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

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| NDA: | 20-496/SE5-015 |
| Name of drug: | Amaryl (Glimepiride) |
| Indication: | Antidiabetric |
| Applicant: | Aventis |
| Dates: | Stamped 03/15/05 |
| Review priority: | P |
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Keywords: NDA review, clinical studies, pediatric exclusivity

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# 1 EXECUTIVE SUMMARY

## 1.1 CONCLUSIONS AND RECOMMENDATIONS

Glimepiride and metformin were both effective in achieving glycemic control from baseline to endpoint in pediatric subjects with type 2 diabetes mellitus, as demonstrated by statistically significant decreases in HbA1c from baseline. However, glimepiride was not shown to be non-inferior to metformin according to the criterion specified in the protocol with or without excluding protocol violators (i.e. subjects taking anti-diabetic treatment with the study medication).

Of the safety population, 81% (115/142) glimepiride and 82% (117/142) metformin completed at least 18 weeks of treatment. Seventy three percent (104/ 142) glimepiride and 75% (107/ 142) metformin- subjects completed the study. A similar proportion met the criteria for the completer population: 75% (107/ 142) glimepiride and 78% (111/ 142) metformin subjects were completers. However, of the 142 subjects in the safety population treated with metformin, only 54 subjects received 1000 mg bid at the end of the study, and only 45 subjects in the safety population treated with metformin who completed 18 weeks of blinded treatment received 1000 mg bid at the end of the study. This has led to some concern with the high number of patients not achieving the full dose potential at the end of the study.

In terms of the secondary outcome variables, there was no significant difference between treatments in mean decreases in fasting SMBG from baseline to each visit for the per-protocol, ITT or safety subjects. There was no significant difference between treatment groups in changes from baseline for total cholesterol, HDL cholesterol, and triglycerides in the per-protocol, ITT or safety subjects as well. A statistically significant difference was observed between glimepiride and metformin in their changes in the calculated LDL cholesterol from baseline in the per-protocol population. However, the change from baseline within each group was not significant; a non-significant increase from baseline was observed with glimepiride and a non-significant decrease was observed with metformin. When LDL cholesterol values were imputed where data were not reported by the laboratory, the difference between the 2 treatment groups in the per-protocol population was not significant. A small and non-significant increase from baseline in was observed at Week 24 in the glimepiride (per-protocol, ITT and safety) subjects, and a decrease in BMI that was statistically significant was observed in the metformin (per-protocol, ITT and safety) group. However, no significant difference between treatments for changes in BMI from baseline to Week 24 was observed for the per-protocol subjects, while there appears to be a statistically significant difference between treatments for the ITT and safety subjects.

## 1.2 BRIEF OVERVIEW OF CLINICAL STUDIES

The primary objective of this statistical review is to assess the accuracy of the data, to assess the computation techniques used by the applicant and to assist the medical officer Dr. Robert Misbin with his clinical review of the efficacy and safety of Amaryl (Glimepiride) as an alternative choice for initial therapy in adolescents with Type 2 diabetes mellitus (DM). This includes detailed evaluations and treatment comparisons in the change in glycemic control from baseline to endpoint (last available post-treatment assessment) as measured by HbA1c in pediatric subjects with type 2 diabetes receiving either glimepiride or metformin as monotherapy. Re-evaluation of study results by dose for both metformin and glimepiride at 18 weeks, as well as by previous anti-diabetic use, was also conducted.

The focus of this review is on one clinical study (HOE 490/4038) conducted by the Applicant. Data from this study have been re-analyzed and will be discussed in this review.

### 1.3 STATISTICAL ISSUES AND FINDINGS

No major statistical issues were identified after reviewing this pediatric supplement. However the quality of data provided by the applicant and the choice of study population used in the primary efficacy analysis can still be improved upon and corrected. These issues are discussed in detail in section 5.1.

## 2 INTRODUCTION

### 2.1 OVERVIEW

This is a review of the clinical data in pediatric patients with Type 2 Diabetes as submitted in the supplemental new drug application, NDA 20-496 (SE5/015) for Glimepiride as Monotherapy. The aim of the study was to demonstrate that glimepiride, with its favorable safety profile, is an appropriate, alternative choice for initial therapy in adolescents with type 2 diabetes. This study evaluated glimepiride and metformin therapy for both safety and efficacy in this patient population.

The applicant, Aventis, Inc. is seeking FDA approval to market Amaryl (Glimepiride) in children 8 to 17 years of age with Type 2 Diabetes. One pediatric study has been conducted in accordance with the requirements of the written request for pediatric studies (WR) submitted on December 31, 2001 and subsequent revisions issued on August 23, 2002, November 13, 2003, and March 19, 2004 to support the claim of pediatric exclusivity.

The submission contains one clinical study (HOE 490/4038) conducted in the pediatric/adolescent population and will be the focus of this review.

### 2.2 DATA SOURCES

This statistical review is based on data submitted in study HOE 490/4038.

The electronic submission of this NDA can be found at:
\\Cdsesub1\n20496\S_015\2005-03-14

The clinical study report for study HOE 490/4038 is located at
\\Cdsesub1\n20496\S_015\2005-03-14\clinstat

The electronic dataset is found under
\\Cdsesub1\n20496\S_015\2005-03-14\crt\datasets\4038

## 3 STATISTICAL EVALUATION

A detailed clinical review of the efficacy and safety of Amaryl (Glimepiride) can be found in Dr. Robert Misbin's review.

## 3.1 EVALUATION OF EFFICACY

### 3.1.1 STUDY DESIGN AND ANALYSIS PLAN

Study HOE 490/4038 was a 26-week (two weeks screening and 24 weeks treatment), multinational, randomized, single-blind (patient only), parallel-group, active-treatment controlled Phase IIIb study in pediatric subjects with type 2 diabetes who had not responded adequately to two weeks of treatment with diet and exercise before randomization, or to at least 3 months of treatment with oral therapy in conjunction with diet and exercise. Subjects whose HbA1c values were > 7.1% and < 12.0% after a 2- week stabilization period were stratified by age (<= 12 years old and > 12 years old) and randomized in a 1: 1 ratio to receive either oral glimepiride or metformin for 24 weeks (12-week titration period and 12-week maintenance period). Subjects were started on glimepiride 1 mg daily and titrated every 4 weeks for up to 3 visits (Week 12) by doubling the dose until the mean fasting SMBG as determined from the SMBG over 3- 5 days before the scheduled visit was < 7.0 mmol/ L (< 126 mg/ dL) or to a maximum of 8 mg daily. The dose was decreased once to the preceding dose in the event of hypoglycemia. Subjects who experienced hypoglycemia with the 1 mg dose were discontinued from the study. Metformin was started at a 500 mg tablet twice daily and titrated only at Week 12 by doubling the dose to 1000 mg twice daily ( 2 tablets twice daily) if the SMBG was >= 126 mg/ dL. Metformin dose was decreased only once by 500 mg after Week 12 if hypoglycemia or GI adverse events occurred. The target SMBG was changed from < 7.8 mmol/ L (140 mg/ dL) to < 7.0 mmol/ L (126 mg/ dL) in Protocol Amendment V.

The primary objective of the study was to compare the change in glycemic control from baseline to endpoint (last available post-treatment assessment) as measured by hemoglobin A1c (HbA1c) in pediatric subjects with type 2 diabetes receiving either glimepiride or metformin as monotherapy.

The secondary objectives were (1) to assess any differences in fasting self- monitored blood glucose (SMBG), fasting plasma lipids ( total cholesterol, low- density lipoprotein [ LDL] cholesterol, high- density lipoprotein [ HDL] cholesterol, and triglycerides), and percent completers between pediatric subjects who received glimepiride versus metformin as monotherapy; and (2) to compare the safety of glimepiride versus metformin as monotherapy by assessing episodes of hypoglycemia, body weight, vital signs, adverse events, menstrual patterns, and laboratory values. The secondary objectives were amended in Protocol Amendment V to state that differences in fasting SMBG, and not FPG, would be assessed.

The primary endpoint was the change in HbA1c from baseline to Week 24 or last evaluable on treatment value. The HbA1c was determined at Screening (Visit 1), Baseline (Visit 2), Week 12 (Visit 5), and Week 24 (Visit 7), or at study discontinuation.

The per-protocol[1] population was the primary population chosen by the Applicant for which all efficacy analyses were performed. Pre-specified analyses were also conducted on the intent-to-treat and completer populations. All statistical tests were 2- sided and performed at a significance level of $\alpha = 0.05$. Treatment effect for the primary analysis of change in HbA1c from baseline to endpoint was analyzed using an analysis of covariance (ANCOVA), with change from baseline to endpoint as the dependent variable, treatment and pooled countries and Tanner stage as fixed effects, and the corresponding baseline value as a covariate. Using a non-inferiority hypothesis testing approach, the null hypothesis was rejected if the upper limit of the 95% confidence interval (CI) for the treatment difference was < 0.3%.

[1] Per Protocol Population: all intent-to-treat subjects who took their study medication for at least 126 days (i.e. to Week 18), who had an evaluable HbA1c measurement at that time, and had no major protocol deviation.

A variety of secondary endpoints were assessed by the Applicant that includes:

1. Change in HbA1c from baseline to Week 12.
2. Responder rate, defined as the proportion of subjects with HbA1c < 7.0% at Week 24 or the last evaluable on- therapy observation.
3. Mean change in fasting SMBG from baseline to each visit at weeks 4, 8, 12, 18 and 24 or last evaluable on- treatment value. Fasting SMBG was measured daily by the subject who had been trained on and provided with a glucose meter (Roche Diagnostic Accucheck Advantage or Accucheck Active).
4. Mean change in fasting plasma glucose (FPG) from baseline to each visit at weeks 4, 8, 12, 18 and 24 or last evaluable on- treatment value. Blood samples were collected for FPG at visit weeks 0, 4, 8, 12, 18, and 24, or at study discontinuation.
5. Percent completers, which was defined by subjects who continued study medication until completion of all requirements of Visit 6 (Week 18).
6. Mean change in lipid levels (total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides) from baseline to Week 24 or last evaluable on- treatment value. Plasma lipids were determined at Visit 2 (Week 0) and Visit 7 (Week 24), or at study discontinuation.
7. Mean change in body mass index (BMI) from baseline to Week 12 and Week 24 or last evaluable on-treatment value. Weight was measured at baseline, Week 12, and Week 24 or study discontinuation, and height was measured at baseline and Week 24 or study discontinuation.

