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 REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number: 21-071 Seq 015 (b) (4)

Drug Name: Avandia (rosiglitazone maleate) Tablets

(b) (4)

Applicant: GlaxoSmithKline

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1. EXECUTIVE SUMMARY OF STATISTICAL FINDINGS

1.1 Conclusions and Recommendations

Pediatric Study 207, designed to assess the efficacy of rosiglitazone for the treatment of Type 2 diabetes, is underpowered to show non-inferiority of rosiglitazone to metformin. With 97 patients in each group of the ITT population, the power is only 53% to rule out a difference of 0.4 or greater. So by design, this study was not likely to show comparability of the two treatment groups. The results bear this out with no analyses showing rosiglitazone non-inferior to metformin by an HbA1c change from baseline margin of 0.4% or less. This lack of power is not uncommon in pediatric studies where recruitment of patients is difficult.

Although no analyses show rosiglitazone to be non-inferior to metformin, labeling for this pediatric study is warranted in order to provide information to physicians on the use of rosiglitazone in a pediatric population. This reviewer recommends that the results for naïve patients be emphasized in the labeling since the results for previously treated patients are notably more favorable to metformin (treatment effects in favor of metformin greater than 0.4%) while the results for naïve patients are more ambiguous (see Table 3.1.8 on page 13). This reviewer also recommends that weight gain data accompany the efficacy results in labeling since weight gain in a pediatric population often suffering from obesity may be a consideration in use of the drug.

1.2 Brief Overview of Clinical Studies

The sponsor has submitted the results of one study entitled "A 24-Week Randomized, Double-Blind, Active-Controlled, Multicenter Study To Evaluate The Safety And Efficacy Of Rosiglitazone When Administered To Pediatric Patients With Type2 Diabetes Mellitus". The trial design is briefly summarized in Table 1.2.1

Table 1.2.1 Clinical Trial

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

Metformin was chosen as a comparator because the applicant believes alternatives to metformin should be available to pediatric patients; the applicant argues that metformin can lose effectiveness over time and has undesirable gastrointestinal side effects.

1.3 Statistical Issues and Findings

The protocol named the within-group change from baseline for rosiglitazone as the primary efficacy comparison and named the non-inferiority comparison of rosiglitazone to metformin as a secondary comparison. The FDA Written Request for a pediatric study asked for the non-inferiority comparison as primary. (b) (4)

(b) (4)

Enrollment criteria were applied only at the screening visit and not at the baseline visit. As a result the patient population included patients (about 30) who reached an HbA1c level of 6.5 or less (a level at which patients would not be ordinarily treated). This reviewer performed an analysis excluding these patients and these are the results recommended for labeling (see Table 3.1.8 for a full description of these results).

The subgroup results are generally consistent with what we have observed in the adult population. Patients with higher BMI's tend to have a higher response on rosiglitazone and patients gain about 2-3 kg on average with a larger gain seen in naïve patients. The weight gain should be carefully described with the results in the labeling in order to provide a clearer risk benefit assessment. Lipid changes were erratic and not consistent with what has been seen in other rosiglitazone studies; this may be due to few measurements being made and the small sample size.

2. Introduction

2.1 Background

Th applicant has submitted the results of one clinical study (b) (4) he study includes patients with prior therapy but no indication is sought for that subgroup.

According to the applicant, the incidence of type 2 diabetes in pediatric patients (usually 12 to 16 years at diagnosis) is rising worldwide and no drug is currently approved for pediatric patients although the American Diabetes Association has recommended metformin as first-line treatment. Metformin use is associated with gastro-intestinal side effects and may lose effectiveness over time so the applicant argues that additional treatments are needed.

2.2 Data Sources

This submission was fully electronic and available in the Electronic Document Room at \\CDSESUB1\N21071\S_015\2004-09-30.

The applicant provided datasets that were appropriately labeled and documented. These datasets are available at \\Cdsesub1\n21071\S_015\2004-09-30\crt.

The appropriate data was available in the datasets provided; however, some data was not in a user friendly format. For example, no change from baseline data was provided and the dosing data was not provided in a readily interpretable format.

3. Statistical Evaluation

3.1 Evaluation of Efficacy
Study BRL-049653/207 (conducted 3/01 to 4/04)

Design

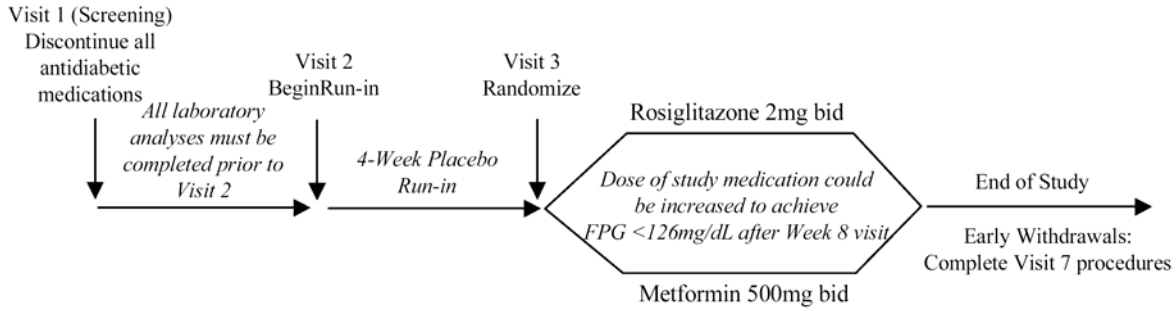
Study BRL-049653/207 (henceforth referred to as Study 207) was a double-blind, randomized, active-controlled 24-week study designed to assess the efficacy and safety of rosiglitazone for the treatment of type 2 diabetes in pediatric patients. Metformin was the active control drug.

After screening, eligible patients entered a 4-week placebo single-blind period to measure the effect of diet and exercise (Figure 3.1.1). According to the protocol, patients were to receive dietary instruction along with a placebo capsule during the run-in; diet instructions were to be reinforced at each visit. There are no details in the protocol regarding the specifics of the dietary instructions and it appears from the case report forms that this was left to the medical personnel seeing the patient at each visit (see Appendix 6.1). After the run-in, patients were randomized, stratified on gender, to rosiglitazone 2 mg BID or metformin 500 mg BID. Note that eligibility for the trial was assessed at screening not at the time of randomization; therefore patients adequately treated with diet and exercise could still be randomized to drug treatment. If after 8 weeks of treatment, the FPG was greater than 126 mg/dL, the treatment dose could be doubled.

HbA1c and FPG were measured at screening (Visit 1), baseline and Weeks 4, 8, 16 and 24. FPG was also measured at the beginning of the run-in (Visit 2).

Figure 3.1.1 Applicant's schematic of the trial design

Figure 1 Study Design Schematic



Inclusion criteria included the following:

- males and females 8-17 years old
- C-peptide≥1.5 ng/dL
- GAD65 and ICA512-antibody negative following a test meal challenge
- no prior anti-diabetic therapy (i.e. naïve), or previously treated with diet and exercise or on monotherapy
- **FPG≤270 mg/dL at screening**
- **HbA1c>6.5% at screening for naïve patients** or patients previously treated with diet and exercise
- **6.5%<HbA1c≤10% at screening for patients previously treated** with monotherapy

Patients were excluded if they used any investigational drug within 30 days or within 5 half-lives of the start of the run-in or if they used a thiazolidinedione in the 3 months prior to screening. Patients on insulin therapy for a week or less within one month of screening or on insulin more than one week within 3 months of screening were excluded. Patients were to have stopped their anti-diabetic medication at the screening visit.

