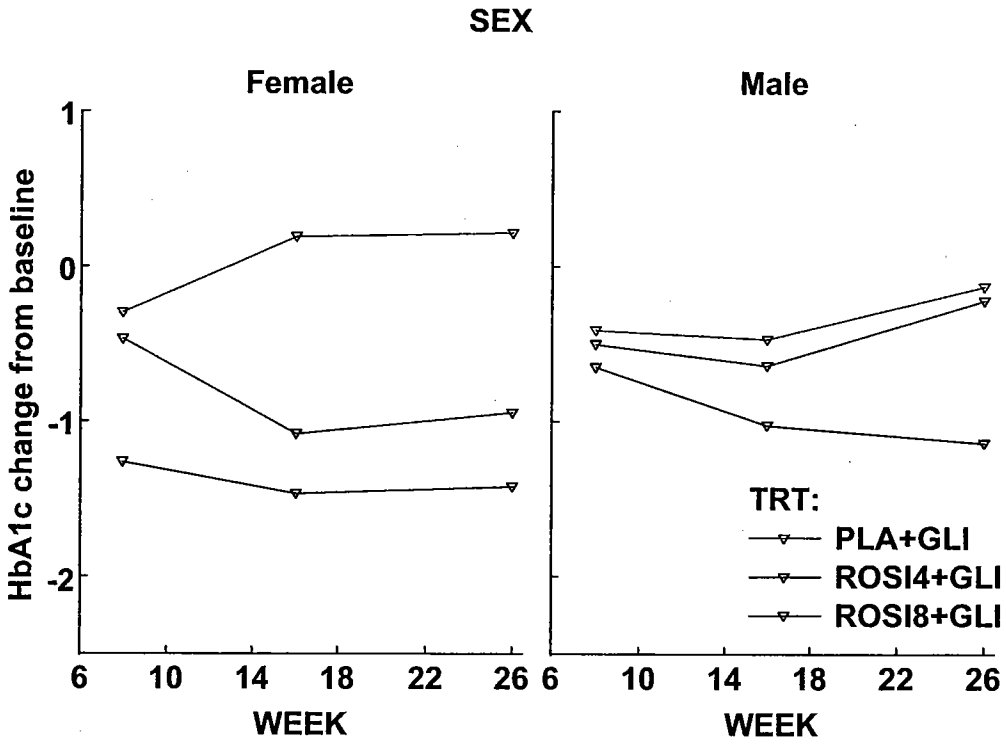
Figure 1 135 Study Design



* Patients will be randomized to one of two treatment groups:
glipizide 10mg BID plus rosiglitazone 4mg OD, or
glipizide 10mg BID plus rosiglitazone matched placebo OD.

Individualize treatment goals will be encouraged. Titration of medications may be performed at anytime according to standard practice guidelines. However, patients having an FPG ≥180mg/dL at any treatment visit after visit 4 must titrate their study medications. Titration of medication will continue until the patient has received the maximum recommended dosages of rosiglitazone and glipizide (4mg BID and 20mg BID, respectively). If FPG ≥180mg/dL (upon confirmation) after patient has received maximum dosages of rosiglitazone and glipizide, patient will be withdrawn from glipizide and will receive treatment with insulin.

5.3 Gender results in Study 234



5.4 Titration scheme for Study 135

Applicant's table

Table 1 Titration Regimen in Study 135

Step 1-4	Current Dosage	FPG Results	Titration
Week 0	rosiglitazone 4 mg or placebo OD (1 tablet in the AM) and Glucotrol 10 mg BID (1 tablet in the AM, I tablet in the PM)		
Step 1 ≥Week 6	Continue on previous dosage	FPG ≥180mg/dL OR at a lower FPG at the Investigator's Discretion ←NO | YES→	Increase rosiglitazone (or placebo) to 1 tablet BID (1 AM, 1 PM)
Step 2 ≥Week 12	Continue on previous dosage (last titrated or unchanged dose)	FPG ≥180mg/dL OR at a lower FPG at the Investigator's Discretion ←NO | YES→	Glucotrol 30 mg a day (1 tablet in AM and 2 tablets in PM)
Step 3 >Week 12	Continue on previous dosage (last titrated or unchanged dose)	FPG ≥180mg/dL OR at a lower FPG at the Investigator's Discretion ←NO | YES→	Glucotrol 40 mg a day (2 tablets In AM and 2 tablets in PM)
Step 4 >Week 12	Continue on previous dosage (last titrated or unchanged dose)	FPG ≥180mg/dL (based on confirmatory FPG≥180mg/dL) ←NO | YES→	Initiate insulin therapy with a 70/30 premix or withdraw from study Note: Glucotrol therapy must be stopped at time of initiation with insulin.
Insulin Maintenance:	Insulin doses could be adjusted 2-4 units every 1-2 weeks based on patient's FPG. If FPG ≥ 200mg/dL after 3 months of insulin therapy, considered adding an injection with breakfast. Insulin doses and regimens could vary according to the individualized patient requirements.		

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Joy Mele
8/13/04 05:20:00 PM
BIOMETRICS

Todd Sahlroot
8/16/04 08:46:50 AM
BIOMETRICS