Statistical tests for the secondary objectives include ANCOVA for continuous variables; as well as the Cochran Mantel Haenszel procedure controlling for pooled countries and by logistic regression controlling for pooled countries and Tanner stage stratum, for the categorical variables.

### 3.1.2 SUMMARY OF APPLICANT'S RESULTS AND CONCLUSION

The following summarizes some of the applicant's results (based on per-protocol population) and conclusions:

> Glimepiride and metformin were both effective and safe in achieving glycemic control in pediatric subjects with type 2 diabetes mellitus. Of the safety population, 73% (104/ 142) glimepiride and 75% (107/ 142) metformin- subjects completed the study. A similar proportion met the criteria for the completer population: 75% (107/ 142) glimepiride and 78% (111/ 142) metformin subjects were completers.
>
> Effective glycemic control from baseline to endpoint, as demonstrated by statistically significant decrease in HbA1c, occurred with glimepiride (P=0.0034) and metformin (P=0.0001). No significant difference was observed between treatment groups in the change in HbA1c from baseline to Week 24, the proportion of subjects who achieved HbA1c <= 7.0%, or the time to achieve this endpoint. The non-inferiority criterion was not met, very likely due to the wide variance observed in the subjects that resulted in low power. There was no significant difference between treatments in the change from baseline to endpoint for HbA1c.
>
> No significant difference was seen between treatments in the number of subjects who achieved a last on- treatment HbA1c value <= 7.0% or in their time to achieve HbA1c <= 7.0% There was no significant difference between treatments in mean decreases in fasting SMBG from baseline to each visit. There was no significant difference between the 2 groups in the proportion of subjects achieving SMBG <= 7.0 mmol/ L, or in their time to reach this endpoint. There was no significant difference between treatment groups in changes from baseline for total cholesterol, HDL cholesterol, and triglycerides. A statistically significant difference was observed between glimepiride and metformin in their changes in LDL cholesterol from baseline (P=0.0415). However, the change from baseline

within each group was not significant; a non-significant increase from baseline was observed with glimepiride and a non-significant decrease was observed with metformin. There was no significant difference between treatments for changes in BMI from baseline to Week 24 for the per- protocol subjects.

In terms of safety, both glimepiride and metformin were well- tolerated. There were no deaths, pregnancies, study medication overdoses, or clinically important laboratory changes. Adverse events were reported with similar frequencies for the glimepiride and metformin treatment groups. The most commonly reported (> 5%) TEAEs in the glimepiride treatment arm were headache (15/ 142 [10.6%]), upper respiratory tract infection (10/ 142 [7.0%]), nasopharyngitis (9/ 142 [6.3%]), and hyperglycemia (8/ 142 [5.6%]). In the metformin treatment arm, the most commonly reported TEAEs included headache (17/ 142 [12.0%]), upper respiratory tract infection (9/ 142 [6.3%]), diarrhea (11/ 142 [7.7%]), and nasopharyngitis (10/ 142 [7.0%]). Most TEAEs were of mild and moderate intensity. The most frequent possibly treatment- related events were events listed in current labeling for each product. Serious adverse events occurred during study treatment in 12 subjects (7 Glimepiride and 5 Metformin). The incidence of serious adverse events and discontinuations from study medication due to an event were similar and low for the 2 groups.

Hypoglycemic episodes occurred at a similar rate in each group (16% glimepiride and 13% metformin). One subject in each group had a severe episode. A mean weight increase of 1.3 kg with glimepiride was statistically significant. Vital signs and menstrual patterns were unchanged.

### 3.1.3 DETAILED REVIEW OF STUDY 4038

A detailed review of Study 4038 is presented in this section. Interpretation of findings is based wholly on statistical interpretation of the results. **I defer all clinical interpretations to Dr. Misbin's review**.

The written request (WR) sample size estimated to be 75 subjects per group was based on safety considerations from the medical reviewer (Dr. Misbin) and not on the non- inferiority hypothesis testing of the primary efficacy variable. Using the non-inferiority margin of 0.3% specified in the WR and standard deviation of 1.2, you need 256 subjects per treatment group in order to achieve 80% power. If a non-inferiority margin of 0.4% is used, a margin applied more recently by the Division in trials with metformin as the active comparator, and with a standard deviation of 1.2, then 144 subjects per treatment group will give 80% power. This number (i.e. 144 subjects per treatment group) is roughly the number of subjects that was randomized

Note that in a letter from the FDA dated April 14, 2004, and received April 19, 2004, the minimum number of subjects to be studied and to complete 18 weeks of treatment was amended to 50 subjects per group instead of 75 subjects per group. This new sample size will be discussed further later in the review.

A total of 536 subjects were enrolled and screened at 96 sites, and the numbers of subjects that constituted the safety, ITT, completer, and per- protocol study populations are summarized in Table 1. Of the 536 subjects screened, 251 were not randomized, primarily due to failure to meet entry criteria. Of the 285 subjects who were randomized at 78 sites (143 to glimepiride and 142 to metformin), 1 subject (0013001) assigned to metformin withdrew before receiving any study medication, resulting in 284 subjects in the safety population. One subject (0003005) was assigned to glimepiride treatment and received metformin; this subject was not included in the efficacy populations due to the lack of at least 1 evaluable HbA1c during study and is included in the safety population as a metformin- treated subject.

Of the 284 subjects in the safety population, 73% (104/ 142) glimepiride- treated and 75% (107/ 142) metformin-treated subjects completed the study. A total of 73 subjects (38 glimepiride and 35 metformin) withdrew from the study. The most common reasons for withdrawal were treatment failure (13

subjects in each group), adverse events (6 glimepiride and 5 metformin), not wishing to continue (5 glimepiride and 7 metformin), and lost to follow up (5 glimepiride and 7 metformin).

Table 1: Disposition of Patients

| | Total | Glimepiride | Metformin |
|---|---|---|---|
| Screened | 536 | | |
| Non-randomized Patients | 251 (47%) | | |
| Inclusion/exclusion criteria not respected | 241 (96%) | | |
| Adverse event | 1(0%) | | |
| Withdrawal of consent | 4 (2%) | | |
| Lost to follow-up | 1 (0%) | | |
| Other | 4 (2%) | | |
| Randomized Population | 285 | 143 | 142 |
| Safety[1] Population | 284 | 142 | 142 |
| Completed | 263 (93%) | 132 (93%) | 131 (92%) |
| Discontinued | 20 (9%) | 10 (7%) | 11 (8%) |
| Disease progression/lack of efficacy | 3 | 2 | 1 |
| Adverse event | 2 | 1 | 1 |
| Poor compliance to protocol | 2 | 2 | 0 |
| Investigator/subject's request | 6 | 1 | 5 |
| Subject's loss to follow-up | 6 | 2 | 4 |
| Other reason | 2 | 2 | 0 |
| ITT[2] population (corrected) | 263 | 132 | 131 |
| Completer[3] Population | 211 | 104 (73%) | 107 (75%) |
| Non-Completer Population | 73 | 38 (27%) | 35 (25%) |
| Disease progression/lack of efficacy | 26 | 13 | 13 |
| Adverse event | 11 | 6 | 5 |
| Poor compliance to protocol | 1 | 1 | 0 |
| Investigator/subject's request | 12 | 5 | 7 |
| Subject's loss to follow-up | 12 | 5 | 7 |
| Entry Criteria not met | 2 | 1 | 1 |
| Other reason | 9 | 7 | 2 |
| Per Protocol[4] Population | 162 | 81 | 81 |

[1] Safety: All randomized subjects who received at least 1 dose of study medication.
[2] ITT: All randomized subjects who received at least 1 dose of study medication and had at least 1 on- treatment value for the primary efficacy variable, HbA1c.
[3] Completer: All ITT subjects who took their study medication for at least 126 days (i.e. to Week 18) and had an evaluable HbA1c measurement at that time.
[4] PP: All completer subjects excluding subjects who had at least one major protocol deviation.

The demographic and general baseline characteristics of the safety population, ITT population, and the per-protocol population are presented in Table 2. The mean age of both treatment groups was 14 years across different study populations. The age, sex, and race distributions of the subjects were not different between treatment groups and across different study populations. The distribution of subjects by Tanner stage was also similar for the treatment groups, with larger proportions of subjects at higher Tanner stage. About 40% of subjects in both groups were at Tanner stage V. Note that race and ethnicity information was collected in the CRFs as White, African- American, Black, Asian/ Oriental/ Pacific Islander, Hispanic, multiracial, native American, and other. However, in a letter dated
7 May 2004, the FDA requested that race and ethnicity be classified into specific categories that were different from those of the CRF. As shown in Table 2, race and ethnicity distribution by the CRF and the FDA categories were similar and with no significant difference between the treatment groups.