The protocol stipulated that the primary comparison would be the within group comparison of the change from baseline of HbA1c. A non-inferiority comparison of rosiglitazone to metformin was named as a secondary comparison. (b) (4) This reviewer will treat the comparison to Metformin (an approved treatment for pediatric patients) as the primary comparison.

Patient Disposition

The applicant planned to screen 383 patients and randomize 215 to obtain a total of a 150 patients completing the trial in keeping with 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 (Table 3.1.1) with more than 90% of the patients completing 10 weeks of treatment.

Table 3.1.1 Patient Disposition

	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%)

The primary reason for dropout in both treatment groups was lack of efficacy (Table 3.1.2, about 10% of the patients); almost all occurred after 3 months of treatment (after the timepoint, Week 8, at which titration of the drug was allowed). Most of the adverse events that led to dropout occurred during the first 3 months of the study.

Table 3.1.2 Reasons for discontinuation

	Metformin (n=101)	Rosiglitazone (n=99)
ADE	5	4
Lack of Efficacy	9	9
Prot. Viol.	5	3
Lost-to-FU	5	2
Other	4	1

Baseline Demographics[1]

The randomized treatment groups were comparable with regard to baseline characteristics. This reviewer also looked at the demographic data for naïve patients versus previously treated patients and found similar results for those groups.

The average age of the patients was 14; about half the patients were 15 to 17 years (see Appendix 6.2 for a distribution of the ages). Several races are well-represented in this study; more than what we traditionally see in typical clinical trials. The majority of patients were of Hispanic origin with whites and blacks well-represented.

The majority of the children were overweight with 75% of the patients having a BMI of 27 kg/m^2 or greater and with about 17% described as obese by the investigator. The distributions of weight by age and by height are presented in Appendix 6.3 .

Table 3.1.3 Patient Demographics

	Metformin (n=101)	Rosiglitazone (n=99)
Age		
Mean (SD)	14 (2.3)	14 (1.9)
Range	8-17	10-17
Gender		
% female	68%	66%
Race		
White	24	21
Black	25	29
Amer. Ind.	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 groups are balanced for prior therapy ($p>0.4$). A little more than half the patients were naïve to previous treatment with anti-diabetic therapy. Almost all of the previously treated patients had been taking metformin monotherapy prior to entering the trial.

1 The applicant has provided in the study report tables for baseline characteristics based on the ITT population (total of 195 patients); this reviewer has included all randomized patients. No notable difference was seen between the ITT and all randomized patients.

Baseline Diabetes Characteristics

The results in this section and subsequent sections are presented by previous experience with diabetes treatment as well as by treatment group. (b) (4)

As would be expected, the years since diagnosis of diabetes is longer for previously treated patients than naïve patients. The majority of naïve patients were diagnosed within a year of entry (denoted as a zero in the database) into the trial while about 80% of the previously treated patients were diagnosed between 1 and 7 years prior to entry.

Table 3.1.4 Baseline diabetes characteristics

	Prev Treated		Naive	
	Metformin (n=49)	Rosiglitazone (n=43)	Metformin (n=52)	Rosiglitazone (n=56)
Years with diabetes [1]				
Mean (SD)	1.8 (1.5)	2.0 (2.6)	0.4 (0.8)	0.3 (0.8)
Median	1	1	0	0
Range	0-6	0-7	0-3	0-4
HbA1c				
Screening				
Mean (SD)	7.9 (1.2)	7.9 (1.1)	8.2 (1.4)	8.3 (1.5)
Range	6.1-11.4	6.4-11.1	6.5-12.6	6.6-12
Baseline				
Mean (SD)	8.5 (1.5)	8.0 (1.6)	7.8 (1.7)	7.8 (1.4)
Range	5.6-12	6-11.4	5.3-12.4	5-11.1
Screen to Baseline				
Mean (SD)	+0.6 (1.2)	+0.04 (1.3)	-0.4 (0.9)	-0.5 (1.3)
Median	+0.6	-0.1	-0.25	-0.3
Range	-4.3-3.6	-2.6-4.2	-3.8-1.2	-4.1-2.4
FPG				
Screening				
Mean (SD)	164 (64)	156 (66)	156 (50)	159 (53)
Range	85-344	26-353	82-304	88-277
Prior to run-in				
Mean (SD)	192 (79)	179 (71)	153 (57)	162 (60)
Range	86-386	84-329	73-337	81-309
Baseline				
Mean (SD)	208 (80)	189 (78)	156 (63)	157 (60)
Range	74-353	92-344	74-343	76-346

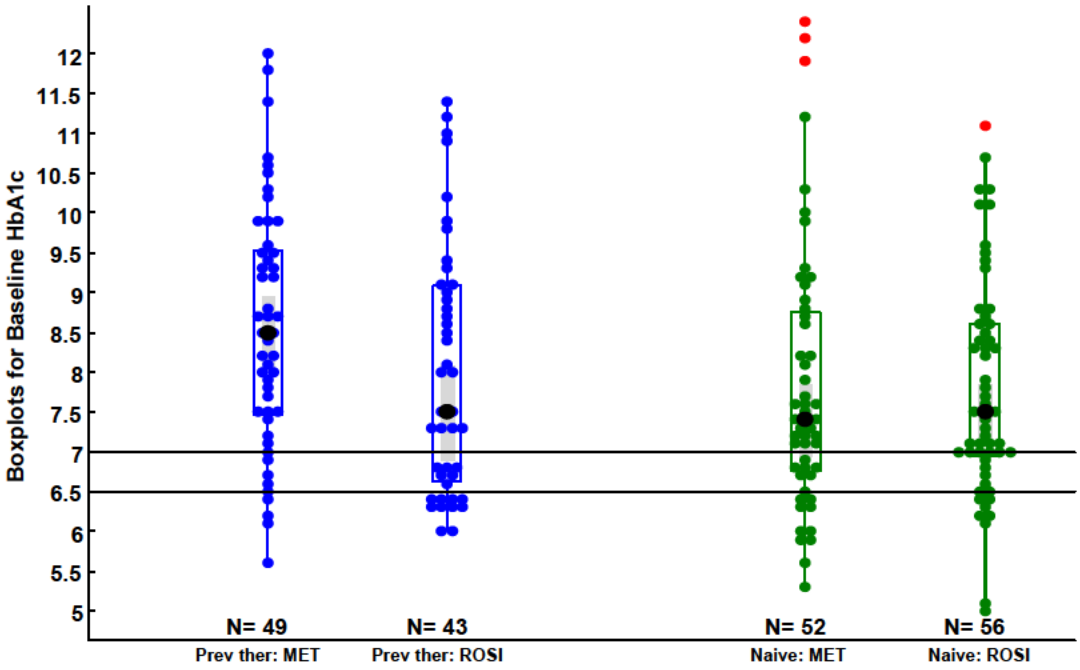
1 – The applicant recorded years with diabetes only in whole numbers so a zero indicates a value below 1 not zero. All patients presented with diabetes at the time of entry into the trial.

Within the naïve group, the treatment groups are comparable with regard to HbA1c and FPG at both screening and baseline. Within the previously treated group, the baseline HbA1c difference between the treatment groups (8.5 versus 8) is borderline significant (p=0.07, Wilcoxon rank sum test). This difference is illustrated in the figure on the following page and supported by the difference between groups for change from screening to baseline. Since randomization takes

place after the run-in, clearly the difference is unrelated to treatment and suggests an imbalance at baseline not only on HbA1c but probably on other factors as well for the patients previously treated.