Table 2: Descriptive Statistics for Demography and Baseline Data

| | Safety Population | | ITT Population | | PP Population | |
|---|---|---|---|---|---|---|
| Variables | Glimepiride | Metformin | Glimepiride | Metformin | Glimepiride | Metformin |
| No. of Subjects* | 142 | 142 | 132 | 131 | 81 | 81 |
| Age (years) | 13.8 (2.3) | 13.9 (2.3) | 13.8 (2.3) | 13.8 (2.3) | 13.7 (2.2) | 13.9 (2.1) |
| Age < 12, N(%) | 26 (18) | 21 (15) | 23 (17) | 21 (16) | 15 (19) | 13 (16) |
| Age >=12, N(%) | 116 (82) | 121 (85) | 109 (83) | 110 (84) | 66 (82) | 68 (84) |
| Sex, N(%) | | | | | | |
| Male | 47 (33) | 47 (33) | 44 (33) | 44 (34) | 25 (31) | 24 (30) |
| Female | 95 (67) | 95 (67) | 88 (67) | 87 (66) | 56 (69) | 57 (70) |
| Race, N(%) | | | | | | |
| White | 19 (13) | 21 (15) | 17 (13) | 21 (16) | 8 (10) | 11 (14) |
| African American | 30 (21) | 30 (21) | 29 (22) | 27 (21) | 17 (21) | 18 (22) |
| Black | 1 (1) | 1 (1) | 1 (1) | 1 (1) | 1 (1) | 0 (0) |
| Asian/PI | 24 (17) | 22 (16) | 23 (17) | 19 (15) | 15 (19) | 11 (14) |
| Hispanic | 57 (40) | 56 (39) | 52 (39) | 52 (40) | 34 (42) | 35 (43) |
| Multiracial | 8 (6) | 7 (5) | 7 (5) | 7 (5) | 4 (5) | 3 (4) |
| Native American | 0 (0) | 2 (1) | 0 (0) | 1 (1) | 0 (0) | 1 (1) |
| Other | 3 (2) | 3 (2) | 3 (2) | 3 (2) | 2 (3) | 2 (3) |
| FDA Race, N(%) | | | | | | |
| White | 20 (14) | 22 (16) | 18 (14) | 22 (17) | 9 (11) | 11 (14) |
| African American | 30 (21) | 30 (21) | 29 (22) | 27 (21) | 17 (21) | 18 (22) |
| Black | 1 (1) | 1 (1) | 1 (1) | 1 (1) | 1 (1) | 0 (0) |
| Asian/PI | 24 (17) | 21 (15) | 23 (17) | 18 (14) | 15 (19) | 11 (14) |
| Hispanic | 57 (40) | 56 (39) | 52 (39) | 52 (40) | 34 (42) | 35 (43) |
| Multiracial | 10 (7) | 9 (6) | 9 (7) | 9 (7) | 5 (6) | 5 (6) |
| Native American | 0 (0) | 2 (1) | 0 (0) | 1 (1) | 0 (0) | 1 (1) |
| Other | 0 (0) | 1 (1) | 0 (0) | 1 (1) | 0 (0) | 0 (0) |
| Tanner Stage, N(%) | | | | | | |
| I | 11 (8) | 11 (8) | 7 (5) | 11 (9) | 4 (5) | 6 (7) |
| II | 9 (6) | 12 (9) | 9 (7) | 11 (9) | 4 (5) | 8 (10) |
| III | 24 (17) | 24 (17) | 24 (18) | 21 (16) | 18 (22) | 13 (16) |
| IV | 42 (30) | 36 (26) | 42 (32) | 34 (26) | 26 (32) | 21 (26) |
| V | 55 (39) | 57 (41) | 49 (37) | 52 (40) | 29 (36) | 33 (41) |

No significant differences were evident between the 2 treatment groups in terms of their diabetes disease (Table 3). In the safety population, about 81% had symptoms of diabetes at study entry. About 76% of subjects had followed a diet and exercise program for about 1 year. About 44% of subjects in each treatment group were receiving drug therapy for their diabetes; about 22% had used insulin for a mean of 14 months (range < 1 month to > 5 years). Baseline variables related to diabetes were also not significant between the treatment groups in the safety, per- protocol or ITT populations. Concomitant medications taken by the safety population consisted of 56% (79/ 142) glimepiride-treated and 51% (73/ 142) metformin-treated subjects.

Table 3: Descriptive Statistics for Diabetes History, Baseline Diabetes Variables, and Concomitant Medications

| | Safety Population | | ITT Population | | PP Population | |
|---|---|---|---|---|---|---|
| Variables | Glimepiride | Metformin | Glimepiride | Metformin | Glimepiride | Metformin |
| No. of Subjects* | 142 | 142 | 132 | 131 | 81 | 81 |
| Symptoms of Diabetes, N(%) | 113 (80%) | 116 (82) | 106 (80) | 105 (80) | 68 (84) | 68 (84) |
| Diet and Exercise, N(%) | 110 (78) | 105 (74) | 102 (77) | 96 (73) | 64 (79) | 57 (70.4) |
| Months, mean (SD) | 12.7 (15.0) | 11.2 (14.4) | 13.0 (15.1) | 10.1 (13.3) | 10.9 (13.7) | 7.5 (11.8) |
| On Diabetes Treatment N(%) | 62 (44) | 63 (44) | 57 (43) | 59 (45) | 34 (42) | 35 (43) |
| Used Insulin, N(%) | 32 (23) | 31 (22) | 27 (21) | 31 (24) | 11 (14) | 17 (21) |
| Months, mean (SD) | 14.2 (16.0) | 13.9 (15.8) | 14.3 (16.4) | 13.9 (15.8) | 8.0 (13.9) | 11.6 (17.5) |
| HBA1c (%) | 8.5 (1.6) | 8.5 (1.6) | 8.5 (1.6) | 8.5 (1.6) | 8.6 (1.3) | 8.7 (1.4) |
| FPG (nmol/L) | 9.7 (3.7) | 9.6 (3.9) | 9.7 (3.7) | 9.6 (3.9) | 9.6 (3.4) | 9.5 (3.6) |
| SMBG (plasma-ref) (nmol/L) | 9.6 (3.4) | 9.3 (3.7) | 9.6 (3.4) | 9.3 (3.7) | 9.6 (3.2) | 9.3 (3.4) |
| Stim. Serum Glucose (nmol/L) | 14.1 (5.1) | 14.2 (5.7) | 14.1 (5.1) | 14.2 (5.7) | 14.5 (4.7) | 14.4 (5.3) |
| Stim. C-peptide (pmol/L) | 2218.8 (1089) | 2153.6 (973.6) | 2218.8 (1089) | 2153.6 (973.6) | 2322.7 (1220) | 2247.3 (1016) |
| Stim. Insulin (pmol/L) | 519.9 (540.5) | 501.8 (487.4) | 519.8 (540.5) | 501.8 (487.4) | 569.6 (627.4) | 507.6 (457.2) |
| BMI ($kg/m^2$) | 31.6 (8.5) | 31.6 (8.2) | 31.6 (8.5) | 31.6 (8.2) | 31.3 (7.1) | 32.6 (8.5) |
| Weight (kg) | 82.6 (25.6) | 83.8 (27.5) | 82.6 (25.6) | 83.8 (27.5) | 81.9 (22.0) | 86.8 (28.5) |
| Concomitant Medications, N(%) | 79 (56) | 73 (51) | | | | |

Primary Outcome Variable:

The primary efficacy variable was the change in HbA1c from baseline to the last scheduled visit at Week 24 or the last post-randomization HbA1c while on treatment or no later than 1 week after the last dose.

The unadjusted and adjusted means and corresponding standard deviation of HbA1c at baseline, at Week 12 and at Week 24 are presented for the per- protocol, ITT, and safety subjects in Table 4. In the per-protocol population, the mean decrease in HbA1c (%) from baseline at 24 weeks in 81 patients with an initial HbA1c range >6 to <12, treated with AMARYL (mean last dose 4 mg) was 0.95 ± 0.41 (unadjusted mean baseline 8.57± 1.3). In 81 patients with an initial HbA1c range >5 to <12 treated with metformin (mean last dose 1469 mg), the mean decrease was 1.39 ± 0.40 (unadjusted mean baseline 8.69 ± 1.4).

There was no statistically significant difference between treatments either at Week 12 or at Week 24 for the per-protocol analysis, ITT analysis, or the safety analysis. Note that the primary analysis tested for non-inferiority with treatment, pooled countries and Tanner stage as fixed effects and baseline HbA1c as a covariate. The adjusted mean treatment difference for the per-protocol population was 0.44% (95% CI - 0.16, 1.05). Because the upper limit of the 95% CI exceeded the predefined limit of 0.3%, the non- inferiority criterion was not met. The non-inferiority criterion was also not met for the ITT subjects using either the observed data 0.29% (95% CI -0.20, 0.78) or LOCF imputed data 0.15% (95% CI -0.34, 0.63), as well as for the safety subjects using either the observed data 0.29% (95% CI -0.20, 0.78) or LOCF imputed data 0.12% (95% CI -0.33, 0.57).

The applicant explained that insufficient power could be the reason for not meeting the non- inferiority criterion. According to the applicant, the sample size for this study was determined based on the assumption that the standard deviation would be 1.2. However, as noted in Table 4, the standard deviations of the mean changes in HbA1c for both treatment groups in the per-protocol analysis (or even in the ITT or safety analysis) was much larger (approximately 2.0), such that the power of the study was only 40%.

As per request of Dr. Misbin, exploratory analysis was conducted to determine the dosage taken by subjects at the end of the study with focus on metformin. Based on the data, average end-of-study dose for metformin was 1469 mg, while the average end-of-study dose for Glimepiride was 4 mg.

According to Dr. Misbin, the dose escalation for Glimepiride was to be based on efficacy, while dose escalation for metformin would be limited by gastrointestinal intolerance. To understand whether glimepiride was non-inferior to the highest metformin dose achieved (i.e. 1000 mg or 2000 mg) at the end of the study, additional analysis was conducted in the per-protocol, ITT, and safety population.

Table 5 presents the number of subjects taking Glimepiride or metformin by highest dose achieved at end of study including subjects who dropped out. Note that the escalated dosing schedule for metformin (500-mg bid initially followed by 1000 mg bid after 12 weeks) was designed to enable as many patients as possible to achieve a full dose. However, as noted in Table 5, titrating the dose of metformin based on fasting blood glucose (FBG) exceeding 126 mg/dl, as was done by the Sponsor, reduced the proportion of patients who achieved a full dose by the end of the study. Using the ITT population, only 54 of the 131 subjects received metformin 1000 mg bid (2000 mg/d). Using the per-protocol population, only 38 of the 81 subjects received 1000 mg bid (2000 mg/d).

Furthermore, the written response (WR) states that "a minimum 50 patients must complete a minimum of 18 weeks of blinded (to the patient) treatment." This added restriction that patients must complete a minimum of 18 weeks of blinded treatment reduced the number of subjects receiving 1000 mg bid (2000 mg/d) at the end of the study (Table 6). Using the ITT population, 117 patients completed 18 weeks of blinded treatment

with metformin but only 45 patients received 1000-mg bid. Using the per protocol population 80 patients completed 18 weeks of blinded treatment with metformin but only 37 patients received 1000 mg bid.