The FDA Written Request said patients were to have an HbA1c greater than 7 in order to be eligible for the trial. The request did not explicitly state at what timepoint the patient should meet the HbA1c criteria. The protocol stated that an HbA1c greater than 6.5 at screening was required for entry; an amendment to the protocol changing the cutoff from 7 to 6.5 was accepted by the FDA. At screening, only 1 naïve patient and 4 previously treated patients had an HbA1c of 6.5 or below; about 20-25% of both naïve and previously treated patients had an HbA1c of 7 or below. At the baseline visit (Figure 3.1.2), about 18% of the naïve rosiglitazone patients and about 21% of the naïve metformin patients had an HbA1c of 6.5 or less. About 1/3 of the naïve patients had baseline HbA1c's of 7 or less at baseline.

Figure 3.1.2 Boxplots of baseline HbA1c by treatment and previous diabetes therapy



So in the naïve group, [redacted] (b) (4) about one-fifth of the patients did not actually require drug therapy having responded sufficiently during the diet/exercise run-in period with HbA1c values of less than 6.5. This reviewer examined this issue further on pages 14 and 18 of this review.

Efficacy Results

The primary goal of the trial according to the protocol was to show significant within-group decreases in HbA1c. However the FDA Written Request asked that the non-inferiority of rosiglitazone be assessed against the effect of metformin. A non-inferiority margin of 0.4% was stipulated in the protocol; so rosiglitazone is comparable to metformin if the upper boundary of the 2-sided 95% confidence interval on the treatment difference (ROSI-MET) is less than 0.4% .

With the proposed 75 patients in each group, the power to meet a non-inferiority boundary of 0.4% using a 95% confidence interval assuming no difference between the groups with an SD of 1.6% is only 33%. With about 97 patients per group (the approximate number in each group of the ITT population) the power is about 53%.

The applicant's analysis model included region (due to the small numbers in some centers), gender and baseline HbA1c. This reviewer ran models with the applicant's proposed factors and as well as including BMI and found similar results. The applicant's model was used for the results reported in the tables of this review. In addition the applicant states that the data was not normally distributed (without providing statistical evidence) and therefore in addition to performing parametric analyses, the applicant also performed non-parametric analyses. This reviewer believes the parametric analyses are sufficient and so the non-parametric results are not shown here.

Results by previous therapy are presented in this section of the review as opposed to the subgroup section (b) (4)

The applicant analyzed the last-observation-carried-forward values for HbA1c for the ITT population, the data for completers and the data for an evaluable population; the results are summarized below in Table 3.1.5. In all groups, the results favor metformin over rosiglitazone though, clearly, metformin is not shown to be superior to rosiglitazone. The applicant also presented the confidence intervals for naïve patients but this reviewer was not able to locate confidence intervals for previously treated patients.

The ITT-LOCF results, the analysis with the most patients, showed that the upper bound was greater than the prespecified margin of 0.4% by almost double that amount. The observed mean HbA1c change for metformin was –0.49% (SD=1.65) and the change for rosiglitazone was –0.14 (SD=1.52). So the treatment difference is less than 0.4 but the upper margin of the confidence interval suggests that differences in favor of metformin of 0.72 are plausible based on this underpowered trial.

Table 3.1.5 Summary of Applicant's results
Week 24 HbA1c change from baseline

Analysis population (Total N)	ROSI-MET LS Mean Diff[1]	p-value	95% Confidence Interval
ITT – LOCF All pts. (195)	(-0.14) – (-0.49) 0.28	0.20	-0.16, 0.72
ITT – LOCF Naïve pts. (105)	(-0.32) – (-0.60) 0.25	0.43	-0.37, 0.87
ITT – Completers (181)	(-0.25) – (-0.62) 0.19	0.43	-0.29, 0.67
Evaluable – LOCF (90)	(-0.35) – (-0.73) 0.19	0.29	-0.24, 0.83

1 – Negative values favor rosiglitazone; positive values favor Metformin.

Patients that were not appropriately titrated were excluded from the applicant's evaluable population. According to the protocol the dose of either drug could be doubled if the FPG was greater than 126mg/dL at Week or later. About 55% of the metformin patients had their dose increased from 500 mg BID to 1,000 mg BID and 49% of the rosiglitazone patients had their dose increased from 2 mg BID to 4 mg BID. There were 9 rosiglitazone patients and 14

metformin patients that were not up-titrated though they met the criteria for titration. Exclusion of these patients as well as other protocol violators did not appreciably change the efficacy results.

Results for analyses of naïve and previously treated patients performed by this reviewer (Table 3.1.6) show that, based on the confidence intervals, the groups are not statistically different however the upper boundary clearly favors metformin. Only in the naïve group is a drop in HbA1c seen for the rosiglitazone group; for the other subgroups, mean increases in HbA1c are seen when switching from previous therapy to rosiglitazone monotherapy. This latter finding is consistent with what has been seen in rosiglitazone trials in adults.

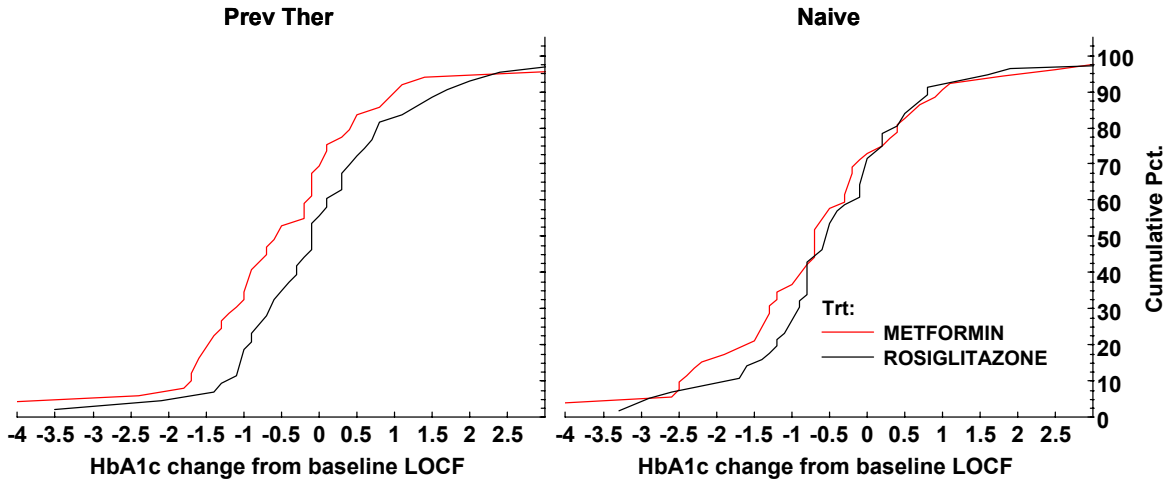
Table 3.1.6 Reviewer's results for Week 24 HbA1c change from baseline ITT LOCF

Analysis population	ROSI-MET LS Mean Diff[1]	p-value	95% Confidence Interval
Naïve pts	(-0.24) – (-0.44) 0.21	0.47	-0.37, 0.80
Monotherapy pts	(+0.19) – (-0.11) 0.30	0.41	-0.41, 1.00
Combination therapy	(+0.48) – (-0.10) 0.58	0.45	-0.94, 2.1

1 – Negative values favor rosiglitazone; positive values favor metformin. The model included treatment, baseline HbA1c, region and previous therapy. Adding gender did not change the treatment effects.

Cumulative distribution plots of HbA1c at Week 24 LOCF show that the rosiglitazone curves are slightly shifted to the left of the metformin curve for both naïve and previously treated patients; though the difference is most evident in previously treated patients. These graphs illustrate that a higher percentage of patients have larger decreases in HbA1c on metformin compared to rosiglitazone treated patients. See Appendix 6.4 for graphs of HbA1c and FPG change from baseline plotted over the duration of the trial.