The applicant had submitted Table 7 in response to the Agency's request for dose distribution table. Table 7 presents the dose break down of both metformin (500, 1000, and 2000 mg) and glimepiride (1, 2, 4, 8, & 12 mg) at 18 weeks done by the applicant. Their results were slightly different from my results because of the way they defined "at 18 weeks". They included subjects who dropped out before week 18 in the analysis, while I excluded these subjects in the analysis. I do not think it is appropriate to include subjects who dropped out before week 18 because we are interested in subjects with at least 18 weeks of treatment.

Since the study was not designed to test the treatment difference within dose subgroup (i.e. metformin 1000 mg/d and metformin 2000 mg/d), any conclusion drawn from Table 8 and Table 9 should be handled with care. Any evidence that may result from the analysis of subgroup should be interpreted with caution. In fact, the metformin data are consistent with the classic "U" shaped response curve for titration to effect designs.

Re-analysis of the primary efficacy data suggests that there are some subjects in the safety, ITT, and PP population that were simultaneously taking anti-diabetic medications and the study drug (called ongoing), and subjects that are previous anti-diabetic users or non-naïve patients, called prevuse (Table 10). Note that the variable antidiab was based on the Applicant's study report (T-26, p.175), while the variables prevdiab and ongoing was based on the post-study report and dataset by the Applicant (T-27, p. 176). The variable prevuse is the flag for all the previous antidiabetic users (i.e. antidiab and prevdiab).

From Table 10, there are 12 subjects in the safety population who were clearly protocol violators (Glimepiride 7 and Metformin 5), and should be excluded in the analysis. In the ITT population, 10 subjects were protocol violators with 5 in each treatment group. Out of these 12 subjects, 3 subjects were also in the PP population (Glimepiride 2 and metformin 1). Re-analysis of the primary efficacy variable removing these subjects (Table 11) resulted in similar conclusions with that of the results from the original primary efficacy analysis in Table 4. In the intent-to-treat population, the mean decrease in HbA1c (%) from baseline at 24 weeks in 127 patients with an initial HbA1c range >5 to <13, treated with AMARYL (mean last dose 3.7 mg) was 0.63 ± 0.30 (unadjusted mean baseline 8.46± 1.54). In 126 patients with an initial HbA1c range >5 to <12 treated with metformin (mean last dose 1400 mg), the mean decrease was 0.83 ± 0.30 (mean baseline 8.51 ± 1.53). The adjusted mean treatment difference for the intent-to-treat population was 0.20% (95% CI -0.28, 0.68). Because the upper limit of the 95% CI exceeded the predefined limit of 0.3%, the non- inferiority criterion was also not met. Similar conclusion can be drawn in the per-protocol population. Thus, the data do not establish that AMARYL is non-inferior to metformin with respect to reducing HbA1c.

Dr. Misbin also requested that the primary outcome (i.e. the change in HbA1c from baseline) be analyzed based on whether the subjects had previous anti-diabetic treatment (non-naïve patients) or not (naïve patients). According to my calculation in Table 10, removing subjects with ongoing treatments, there were 43% subjects (55/127) in the glimepiride group, and 45% (57/126) in the metformin group previously treated with anti-diabetic medications in the intent to treat population. The most frequently used previous medications were metformin or insulin products. Table 12 summarized the unadjusted and adjusted means and corresponding standard deviation of HbA1c at baseline, at Week 12 and at Week 24, and the mean treatment difference at weeks 12 and 24 for the per-protocol, ITT and safety population. In the intent-to-treat population, the mean increase in HbA1c (%) from baseline at 24 weeks in the non-naïve patients treated with Glimepiride (mean last dose 4.5 mg) was 0.17± 0.7 (unadjusted mean baseline 8.84 ± 1.5), while non-naïve patients treated with metformin had a mean decrease (mean last dose 1596 mg) of 0.23 ± 0.7 (unadjusted mean baseline 9.05 ± 1.5). In contrast, naïve patients treated with either Glimepiride or metformin had a mean decrease in HbA1c (%) from baseline at 24 weeks. Glimepiride-treated patients (mean last dose 3.1) had a mean decrease of 0.97 ± 0.3 (unadjusted mean baseline 8.17± 1.5), while metformin-

treated patients (mean last dose 1239 mg) had a mean decrease of 1.18 ± 0.3 (unadjusted mean baseline 8.06 ± 1.4). There is an apparent shift in mean change from baseline in the glimepiride group between non-naïve and naïve patients (+0.17 to -0.97). There is also difference in end-of-study dose in the glimepiride group between these two populations (non-naïve: 4.5 mg, naïve: 3.1), as well as in the metformin group (non-naïve: 1596 mg, naïve: 1239 mg).

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Table 4: HbA1c (%): Analysis of Covariance (ANCOVA) Results

| | Unadjusted Mean (SD) | | | | Adjusted Mean Change from Baseline (SE) | | Difference: Glimepiride - Metformin | | |
|---|---|---|---|---|---|---|---|---|---|
| | N | Glimepiride | N | Metformin | Glimepiride | Metformin | Adjusted Mean | 95% CI | p-value |
| Per Protocol | | | | | | | | | |
| Baseline | 81 | 8.57 (1.3) | 81 | 8.69 (1.4) | | | | | |
| Week 12 | 75 | 7.93 (1.9) | 77 | 7.61 (2.1) | -1.04 (0.4) | -1.37 (0.4) | 0.33 | (-0.22, 0.88) | 0.2417 |
| Week 24 | 81 | 7.88 (2.1) | 81 | 7.46 (2.1) | -0.95 (0.4) | -1.39 (0.4) | 0.44 | (-0.16, 1.05) | 0.1499 |
| Intent-to-Treat | | | | | | | | | |
| Baseline | 132 | 8.52 (1.6) | 131 | 8.54 (1.6) | | | | | |
| Week 12 | 120 | 7.98 (1.9) | 124 | 7.89 (2.5) | -0.69 (0.3) | -0.76 (0.3) | 0.07 | (-0.37, 0.52) | 0.7488 |
| Week 24 | 114 | 7.89 (2.1) | 118 | 7.66 (2.3) | -0.85 (0.3) | -1.14 (0.3) | 0.29 | (-0.20, 0.78) | 0.2474 |
| Week 24 (LOCF) | 132 | 7.99 (2.1) | 131 | 7.83 (2.5) | -0.70 (0.3) | -0.84 (0.3) | 0.15 | (-0.34, 0.63) | 0.5525 |
| Safety Population | | | | | | | | | |
| Baseline | 142 | 8.46(1.6) | 142 | 8.62 (1.6) | | | | | |
| Week 12 | 124 | 7.98 (1.9) | 124 | 7.89 (2.5) | -0.69 (0.3) | -0.76 (0.3) | 0.07 | (-0.37, 0.52) | 0.7488 |
| Week 24 | 118 | 7.86 (2.1) | 118 | 7.66 (2.3) | -0.85 (0.3) | -1.14 (0.3) | 0.29 | (-0.20, 0.78) | 0.2474 |
| Week 24 (LOCF) | 142 | 7.96 (2.1) | 142 | 7.97 (2.5) | -0.59 (0.3) | -0.71 (0.3) | 0.12 | (-0.33, 0.57) | 0.5987 |

Analysis of covariance with treatment, country, and tanner stage effects and the corresponding baseline value as covariate was used for the change from baseline

Table 5: (From Data provided) Number of subjects taking Glimepiride and metformin by highest dose achieved **at end of study (including those who dropped out)**

| | Glimepiride | | | | Metformin | | |
|---|---|---|---|---|---|---|---|
| | 1 mg | 2 mg | 4 mg | 8 mg | 500 mg | 1000 mg | 2000 mg |
| Safety | 63/142 | 17/142 | 19/142 | 43/142 | 2/142 | 86/142 | 54/142 |
| ITT | 56/132 | 15/132 | 18/132 | 43/132 | 1/131 | 76/131 | 54/131 |
| Completer | 46/107 | 13/107 | 14/107 | 34/107 | 0/111 | 66/111 | 45/111 |
| PP | 31/81 | 9/81 | 12/81 | 29/81 | 0/81 | 43/81 | 38/81 |

Table 6: (From Data provided) Number of subjects taking Glimepiride and metformin by highest dose achieved at end of study who had at least 18 weeks of treatment (drop-out before week 18 are excluded from the table)

| | Glimepiride | | | | Metformin | | |
|---|---|---|---|---|---|---|---|
| | 1 mg | 2 mg | 4 mg | 8 mg | 500 mg | 1000 mg | 2000 mg |
| Safety | 51/115 | 14/115 | 16/115 | 34/115 | 1/117 | 71/117 | 45/117 |
| ITT | 50/114 | 14/114 | 16/114 | 34/114 | 1/117 | 71/117 | 45/117 |
| Completer | 46/106 | 13/106 | 14/106 | 33/106 | 0/109 | 66/109 | 43/109 |
| PP | 31/80 | 9/80 | 12/80 | 28/80 | 0/80 | 43/80 | 37/80 |

PP=1; ID = 0300003 TRGP=Glimepiride 8 mg Did not withdraw, but dosage up to day 126
PP=1; ID = 0003001 TRGP=Metformin 2000 mg; Withdrew, dosage up to day 126

Table 7: Number (Percent) of Subjects of Glimepiride (mg) and metformin (mg) by highest dose achieved at 18 weeks (Applicant's)

Table Number (percent) of subjects of glimepiride (mg) and metformin (mg) at 18 weeks

| | Glimepriride | | | | | | | | | | Metformin | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1 mg | | 2 mg | | 4 mg | | 8 mg | | 12 mg | | 500 mg | | 1000 mg | | 2000 mg | |
| Population | n/N | % | n/N | % | n/N | % | n/N | % | n/N | % | n/N | % | n/N | % | n/N | % |
| Safety | 63/142 | 44.4% | 17/142 | 12.0% | 18/142 | 12.7% | 44/142 | 31.0% | 0/142 | 0.0% | 2/142 | 1.4% | 88/142 | 62.0% | 52/142 | 36.6% |
| Intent-to-treat | 56/132 | 42.4% | 15/132 | 11.4% | 17/132 | 12.9% | 44/132 | 33.3% | 0/132 | 0.0% | 1/131 | 0.8% | 78/131 | 59.5% | 52/131 | 39.7% |
| Per-Protocol | 31/ 81 | 38.3% | 9/ 81 | 11.1% | 12/ 81 | 14.8% | 29/ 81 | 35.8% | 0/ 81 | 0.0% | 0/ 81 | 0.0% | 45/ 81 | 55.6% | 36/ 81 | 44.4% |
| ITT with MPV | 25/ 51 | 49.0% | 6/ 51 | 11.8% | 5/ 51 | 9.8% | 15/ 51 | 29.4% | 0/ 51 | 0.0% | 1/ 50 | 2.0% | 33/ 50 | 66.0% | 16/ 50 | 32.0% |

Table 8: HbA1c (%): Analysis of Covariance (ANCOVA) Results by Metformin (mg/d) dosage at the end of study

| | Baseline | | Unadjusted Mean (SD) | | Adjusted Mean Change from Baseline (SE) | | Difference: Glimepiride – Metformin | |
|---|---|---|---|---|---|---|---|---|
| | Glimepiride | Metformin | Glimepiride | Metformin | Glimepiride | Metformin | Adjusted Mean | 95% CI |
| Per Protocol | | | | | | | | |
| Metformin = 1000 mg/d | 8.57 (1.3) | 8.35 (1.3) | 7.88 (2.1) | 6.40 (1.4) | -1.05 (0.4) | -2.33 (0.5) | 1.27 | (0.57, 1.97) |
| Metformin = 1000 mg **(LOCF)** | | | 7.88 (2.1) | 6.40 (1.4) | -1.05 (0.4) | -2.33 (0.5) | 1.27 | (0.57, 1.97) |
| Metformin = 2000 mg/d | 8.57 (1.3) | 9.08 (1.4) | 7.88 (2.1) | 8.65 (2.1) | -1.14 (0.5) | -0.71 (0.5) | -0.42 | (-1.19, 0.34) |
| Metformin = 2000 mg (LOCF) | | | 7.88 (2.1) | 8.65 (2.1) | -1.14 (0.5) | -0.71 (0.5) | -0.42 | (-1.19, 0.34) |
| ITT | | | | | | | | |
| Metformin = 1000 mg/d | 8.52 (1.6) | 7.95 (1.3) | 7.89 (2.1) | 6.55 (1.3) | -0.65 (0.3) | -1.67 (0.3) | 1.02 | (0.49, 1.55) |
| Metformin = 1000 mg **(LOCF)** | | | 7.99 (2.1) | 6.71 (1.6) | -0.44 (0.3) | -1.33 (0.3) | 0.89 | (0.37, 1.41) |
| Metformin = 2000 mg/d | 8.52 (1.6) | 7.89 (2.1) | 7.89 (2.1) | 9.22 (2.5) | -1.03 (0.4) | -0.51 (0.4) | -0.52 | (-1.18, 0.14) |
| Metformin = 2000 mg (LOCF) | | | 7.99 (2.1) | 9.44 (2.7) | -0.99 (0.3) | -0.51 (0.4) | -0.68 | (-1.31, -0.05) |
| Safety | | | | | | | | |
| Metformin = 1000 mg/d | 8.46 (1.6) | 8.12 (1.4) | 7.89 (2.1) | 6.55 (1.3) | -0.65 (0.3) | -1.67 (0.3) | 1.02 | (0.49, 1.55) |
| Metformin = 1000 mg **(LOCF)** | | | 7.96 (2.1) | 7.02 (1.9) | -0.39 (0.3) | -1.07 (0.3) | 0.68 | (0.20, 1.16) |
| Metformin = 2000 mg/d | 8.46 (1.6) | 9.42 (1.5) | 7.89 (2.1) | 9.22 (2.5) | -1.03 (0.4) | -0.51 (0.4) | -0.52 | (-1.18, 0.14) |
| Metformin = 2000 mg (LOCF) | | | 7.96 (2.1) | 9.44 (2.7) | -0.83 (0.3) | -0.18 (0.4) | -0.65 | (-1.25, -0.04) |

Table 9: HbA1c (%): Analysis of Covariance (ANCOVA) Results by Metformin (mg/d) dosage restricted to those subjects who had at least 18 weeks of treatment

| | Baseline | | Unadjusted Mean (SD) | | Adjusted Mean Change from Baseline (SE) | | Difference: Glimepiride – Metformin | |
|---|---|---|---|---|---|---|---|---|
| | Glimepiride | Metformin | Glimepiride | Metformin | Glimepiride | Metformin | Adjusted Mean | 95% CI |
| Per Protocol | | | | | | | | |
| Subset | 8.54 (1.3) | 8.68 (1.4) | 7.86 (2.1) | 7.38 (2.0) | -0.89 (0.4) | -1.40 (0.4) | 0.51 | (-0.08, 1.11) |
| Subset (LOCF) | | | 7.86 (2.1) | 7.38 (2.0) | -0.89 (0.4) | -1.40 (0.4) | 0.51 | (-0.08, 1.11) |
| Metformin=1000/d | 8.54 (1.3) | 8.35 (1.3) | 7.86 (2.1) | 6.40 (1.4) | -1.04 (0.4) | -2.32 (0.5) | 1.27 | (0.57, 1.98) |
| Metformin=1000 (LOCF) | | | 7.86 (2.1) | 6.40 (1.4) | -1.04 (0.4) | -2.32 (0.5) | 1.27 | (0.57, 1.98) |
| Metformin=2000/d | 8.54 (1.3) | 9.06 (1.4) | 7.86 (2.1) | 8.52 (2.0) | -1.07 (0.5) | -0.76 (0.5) | -0.30 | (-1.06, 0.46) |
| Metformin=2000 (LOCF) | | | 7.86 (2.1) | 8.52 (2.0) | -1.07 (0.5) | -0.76 (0.5) | -0.30 | (-1.06, 0.46) |
| ITT | | | | | | | | |
| Subset | 8.38 (1.5) | 8.44 (1.5) | 7.79 (2.1) | 7.48 (2.2) | -0.80 (0.3) | -1.17 (0.3) | 0.37 | (-0.12, 0.88) |
| Subset (LOCF) | | | 7.79 (2.1) | 7.46 (2.1) | -0.73 (0.3) | -1.09 (0.3) | 0.36 | (-0.12, 0.84) |
| Metformin=1000/d | 8.38 (1.5) | 7.96 (1.3) | 7.79 (2.1) | 6.56 (1.3) | -0.67 (0.3) | -1.66 (0.3) | 0.98 | (0.44, 1.53) |
| Metformin=1000 (LOCF) | | | 7.79 (2.1) | 6.56 (1.3) | -0.67 (0.3) | -1.67 (0.3) | 0.99 | (0.47, 1.52) |
| Metformin=2000/d | 8.38 (1.5) | 9.24 (1.5) | 7.79 (2.1) | 8.93 (2.5) | -0.99 (0.4) | -0.62 (0.4) | -0.37 | (-1.07, 0.33) |
| Metformin=2000 (LOCF) | | | 7.79 (2.1) | 8.92 (2.4) | -0.91 (0.3) | -0.48 (0.4) | -0.43 | (-1.11, 0.25) |
| Safety | | | | | | | | |
| Subset | 8.36 (1.5) | 8.44 (1.5) | 7.79 (2.1) | 7.48 (2.2) | -0.80 (0.3) | -1.17 (0.3) | 0.37 | (-0.12, 0.88) |
| Subset (LOCF) | | | 7.78 (2.1) | 7.46 (2.1) | -0.73 (0.3) | -1.09 (0.3) | 0.36 | (-0.12, 0.84) |
| Metformin=1000/d | 8.36 (1.5) | 7.96 (1.3) | 7.79 (2.1) | 6.56 (1.3) | -0.67 (0.3) | -1.66 (0.3) | 0.98 | (0.44, 1.53) |
| Metformin=1000 (LOCF) | | | 7.78 (2.1) | 6.56 (1.3) | -0.68 (0.3) | -1.66 (0.3) | 0.99 | (0.47, 1.51) |
| Metformin=2000/d | 8.36 (1.5) | 9.24 (1.5) | 7.79 (2.1) | 8.93 (2.5) | -0.99 (0.4) | -0.62 (0.4) | -0.37 | (-1.07, 0.33) |
| Metformin=2000 (LOCF) | | | 7.78 (2.1) | 8.92 (2.4) | -0.91 (0.3) | -0.48 (0.4) | -0.43 | (-1.10, 0.25) |

Table 10: Previous and Ongoing Anti-diabetic Usage – N(%)

| | ANTIDIAB | | PREVDIAB | | PREVUSE | | ONGOING | |
|---|---|---|---|---|---|---|---|---|
| | Glimepiride | Metformin | Glimepiride | Metformin | Glimepiride | Metformin | Glimepiride | Metformin |
| Safety (142/142) | 19 | 20 | 46 | 47 | 58 | 62 | 7 | 5 |
| | (13%) | (14%) | (32%) | (33%) | (42%) | (44%) | (5%) | (4%) |
| PP (81/81) | 10 | 11 | 26 | 27 | 33 | 36 | 2 | 1 |
| | (12%) | (14%) | (32%) | (33%) | (41%) | (44%) | (2%) | (1%) |
| ITT (132/131) | 19 | 17 | 43 | 45 | 55 | 57 | 5 | 5 |
| | (14%) | (13%) | (33%) | (34%) | (42%) | (44%) | (4%) | (4%) |