Figure 3.1.3 Cumulative distribution plots of HbA1c change from baseline at Week 24 LOCF by treatment and previous diabetes therapy



In addition to analyzing change from baseline, the applicant has looked at change from

screening. Looking at the previously treated patients in this way may address whether previously treated patients reach HbA1c levels comparable to their screening values. The drawback to this approach is that we have no information about the adequacy and duration of prior therapy so we do not know if the value at screening is representative of the magnitude of response that one could expect from usual care. Nevertheless this is useful descriptive data. Of the patients previously treated with antidiabetic drugs, 61% of the metformin patients and 51% of the rosiglitazone patients returned to their HbA1c screening value or lower by the end of the treatment period; a 10% treatment difference. This result is consistent with the change from baseline results.

(b) (4) So this reviewer thought it would be interesting to see how naïve patients do during the run-in period compared to on treatment. Again this is purely for descriptive purposes. Since the run-in is too short to expect to see changes in HbA1c, only FPG is summarized below.

A small mean change in FPG is seen during the run-in but the bulk of the decrease is seen on treatment . Of the naïve patients 56% of metformin patients and 57% of the rosiglitazone patients had a larger decrease in FPG during the treatment period than during the diet only run-in.

Table 3.1.7 FPG run-in/diet change and change from baseline on treatment - Naïve patients only

	Metformin (n=52)	Rosiglitazone (n=56)
Run-in Change	-0.09 (40)	-1.2 (51)
Treatment Change	-15.5 (56)	-7.1 (45)
Difference	**+15 (79)**	**+3.9 (79)**

A positive value for difference indicates a larger decrease in HbA1c on treatment than on diet alone.

As mentioned earlier in this review, patients were randomized to treatment in this study who would not ordinarily receive treatment due to an HbA1c of 6.5 or less (21 naïve patients and 15 previously treated patients). This reviewer analyzed the data excluding these patients.

Table 3.1.8 Analysis excluding patients with baseline HbA1c of 6.5 or less
Week 24 HbA1c change from baseline LOCF

	Metformin Mean (SD)	Rosiglitazone Mean (SD)	p-value	LS Mean Diff[1] (95% CI)
Naïve pts	(n=41)	(n=46)		
Baseline	8.3 (1.5)	8.2 (1.2)		
Change	-0.7 (1.7)	-0.5 (1.6)	0.67	+0.15 (-0.5, +0.8)
Prev. Monotherapy	(n=37)	(n=27)		
Baseline	8.7 (1.4)	8.4 (1.4)		
Change	-0.4 (1.9)	+0.01 (1.6)	0.33	+0.40 (-0.4, +1.2)
Prev. Comb.Ther.	(n=7)	(n=6)		
Baseline	9.3 (1.4)	8.8 (1.7)		
Change	-0.6 (1.0)	+0.3 (1.1)	0.45	+0.69 (-1.1, +2.5)

1 – Least squares means are means adjusted for baseline. Negative values favor rosiglitazone; positive values favor Metformin.

The results excluding patients with an HbA1c of 6.5 or less at baseline are consistent with the overall results of the study. For the naïve patients, the treatment difference is not clinically important however the confidence interval suggests that values as high as 0.8 in favor of

metformin are possible. The difference in the previously treated patients (both monotherapy and combination therapy) is clinically relevant and accompanied by a confidence interval that clearly favors metformin.

3.2 Evaluation of Safety

There are several parameters that have been shown in adults to change with rosiglitazone treatment. Changes seen with adults include increases in lipid parameters, decreases in HCT/Hb and increases in weight. These changes are likewise seen for children (see Table 3.2) however the lipid changes are more variable and do not consistently show increases. The large standard deviations, the lack of repeated values on study (lipids were only measured at baseline and Week 24) and the small sample size may have contributed to the poor estimates of change in lipids.

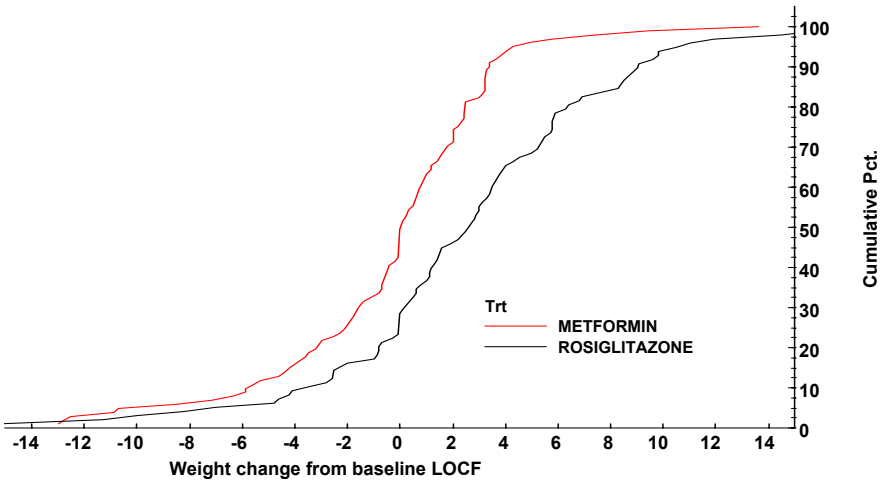
Average increases in weight of about 2 to 3 kg are seen for rosiglitazone patients regardless of age; the largest weight gains (median of 4 kg) are seen for patients starting in the lowest tertile of baseline weight (see Appendix 6.5).

Table 3.2.1 Change from baseline Week 24 LOCF for weight, hemoglobin and lipid parameters.

	Prev Treated		Naive	
	Metformin (n=49)	Rosiglitazone (n=43)	Metformin (n=52)	Rosiglitazone (n=56)
Weight Ch (kg)				
Mean (SD)	+0.6 (4.3)	+2.4 (4.9)	-1.1 (4.1)	+2.9 (5.7)
25%	-0.5	0	-3.4	0
50%	+1.2	+1.6	-0.5	+3
75%	+2.5	+5.5	+1.0	+6.3
Range	-12 to +14	-10 to +16	-13 to +9.4	-15 to +16
Hemoglobin Ch				
Mean (SD)	-0.25 (1.0)	-0.39 (0.7)	+0.01 (0.6)	-0.15 (0.8)
Range	-5.8 to 1.6	-1.7 to 1.0	-1.3 to 1.6	-2.1 to 1.5
Lipids	n=35	n=32	n=45	n=47
TC	+0.9% (20)	+2.1% (15)	+1.7% (17)	+1% (18)
LDL	+9.4% (48)	-4.7% (14)	+5.9% (37)	+14% (90)
HDL	+7.9% (22)	+2.2% (24)	+2.9% (27)	+7% (32)

The cumulative distribution plot below illustrates the treatment difference in weight gain with larger gains indicated by a shift to the right of the rosi curve (p<.0001, Wilcoxon test, Figure 3.2.1).

Figure 3.2.1 Cumulative distribution plot of weight change from baseline at Wk 24 LOCF



Decreases in HCT and Hb (see table above) are seen in the rosiglitazone group (p=0.09 for comparison to metformin). The correlation between weight gain and decreases in hemoglobin was weak.

The effect of medications on growth in a pediatric population is important to examine. In this application, height was poorly measured as demonstrated by 11% of the children having a reported decrease in height of 1 cm or more at the end of treatment. About 40% of patients had no change or a decrease in height over the 6 month treatment period. In the future, to assess effects on growth rates, the applicant should record height velocity as a score standardized for gender and age.

This reviewer looked at the changes in HCT, weight and LDL by dose and found no dose related changes for rosiglitazone in this titration study

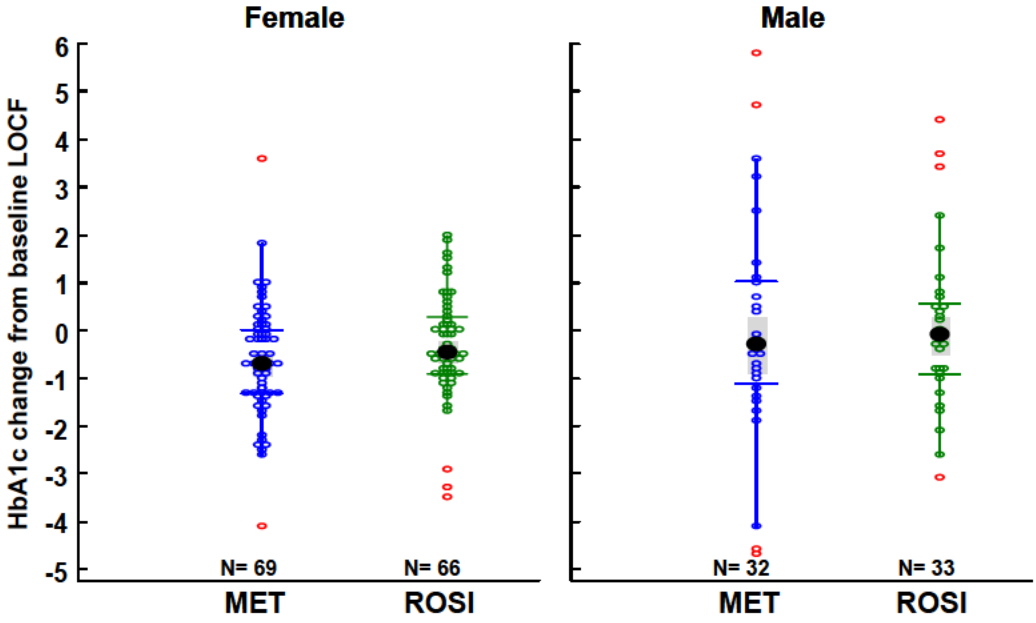
4. Findings in Special/Subgroup Populations

For the presentation of the results by subgroups, the data is not shown for naïve patients and previously treated patients separately. Further subgrouping would result in small numbers of patients to interpret in each treatment group.

4.1 Gender, Race and Age

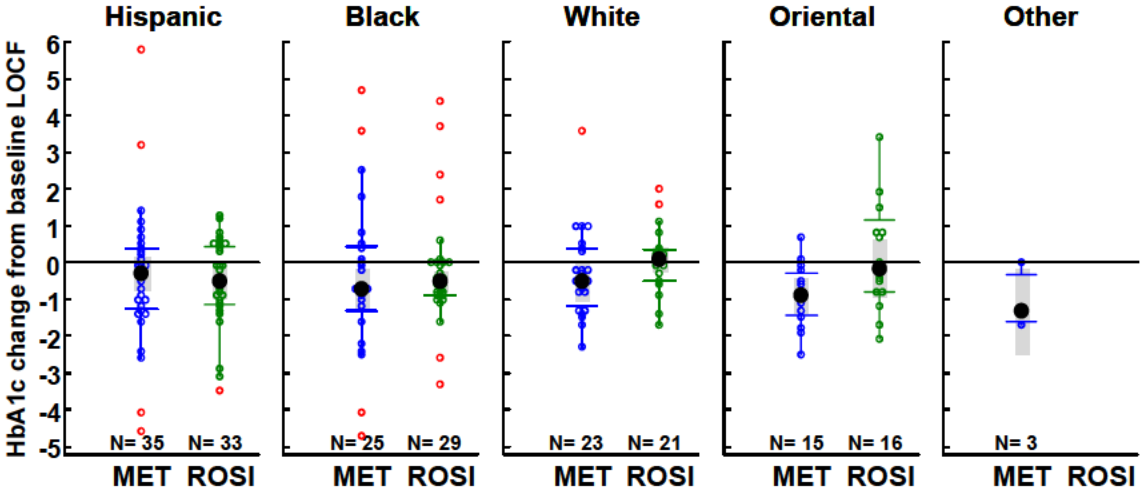
The interaction of treatment and gender was not significant (p=0.22); generally in the adult population a significantly larger treatment effect has been seen for females than males.

Figure 4.1.1 HbA1c change from baseline Week 24 LOCF by gender



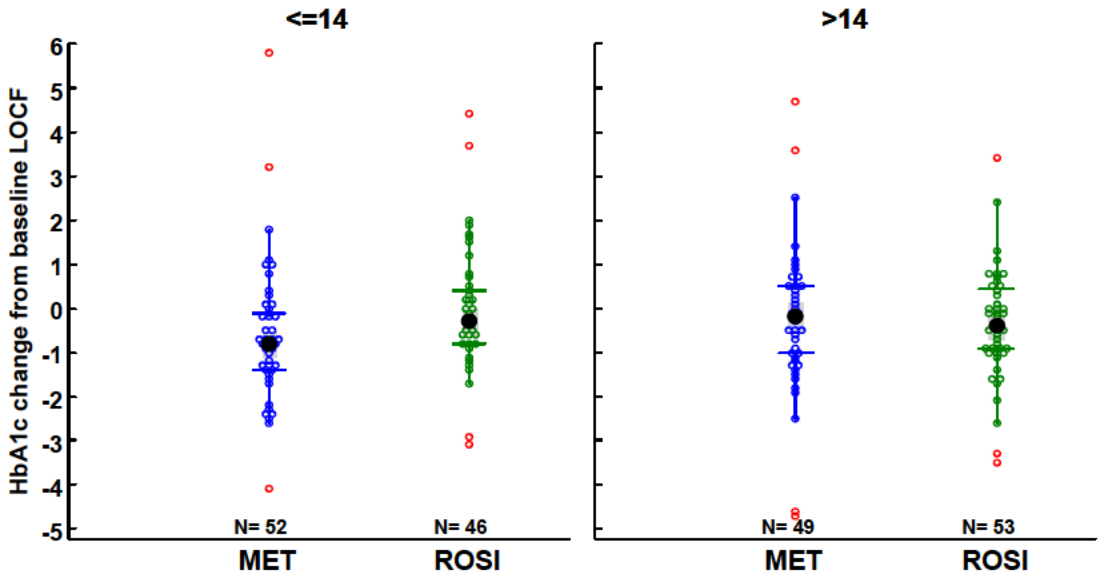
The largest racial group in this pediatric study was Hispanic with about a third of the patients; this group also had the largest treatment effect in favor of rosiglitazone. The interaction of race and treatment was not statistically significant.

Figure 4.1.2 HbA1c change from baseline Week 24 LOCF by race



Patients ranged in age from 8 to 17 (see Appendix 6.2). The interaction of median age by treatment was borderline significant with a p-value of 0.09. If weight is taken into consideration, the treatment effect for younger patients is more favorable to rosiglitazone for heavier patients.