Table 11 HbA1c (%): analysis of covariance (ANCOVA) results - excluding subjects taking anti-diabetic medication

| | Unadjusted Mean (SD) | | | | Adjusted Mean Change from Baseline (SE) | | Difference: Glimepiride - Metformin | | |
|---|---|---|---|---|---|---|---|---|---|
| | N | Glimepiride | N | Metformin | Glimepiride | Metformin | Adjusted Mean | 95% CI | p-value |
| Per Protocol | | | | | | | | | |
| Baseline | 79 | 8.56 (1.3) | 80 | 8.69 (1.4) | | | | | |
| Week 12 | 73 | 7.92 (1.9) | 76 | 7.58 (2.1) | -1.03 (0.4) | -1.37 (0.4) | 0.34 | (-0.22, 0.90) | 0.2319 |
| Week 24 | 79 | 7.86 (2.1) | 80 | 7.45 (2.1) | -0.95 (0.4) | -1.38 (0.4) | 0.43 | (-0.18, 1.05) | 0.1663 |
| Intent-to-Treat | | | | | | | | | |
| Baseline | 127 | 8.46 (1.5) | 126 | 8.51 (1.5) | | | | | |
| Week 12 | 116 | 7.94 (1.9) | 121 | 7.84 (2.4) | -0.66 (0.3) | -0.75 (0.3) | 0.09 | (-0.35, 0.54) | 0.6892 |
| Week 24 (LOCF) | 127 | 7.92 (2.1) | 126 | 7.73 (2.4) | -0.63 (0.3) | -0.83 (0.3) | 0.20 | (-0.28, 0.68) | 0.4195 |
| Safety Population | | | | | | | | | |
| Baseline | 135 | 8.42(1.5) | 137 | 8.60 (1.6) | | | | | |
| Week 12 | 116 | 7.94 (1.9) | 121 | 7.84 (2.4) | -0.66 (0.3) | -0.75 (0.3) | 0.09 | (-0.35, 0.54) | 0.6892 |
| Week 24 (LOCF) | 135 | 7.92 (2.1) | 137 | 7.89 (2.4) | -0.55 (0.3) | -0.70 (0.3) | 0.15 | (-0.30, 0.60) | 0.5123 |

Analysis of covariance with treatment, country, and tanner stage effects and the corresponding baseline value as covariate was used for the change from baseline
Source: re-analysis of data and from sponsor's 2ef0001tx doc and 2ef0002tx doc

Table 12: HbA1c (%): Analysis of Covariance (ANCOVA) Results by Previous Anti-diabetic Use, removing subjects that have ongoing anti-diabetic treatment during study period.

| | | Unadjusted Mean (SD) | | | Adjusted Mean Change from Baseline (SE) | | Difference: Glimepiride - Metformin | | |
|---|---|---|---|---|---|---|---|---|---|
| Population | Subgroup | N | Glimepiride | N | Metformin | Glimepiride | Metformin | Adjusted Mean | 95% CI | p-value |
| Per Protocol | Previously AB Treated | | | | | | | | | |
| | Baseline | 33 | 8.76 (1.4) | 36 | 9.16 (1.3) | | | | | |
| | Week 12 | 32 | 8.80 (1.9) | 36 | 8.53 (2.5) | 0.14 (0.8) | -0.29 (0.8) | 0.43 | (-0.53, 1.39) | 0.3706 |
| | Week 24 (LOCF) | 33 | 9.00 (2.2) | 36 | 8.39 (2.4) | 0.75 (0.9) | -0.13 (0.9) | 0.88 | (-0.19, 1.94) | 0.1041 |
| | Not Previously Treated | | | | | | | | | |
| | Baseline | 46 | 8.42 (1.3) | 44 | 8.31 (1.4) | | | | | |
| | Week 12 | 41 | 7.05 (1.6) | 40 | 6.74 (1.2) | -1.43 (0.4) | -1.86 (0.4) | 0.43 | (-0.18, 1.04) | 0.1631 |
| | Week 24 (LOCF) | 46 | 7.05 (1.7) | 44 | 6.68 (1.4) | -1.47 (0.4) | -1.79 (0.4) | 0.32 | (-0.35, 0.98) | 0.3447 |
| ITT | Previously AB Treated | | | | | | | | | |
| | Baseline | 55 | 8.84 (1.5) | 57 | 9.05 (1.5) | | | | | |
| | Week 12 | 51 | 8.79 (2.0) | 57 | 8.97 (2.8) | 0.01 (0.6) | -0.004 (0.6) | 0.02 | (-0.75, 0.78) | 0.9647 |
| | Week 24 (LOCF) | 55 | 8.99 (2.2) | 57 | 8.82 (2.7) | 0.17 (0.7) | -0.23 (0.7) | 0.39 | (-0.44, 1.22) | 0.3488 |
| | Not Previously Treated | | | | | | | | | |
| | Baseline | 72 | 8.17 (1.5) | 69 | 8.06 (1.4) | | | | | |
| | Week 12 | 65 | 7.28 (1.6) | 64 | 6.83 (1.3) | -0.93 (0.3) | -1.28 (0.2) | 0.35 | (-0.10, 0.80) | 0.1324 |
| | Week 24 (LOCF) | 72 | 7.10 (1.6) | 69 | 6.84 (1.6) | -0.97 (0.3) | -1.18 (0.3) | 0.21 | (-0.29, 0.70) | 0.4136 |
| Safety | Previously AB Treated | | | | | | | | | |
| | Baseline | 58 | 8.81 (1.5) | 62 | 9.15 (1.5) | | | | | |
| | Week 12 | 51 | 8.79 (2.0) | 57 | 8.97 (2.8) | 0.01 (0.6) | -0.004 (0.6) | 0.02 | (-0.75, 0.78) | 0.9647 |
| | Week 24 (LOCF) | 58 | 8.97 (2.1) | 62 | 8.93 (2.7) | 0.22 (0.6) | -0.11 (0.6) | 0.33 | (-0.45, 1.10) | 0.4048 |
| | Not Previously Treated | | | | | | | | | |
| | Baseline | 77 | 8.13 (1.5) | 75 | 8.14 (1.5) | | | | | |
| | Week 12 | 65 | 7.28 (1.6) | 64 | 6.83 (1.3) | -0.93 (0.3) | -1.28 (0.2) | 0.35 | (-0.10, 0.80) | 0.1324 |
| | Week 24 (LOCF) | 77 | 7.13 (1.6) | 75 | 7.02 (1.7) | -1.00 (0.3) | -1.11 (0.3) | 0.11 | (-0.36, 0.59) | 0.6424 |

Analysis of covariance with treatment, country, and tanner stage effects and the corresponding baseline value as covariate was used for the change from baseline
Source: Re-analysis of data and sponsor's results 2ef0001ty doc, 2ef0002ty doc, 2ef0001tz doc, 2ef0002tz doc,

Secondary Outcome Variables:

Fasting Self-Monitored Blood Glucose

As shown in Table 13, since the 95% CI included zero, the null hypothesis was not rejected, and no significant difference was observed between the per- protocol treatment groups, as well as the ITT and the safety treatment groups, in their mean differences from baseline to any visit when change in fasting SMBG (mmol/ L) was analyzed with treatment, pooled countries, and Tanner stage as fixed effects and baseline SMBG as a covariate. Note that there were slight discrepancies in the mean values and mean treatment difference values at Weeks 18 and 24 generated by me and reported by the Applicant (Tables T-37, p. 187 and T-38, p. 188). Nonetheless, the conclusions remain the same.

Fasting Plasma Glucose

Table 14 presents the descriptive statistics and statistical analyses of treatment difference in FPG for the per-protocol, ITT, and safety subjects. According to the applicant, a notable difference in the results of FPG compared with SMBG is evident in the changes from baseline. While significant changes from baseline were observed in fasting SMBG for most visit days for both treatment groups of per-protocol subjects (Clinical Study Report T-38 p.188), no significant change from baseline (in terms of mmol/ L) was observed in FPG at any visit day for either treatment group (Clinical Study Report – T33p. 183). One possible explanation for the absence of significant decreases in FPG might be that some subjects in both groups did not maintain a fasting state by the time they came to their study visit. According to the applicant, this possibility is supported by the means, medians, and maxima values for FPG being higher than SMBG for most visit days. No significant difference was observed between the treatment groups in their changes in FPG (Table 14) for the per-protocol, the ITT or the safety subjects.

Fasting Plasma Lipids (Total Cholesterol, LDL, HDL, and Triglyceride)

Descriptive statistics and statistical analyses of treatment difference in Fasting Plasma Lipids, as well as BMI for the per-protocol, ITT and safety subjects are presented in Table 15. Again, the results are slightly different between mine and the Applicant's because of data imputation. Note that I used only observed data for analysis. However, this discrepancy did not affect the overall result.

In terms of total cholesterol, there is no significant difference between treatment groups in their change in total cholesterol from baseline among the per-protocol population. These tables also indicate that the results were similar for the ITT and safety subjects. Similarly, there is no evidence of a significant difference between treatment groups in terms of change in HDL from baseline, as well change in Triglyceride from baseline for the per-protocol, ITT, or safety subjects.

There appears to be a significant treatment difference in the change in calculated LDL cholesterol in the per-protocol population ($p=0.0415$). However, because of possible multiplicity issue, this significant difference should be interpreted with caution.

Body Mass Index

A small and non-significant increase from baseline in was observed at Week 24 in the glimepiride (per-protocol, ITT and safety) subjects, and a decrease in BMI that was statistically significant was observed in the metformin (per-protocol, ITT and safety) group. However, no significant difference between treatments for changes in BMI from baseline to Week 24 was observed for the per-protocol subjects, while there appears to be a statistically significant difference between treatments for the ITT and safety subjects (Table 16).