Figure 4.1.3 HbA1c change from baseline Week 24 LOCF by median age

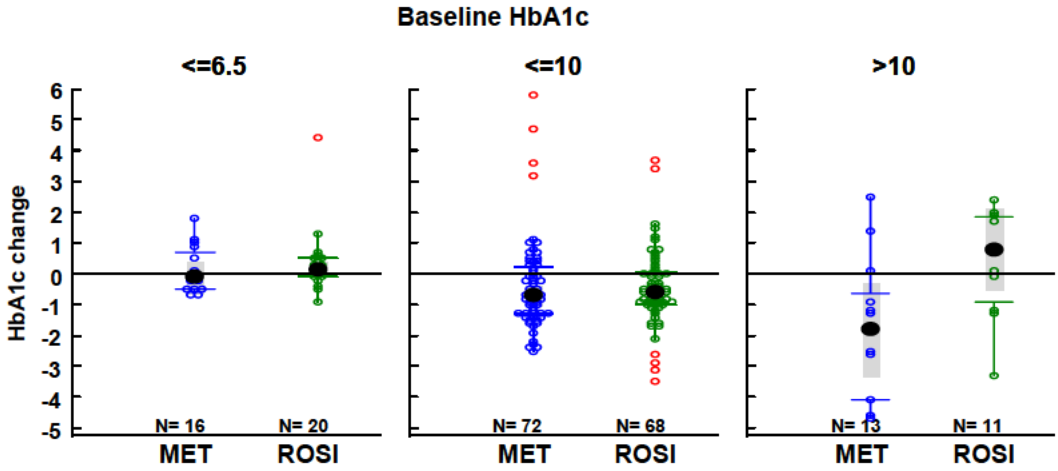


4.2 Other Special/Subgroup Populations

Baseline HbA1c was a stronger predictor of response in the metformin group (r=-0.31, p=0.001) than in the rosiglitazone group (r=-0.01, p=0.91); however, there was no significant baseline*treatment interaction (p>0.5).

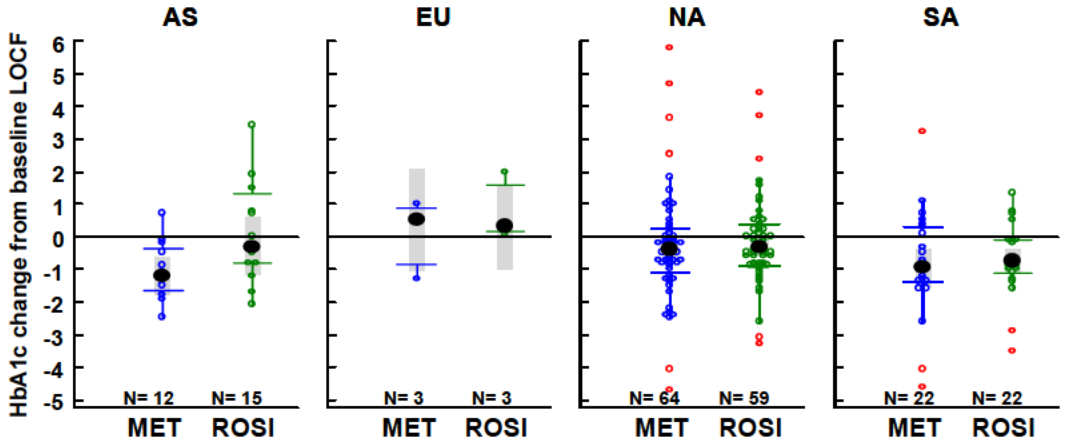
The entry criteria required patients to have an HbA1c at screening of greater than 6.5. A total of 36 patients had an HbA1c of 6.5 or lower at baseline and therefore would not have qualified for the trial. Boxplots of change from baseline show that patients with low HbA1c at baseline reap little benefit, as would be expected. Though the sample size is very small, patients with a large HbA1c of greater than 10 appear also to receive little benefit from rosiglitazone treatment; more patients would be required to determine if this observation is valid.

Figure 4.2.1 HbA1c change from baseline Week 24 LOCF by race



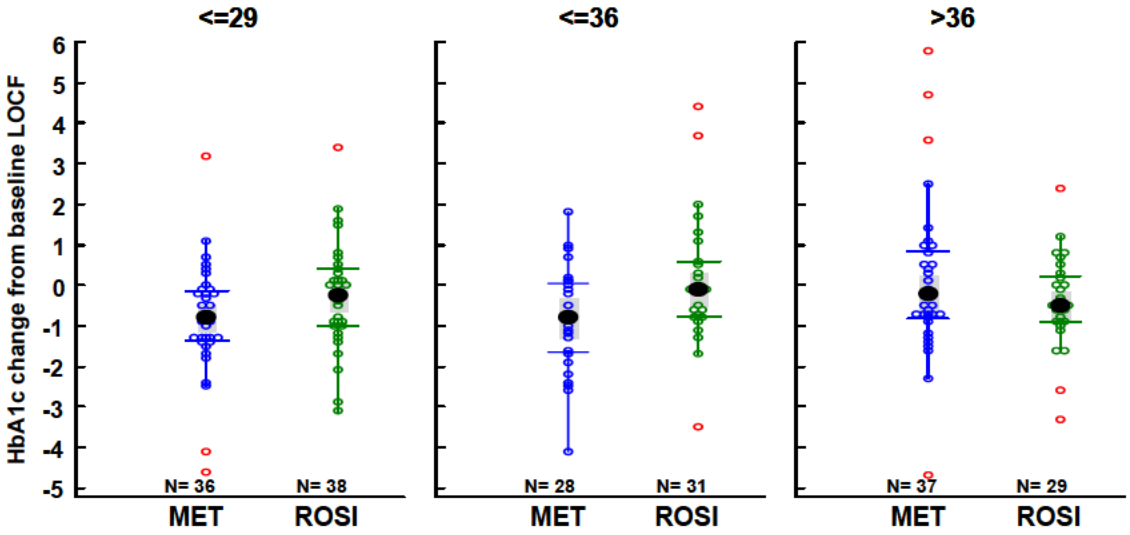
The treatment by region interaction was highly significant (p=0.02). The interaction appears to be primarily quantitative with only 6 European patients showing a reverse effect (i.e. rosiglitazone better than metformin).

Figure 4.2.2 HbA1c change from baseline Week 24 LOCF by region



The treatment by BMI (by tertiles) interaction was highly significant (p=0.02) with heavier pts responding better to rosiglitazone. This finding is consistent with the adult data where overweight patients showed larger treatment effects than normal weight patients.

Figure 4.2.3 HbA1c change from baseline Week 24 LOCF by bmi tertiles



5. Summary and Conclusions

5.1 Statistical Issues and Collective Evidence

[Note that this section is identical to Section 1.3 of this review.]

The protocol named the within-group change from baseline for rosiglitazone as the primary efficacy comparison and named the non-inferiority comparison of rosiglitazone to metformin as a secondary comparison. The FDA Written Request for a pediatric study asked for the non-inferiority comparison as primary. (b) (4)

Enrollment criteria were applied only at the screening visit and not at the baseline visit. As a result the patient population included patients (about 30) who reached an HbA1c level of 6.5 or less (a level at which patients would not be ordinarily treated). This reviewer performed an analysis excluding these patients and these are the results recommended for labeling (see Table 3.1.8 for a full description of these results).

The subgroup results are generally consistent with what we have observed in the adult population. Patients with higher BMI's tend to have a higher response on rosiglitazone and patients gain about 2-3 kg on average with a larger gain seen in naïve patients. The weight gain should be carefully described with the results in the labeling in order to provide a clearer risk benefit assessment. Lipid changes were erratic and not consistent with what has been seen in other rosiglitazone studies; this may be due to few measurements being made and the small sample size.

5.2 Conclusions and Recommendations

[Note that this section is identical to Section 1.1 of this review.]

Pediatric Study 207, designed to assess the efficacy of rosiglitazone for the treatment of Type 2 diabetes, is underpowered to show non-inferiority of rosiglitazone to metformin. With 97 patients in each group of the ITT population, the power is only 53% to rule out a difference of 0.4 or greater. So by design, this study was not likely to show comparability of the two treatment groups. The results bear this out with no analyses showing rosiglitazone non-inferior to metformin by an HbA1c change from baseline margin of 0.4% or less. This lack of power is not uncommon in pediatric studies where recruitment of patients is difficult.

Although no analyses show rosiglitazone to be non-inferior to metformin, labeling for this pediatric study is warranted in order to provide information to physicians on the use of rosiglitazone in a pediatric population. This reviewer recommends that the results for naïve patients be emphasized in the labeling since the results for previously treated patients are notably more favorable to metformin (treatment effects in favor of metformin greater than 0.4%) while the results for naïve patients are more ambiguous (see Table 3.1.8 on page 13). This reviewer also recommends that weight gain data accompany the efficacy results in labeling since weight gain in a pediatric population often suffering from obesity may be a consideration in use of the drug.

6. Appendices

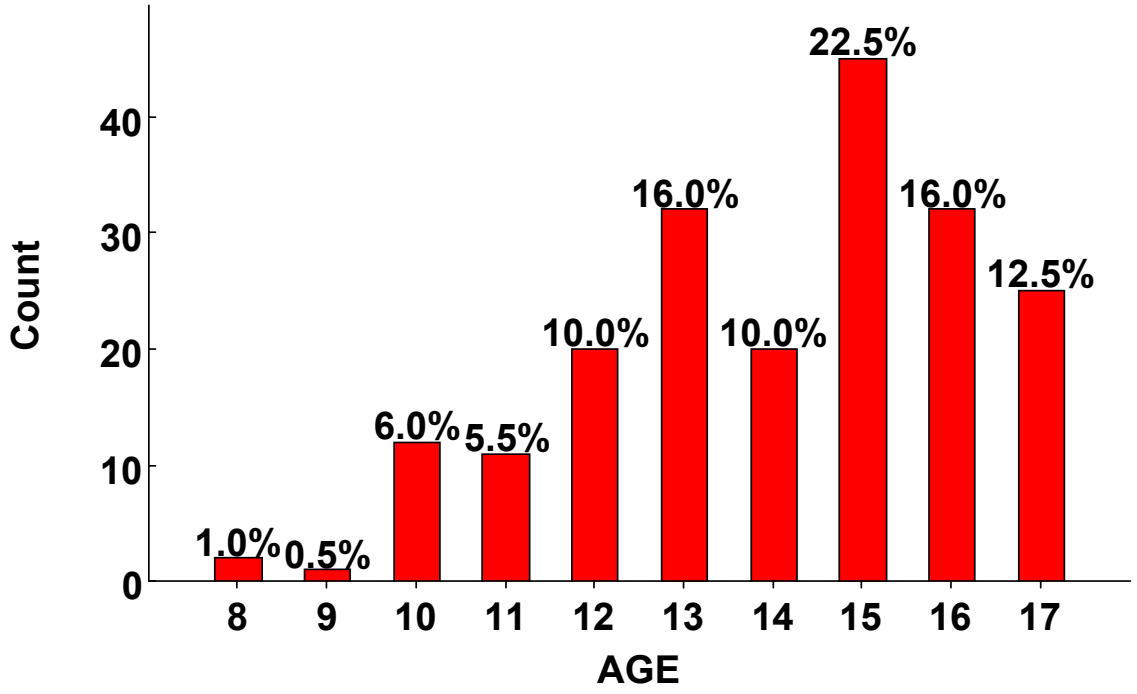
6.1 Dietary instructions

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.

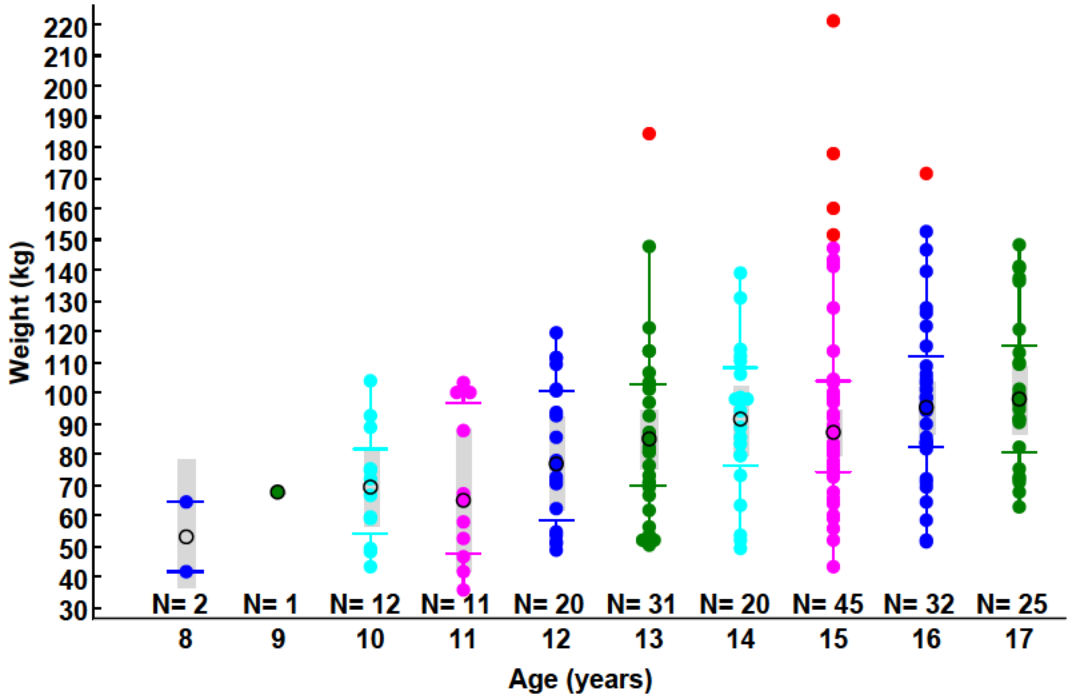
6.2 Histogram of age at baseline

Note that age was recorded as whole numbers in the database.