Table 13: Self-monitored blood glucose (plasma-ref) (nmol/L): Analysis of Covariance (ANCOVA) Results – LOCF

| | Unadjusted Mean (SD) | | Adjusted Mean Change from Baseline (SE) | | Difference: Glimepiride - Metformin | | |
|---|---|---|---|---|---|---|---|
| | Glimepiride | Metformin | Glimepiride | Metformin | Adjusted Mean | 95% CI | p-value |
| Per Protocol | | | | | | | |
| Baseline | 9.63 (3.2) | 9.30 (3.4) | | | | | |
| Week 4 | 9.29 (3.7) | 8.66 (3.6) | -0.53 (0.6) | -0.85 (0.5) | 0.32 | (-0.51, 1.16) | 0.4480 |
| Week 8 | 8.45 (3.1) | 8.39 (3.4) | -0.86 (0.5) | -0.69 (0.5) | -0.17 | (-0.99, 0.65) | 0.6896 |
| Week 12 | 8.55 (3.4) | 8.43 (3.3) | -0.87 (0.6) | -0.75 (0.6) | -0.12 | (-0.99, 0.75) | 0.7836 |
| Week 18 | 8.48 (3.2) | 7.84 (2.9) | -1.29 (0.6) | -1.73 (0.6) | 0.45 | (-0.42, 1.31) | 0.3074 |
| Week 24 | 8.81 (3.7) | 7.84 (2.9) | -1.25 (0.6) | -1.97 (0.6) | 0.72 | (-0.22, 1.66) | 0.1340 |
| Intent-to-Treat | | | | | | | |
| Baseline | 9.62 (3.4) | 9.29 (3.7) | | | | | |
| Week 4 | 9.56 (3.9) | 8.96 (3.9) | -0.16 (0.4) | -0.49(0.4) | 0.33 | (-0.33, 0.98) | 0.3302 |
| Week 8 | 8.77 (3.6) | 8.80 (3.9) | -0.62 (0.4) | -0.35 (0.4) | -0.27 | (-0.98, 0.45) | 0.4631 |
| Week 12 | 8.86 (3.8) | 8.86 (4.0) | -0.44 (0.5) | -0.21 (0.5) | -0.23 | (-0.99, 0.52) | 0.5391 |
| Week 18 | 8.72 (3.6) | 8.38 (3.6) | -0.77 (0.5) | -0.90 (0.5) | 0.13 | (-0.62, 0.89) | 0.7259 |
| Week 24 | 8.97 (4.0) | 8.41 (3.7) | -0.80 (0.5) | -1.12 (0.5) | 0.33 | (-0.48, 1.13) | 0.4238 |
| Safety Population | | | | | | | |
| Baseline | 9.73 (3.6) | 9.50 (3.9) | | | | | |
| Week 4 | 9.65 (3.9) | 9.06 (4.0) | 0.21 (0.4) | -0.20 (0.4) | 0.41 | (-0.25, 1.06) | 0.2216 |
| Week 8 | 8.89 (3.6) | 8.89 (3.9) | -0.18 (0.4) | -0.01 (0.4) | -0.17 | (-0.96, 0.45) | 0.4838 |
| Week 12 | 8.99 (3.9) | 8.95 (4.0) | -0.05 (0.4) | 0.09 (0.4) | -0.14 | (-0.87, 0.60) | 0.7132 |
| Week 18 | 8.85 (3.7) | 8.49 (3.7) | -0.27 (0.4) | -0.49 (0.4) | 0.22 | (-0.51, 0.96) | 0.5544 |
| Week 24 | 9.08 (4.0) | 8.52 (3.7) | -0.30 (0.5) | -0.71 (0.5) | 0.41 | (-0.37, 1.19) | 0.3063 |

Table 14: Fasting Plasma Glucose (nmol/L): Analysis of Covariance (ANCOVA) Results – Observed Data

| | Unadjusted Mean (SD) | | Adjusted Mean Change from Baseline (SE) | | Difference: Glimepiride - Metformin | | |
|---|---|---|---|---|---|---|---|
| | Glimepiride | Metformin | Glimepiride | Metformin | Adjusted Mean | 95% CI | p-value |
| Per Protocol | | | | | | | |
| Baseline | 9.64 (3.4) | 9.46 (3.6) | | | | | |
| Week 4 | 9.67 (4.0) | 9.50 (5.0) | -0.49 (0.6) | -0.53 (0.6) | 0.04 | (-0.90, 0.97) | 0.9393 |
| Week 8 | 9.47 (4.0) | 9.24 (4.6) | -0.45 (0.6) | -0.39 (0.6) | -0.05 | (-0.99, 0.83) | 0.8667 |
| Week 12 | 9.42 (3.9) | 9.23 (4.2) | -0.31 (0.6) | -0.27 (0.6) | 0.04 | (-0.89, 0.82) | 0.9311 |
| Week 18 | 9.35 (3.9) | 8.88 (4.0) | -0.68 (0.6) | -0.98 (0.6) | 0.30 | (-0.64, 1.24) | 0.5297 |
| Week 24 | 9.62 (4.2) | 8.92 (4.3) | -0.70 (0.7) | -1.23 (0.7) | 0.52 | (-0.56, 1.61) | 0.3412 |
| Intent-to-Treat | | | | | | | |
| Baseline | 9.68 (3.7) | 9.55 (3.9) | | | | | |
| Week 4 | 9.90 (4.4) | 9.63 (5.1) | -0.16 (0.4) | -0.32 (0.4) | 0.16 | (-0.54, 0.86) | 0.6548 |
| Week 8 | 9.42 (4.0) | 9.63 (5.1) | -0.34 (0.5) | -0.01 (0.5) | -0.34 | (-1.10, 0.42) | 0.3820 |
| Week 12 | 9.52 (4.2) | 9.73 (5.0) | -0.28 (0.5) | 0.05 (0.5) | -0.33 | (-1.06, 0.41) | 0.3806 |
| Week 18 | 9.51 (4.1) | 9.35 (4.8) | -0.17 (0.5) | -0.26 (0.5) | 0.09 | (-0.70, 0.87) | 0.8240 |
| Week 24 | 10.02 (5.0) | 9.42 (5.0) | 0.11 (0.6) | -0.42 (0.6) | 0.53 | (-0.44, 1.50) | 0.2854 |
| Safety Population | | | | | | | |
| Baseline | 9.79 (3.9) | 9.79 (4.2) | | | | | |
| Week 4 | 10.03 (4.4) | 9.72 (5.0) | 0.04 (0.4) | -0.24 (0.4) | 0.28 | (-0.41, 0.97) | 0.4226 |
| Week 8 | 9.52 (4.1) | 9.70 (5.1) | -0.19 (0.4) | 0.02 (0.4) | -0.22 | (-0.95, 0.52) | 0.5631 |
| Week 12 | 9.61 (4.3) | 9.72 (4.9) | -0.32 (0.4) | -0.16 (0.4) | -0.17 | (-0.88, 0.55) | 0.6504 |
| Week 18 | 9.61 (4.2) | 9.37 (4.7) | -0.22 (0.5) | -0.44 (0.5) | 0.22 | (-0.54, 0.97) | 0.5751 |
| Week 24 | 10.09 (5.0) | 9.44 (4.9) | 0.05 (0.6) | -0.58 (0.6) | 0.63 | (-0.30, 1.56) | 0.1844 |

Table 15: Fasting Plasma Lipids (nmol/L): Analysis of Covariance (ANCOVA) Results – Observed Data

| | Unadjusted Mean (SD) | | Adjusted Mean Change from Baseline (SE) | | Difference: Glimepiride - Metformin | | |
|---|---|---|---|---|---|---|---|
| | Glimepiride | Metformin | Glimepiride | Metformin | Adjusted Mean | 95% CI | p-value |
| Total Cholesterol | | | | | | | |
| Per Protocol | | | | | | | |
| Baseline | 4.34 (0.9) | 4.47 (0.9) | | | | | |
| Week 24 | 4.56 (1.1) | 4.45 (0.9) | 0.18 (0.1) | -0.01 (0.1) | 0.19 | (-0.02, 0.40) | 0.0739 |
| ITT | | | | | | | |
| Baseline | 4.32 (0.9) | 4.40 (0.9) | | | | | |
| Week 24 | 4.51 (1.1) | 4.41 (0.8) | 0.12 (0.1) | -0.01 (0.1) | 0.13 | (-0.03, 0.29) | 0.1214 |
| Safety | | | | | | | |
| Baseline | 4.32 (0.9) | 4.44 (0.9) | | | | | |
| Week 24 | 4.51 (1.1) | 4.41 (0.8) | 0.12 (0.1) | -0.01 (0.1) | 0.13 | (-0.03, 0.29) | 0.1214 |
| HDL Cholesterol | | | | | | | |
| Per Protocol | | | | | | | |
| Baseline | 1.07 (0.2) | 1.04 (0.2) | | | | | |
| Week 24 | 1.09 (0.3) | 1.07 (0.2) | 0.05 (0.0) | 0.05 (0.0) | 0.006 | (-0.05, 0.06) | 0.8199 |
| ITT | | | | | | | |
| Baseline | 1.10 (0.2) | 1.08 (0.2) | | | | | |
| Week 24 | 1.11 (0.3) | 1.11 (0.3) | 0.06 (0.0) | 0.06 (0.0) | -0.002 | (-0.05, 0.04) | 0.9349 |
| Safety | | | | | | | |
| Baseline | 1.10 (0.2) | 1.07 (0.2) | | | | | |
| Week 24 | 1.11 (0.3) | 1.11 (0.3) | 0.06 (0.0) | 0.06 (0.0) | -0.002 | (-0.05, 0.04) | 0.9349 |
| Calculated LDL Cholesterol | | | | | | | |
| Per Protocol | | | | | | | |
| Baseline | 2.44 (0.6) | 2.53 (0.7) | | | | | |
| Week 24 | 2.57 (0.9) | 2.44 (0.7) | 0.11 (0.1) | -0.06 (0.1) | 0.18 | (0.01, 0.34) | 0.0415 |
| ITT | | | | | | | |
| Baseline | 2.43 (0.7) | 2.49 (0.7) | | | | | |
| Week 24 | 2.52 (0.9) | 2.44 (0.7) | 0.06 (0.1) | -0.05 (0.1) | 0.10 | (-0.03, 0.23) | 0.1222 |
| Safety | | | | | | | |
| Baseline | 2.44 (0.7) | 2.52 (0.7) | | | | | |
| Week 24 | 2.52 (0.9) | 2.44 (0.7) | 0.06 (0.1) | -0.05 (0.1) | 0.10 | (-0.03, 0.23) | 0.1222 |