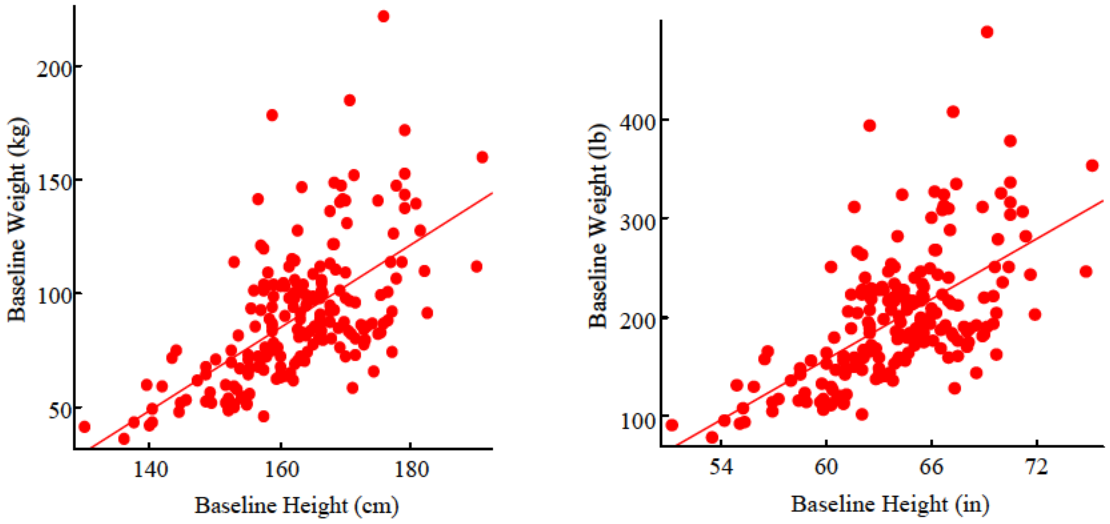


6.3 Baseline Weight

Baseline weight by age

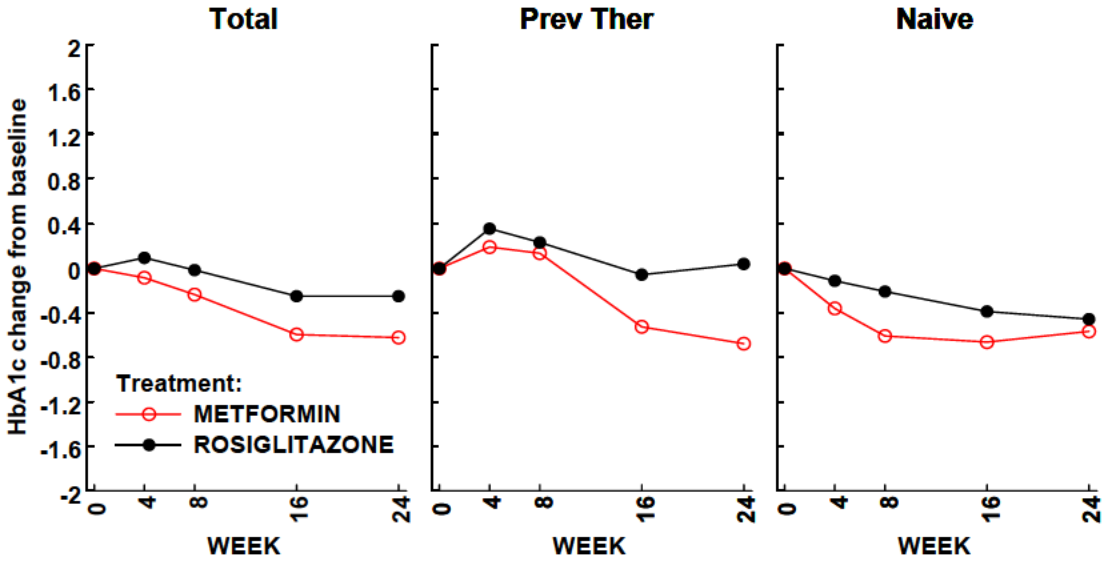


Baseline weight by height (metric and US)

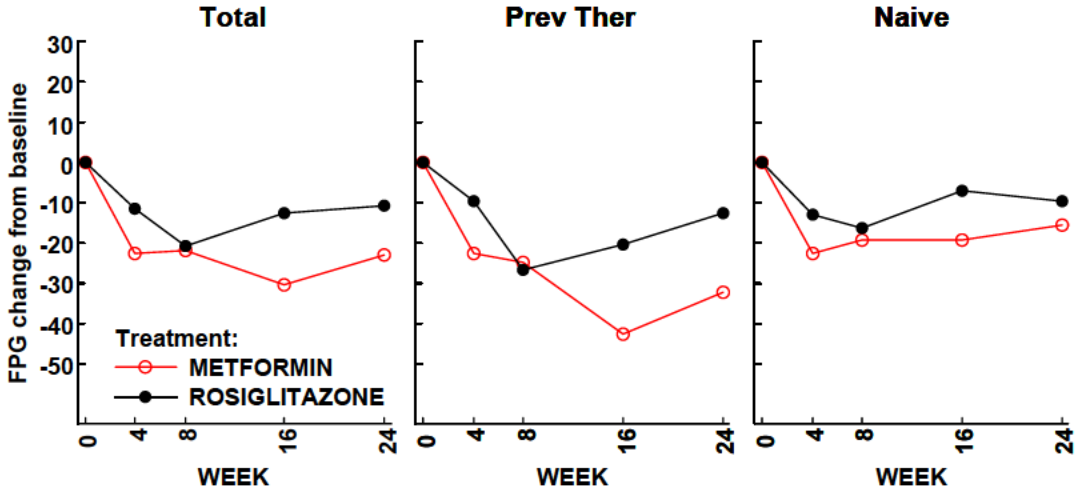


6.4 Changes from baseline (observed cases) for HbA1c and FPG overtime

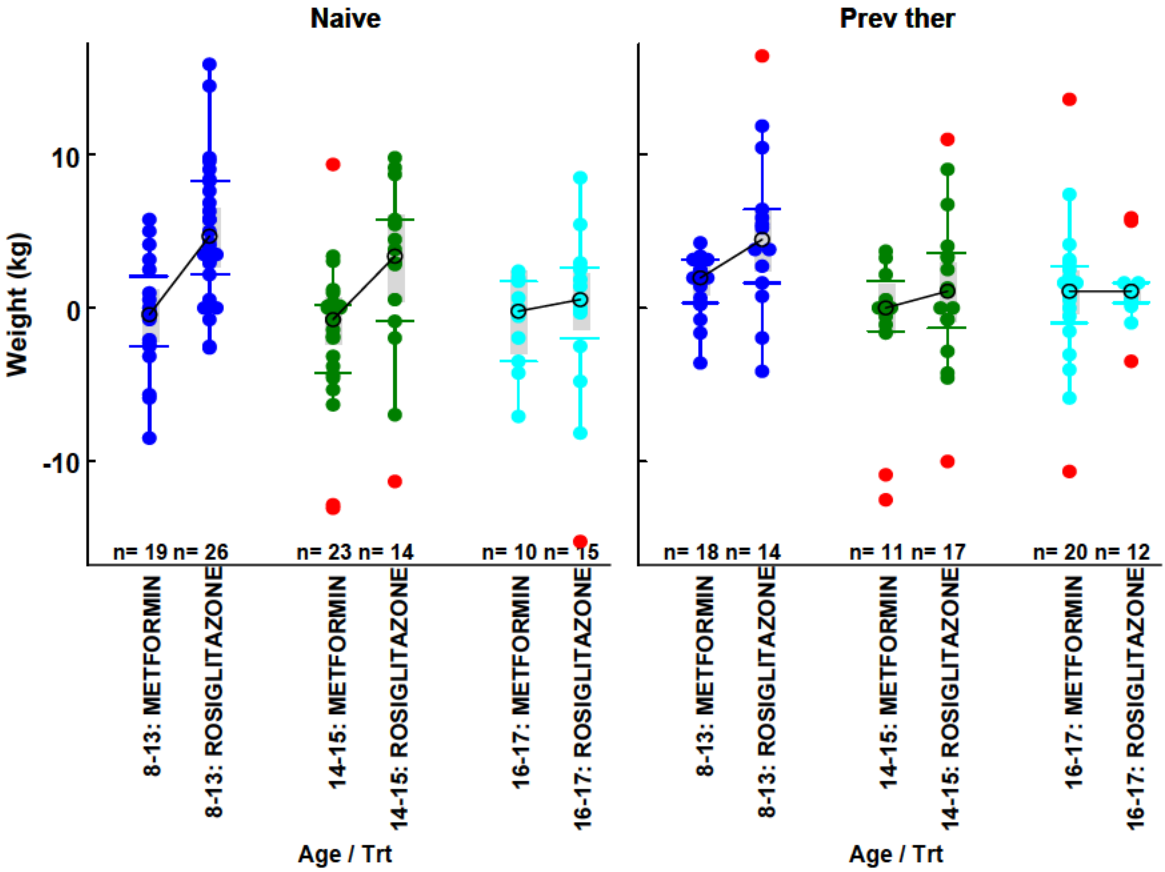
HbA1c change from baseline



FPG change from baseline



6.5 Weight change from baseline by age, treatment and previous diabetic therapy



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