Table 15 (Continued)

| | Unadjusted Mean (SD) | | Adjusted Mean Change from Baseline (SE) | | Difference: Glimepiride - Metformin | | |
|---|---|---|---|---|---|---|---|
| | Glimepiride | Metformin | Glimepiride | Metformin | Adjusted Mean | 95% CI | p-value |
| Imputed LDL Cholesterol | | | | | | | |
| Per Protocol | | | | | | | |
| Baseline | | | | | | | |
| Week 24 | 2.43 (0.6) | 2.52 (0.7) | | | | | |
| ITT | 2.49 (1.0) | 2.38 (0.8) | 0.11 (0.1) | -0.09 (0.1) | 0.19 | (-0.00, 0.39) | 0.0521 |
| Baseline | | | | | | | |
| Week 24 | 2.41 (0.7) | 2.47 (0.7) | | | | | |
| Safety | 2.46 (0.9) | 2.38 (0.8) | 0.06 (0.1) | -0.05 (0.1) | 0.11 | (-0.04, 0.26) | 0.1360 |
| Baseline | | | | | | | |
| Week 24 | 2.40 (0.8) | 2.49 (0.7) | | | | | |
| | 2.46 (0.9) | 2.38 (0.8) | 0.06 (0.1) | -0.05 (0.1) | 0.11 | (-0.04, 0.26) | 0.1360 |
| Triglycerides | | | | | | | |
| Per Protocol | | | | | | | |
| Baseline | 1.85 (1.1) | 1.98 (1.3) | | | | | |
| Week 24 | 2.23 (2.7) | 2.25 (1.9) | 0.16 (0.4) | 0.09 (0.4) | 0.06 | (-0.052, 0.64) | 0.8315 |
| ITT | | | | | | | |
| Baseline | 1.80 (1.1) | 1.93 (2.2) | | | | | |
| Week 24 | 2.15 (2.4) | 2.12 (2.4) | 0.08 (0.3) | -0.00 (0.3) | 0.09 | (-0.33, 0.50) | 0.6780 |
| Safety | | | | | | | |
| Baseline | 1.80 (1.2) | 1.99 (2.3) | | | | | |
| Week 24 | 2.15 (2.4) | 2.12 (2.4) | 0.08 (0.3) | -0.00 (0.3) | 0.09 | (-0.33, 0.50) | 0.6780 |

Table 16: Body Mass Index (kg/m$^2$)): Analysis of Covariance (ANCOVA) Results – Observed Data

| | Unadjusted Mean (SD) | | Adjusted Mean Change from Baseline (SE) | | Difference: Glimepiride - Metformin | | |
|---|---|---|---|---|---|---|---|
| | Glimepiride | Metformin | Glimepiride | Metformin | Adjusted Mean | 95% CI | p-value |
| BMI (kg/m$^2$) | | | | | | | |
| Per Protocol | | | | | | | |
| Baseline | 31.3 (7.1) | 32.6 (8.5) | | | | | |
| Week 12 | 31.8 (7.4) | 32..5 (8.5) | 0.62 (0.3) | 0.07 (0.2) | 0.56 | (0.19, 0.92) | 0.0029 |
| Week 24 | 31.3 (7.6) | 32.1 (8.1) | 0.30 (0.4) | -0.25 (0.4) | 0.55 | (-0.01, 1.11) | 0.0553 |
| ITT | | | | | | | |
| Baseline | 31.4 (8.4) | 31.7 (8.1) | | | | | |
| Week 12 | 31.5 (7.9) | 31.4 (8.2) | 0.55 (0.2) | 0.06 (0.2) | 0.50 | (0.22, 0.77) | 0.0005 |
| Week 24 | 31.3 (7.9) | 31.2 (7.9) | 0.29 (0.3) | -0.30 (0.3) | 0.59 | (0.20, 0.98) | 0.0032 |
| Safety | | | | | | | |
| Baseline | 31.3 (8.3) | 31.9 (8.4) | | | | | |
| Week 12 | 31.5 (7.9) | 31.4 (8.2) | 0.46 (0.2) | 0.02 (0.2) | 0.48 | (0.20, 0.76) | 0.0009 |
| Week 24 | 31.2 (7.9) | 31.2 (7.9) | 0.22 (0.2) | -0.35 (0.2) | 0.58 | (0.19, 0.97) | 0.0038 |

Table 17: HbA1c (%): analysis of covariance (ANCOVA) results by subgroup - per- protocol subjects

| | | Change from Baseline | | | | | | Diff: Glimepiride - Meformin | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Glimepiride Adjusted | | | Metformin Adjusted | | | Adjusted | | | | | Interaction |
| Subgroup | Value | N | Mean | SE | N | Mean | SE | Mean | 95% CI | | SE | Prob | P-Value |
| Gender | Male | 25 | -1.19 | 0.515 | 24 | -1.39 | 0.507 | 0.20 | ( -0.9; | 1.3) | 0.562 | 0.7211 | 0.6015 |
| | Female | 56 | -0.80 | 0.449 | 57 | -1.36 | 0.437 | 0.55 | ( -0.2; | 1.3) | 0.370 | 0.1360 | |
| Age | < 12 years | 15 | -0.70 | 0.611 | 13 | -1.59 | 0.602 | 0.89 | ( -0.7; | 2.4) | 0.789 | 0.2625 | 0.5410 |
| | >= 12 years | 66 | -0.97 | 0.447 | 68 | -1.33 | 0.452 | 0.35 | ( -0.3; | 1.0) | 0.340 | 0.2996 | |
| Race | White | 8 | -1.60 | 0.879 | 11 | -1.88 | 0.812 | 0.29 | ( -1.5; | 2.1) | 0.911 | 0.7540 | 0.6965 |
| | African American | 17 | -1.19 | 0.745 | 18 | -1.63 | 0.737 | 0.43 | ( -0.9; | 1.8) | 0.675 | 0.5231 | |
| | Asian | 15 | -0.89 | 0.707 | 11 | -1.29 | 0.787 | 0.40 | ( -1.2; | 2.0) | 0.789 | 0.6154 | |
| | Hispanic | 34 | -0.66 | 0.631 | 35 | -1.39 | 0.629 | 0.73 | ( -0.2; | 1.7) | 0.472 | 0.1260 | |
| | Other | 7 | -1.05 | 0.917 | 6 | 0.03 | 0.959 | -1.08 | ( -3.3; | 1.2) | 1.136 | 0.3420 | |
| Obesity | BMI >= 30 kg/m**2 | 43 | -1.22 | 0.475 | 47 | -1.73 | 0.482 | 0.50 | ( -0.3; | 1.3) | 0.419 | 0.2315 | 0.9624 |
| | 25 < BMI < 30 kg/m**2 | 19 | -1.10 | 0.573 | 18 | -1.40 | 0.556 | 0.30 | ( -1.0; | 1.6) | 0.647 | 0.6445 | |
| | BMI <= 25 kg/m**2 | 18 | -0.50 | 0.593 | 16 | -0.88 | 0.582 | 0.38 | ( -1.0; | 1.7) | 0.675 | 0.5768 | |
| Baseline Insulin | < median baseline fasting serum insulin | 38 | -0.96 | 0.471 | 37 | -1.37 | 0.467 | 0.40 | ( -0.5; | 1.3) | 0.455 | 0.3754 | 0.7992 |
| | >= median baseline fasting serum insulin | 41 | -0.91 | 0.478 | 43 | -1.47 | 0.459 | 0.56 | ( -0.3; | 1.4) | 0.430 | 0.1915 | |
| Baseline C-Peptide | < median baseline c-peptide | 37 | -0.76 | 0.467 | 36 | -1.18 | 0.482 | 0.42 | ( -0.5; | 1.3) | 0.459 | 0.3643 | 0.8712 |
| | >= median baseline c-peptide | 42 | -1.10 | 0.472 | 44 | -1.62 | 0.445 | 0.52 | ( -0.3; | 1.4) | 0.425 | 0.2229 | |
| Baseline HbA1c | HbA1c < 7.5% | 16 | -0.06 | 0.790 | 17 | 0.19 | 0.804 | -0.25 | ( -1.6; | 1.1) | 0.673 | 0.7063 | 0.6006 |
| | 7.5% =< HbA1c < 8.5% | 29 | -0.26 | 0.541 | 18 | -1.16 | 0.630 | 0.90 | ( -0.3; | 2.1) | 0.583 | 0.1255 | |
| | 8.5% =< HbA1c =< 9.5% | 14 | -0.70 | 0.631 | 22 | -1.41 | 0.539 | 0.71 | ( -0.6; | 2.0) | 0.659 | 0.2808 | |
| | HbA1c > 9.5% | 22 | -2.68 | 0.806 | 24 | -2.98 | 0.771 | 0.29 | ( -0.9; | 1.5) | 0.589 | 0.6192 | |
| Titration Schedule | FPG target < 7.8 mmol/L (140 mg/dL) | 79 | -0.83 | 0.422 | 79 | -1.27 | 0.406 | 0.44 | ( -0.2; | 1.1) | 0.309 | 0.1529 | 0.9301 |
| | FPG target < 7.0 mmol/L (126 mg/dL) | 2 | -2.65 | 1.410 | 2 | -2.92 | 1.432 | 0.27 | ( -3.7; | 4.2) | 1.998 | 0.8940 | |
| Plasma/whole blood | Used 'plasma-like' results | 42 | -1.12 | 0.422 | 42 | -1.44 | 0.425 | 0.31 | ( -0.5; | 1.2) | 0.433 | 0.4686 | 0.5861 |
| | Used 'whole blood' results | 39 | -1.02 | 0.432 | 39 | -1.68 | 0.408 | 0.66 | ( -0.2; | 1.5) | 0.448 | 0.1458 | |
| Country (Pooled) | United States of America | 42 | -1.18 | 0.423 | 42 | -1.48 | 0.425 | 0.31 | ( -0.5; | 1.1) | 0.427 | 0.4759 | 0.6907 |
| | Argentina,Brazil,Costa Rica,Mexico,Peru | 22 | -1.32 | 0.514 | 25 | -2.23 | 0.478 | 0.91 | ( -0.2; | 2.0) | 0.570 | 0.1119 | |
| | Germany,Hungary,Poland | 2 | -2.03 | 1.418 | 3 | 0.21 | 1.171 | -2.24 | ( -5.8; | 1.3) | 1.779 | 0.2106 | |
| | India | 4 | -1.17 | 1.029 | 4 | -1.59 | 1.031 | 0.42 | ( -2.3; | 3.2) | 1.384 | 0.7626 | |
| | South Korea,Taiwan | 7 | 0.28 | 0.778 | 5 | -0.22 | 0.894 | 0.50 | ( -1.8; | 2.8) | 1.141 | 0.6600 | |
| | South Africa | 4 | -1.43 | 1.044 | 2 | -2.19 | 1.377 | 0.76 | ( -2.6; | 4.2) | 1.723 | 0.6585 | |

Table 18: HbA1c (%): analysis of covariance (ANCOVA) results by subgroup – ITT subjects

| | | Change from Baseline | | | | | | Diff: Glimepiride - Meformin | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Glimepiride Adjusted | | | Metformin Adjusted | | | Adjusted | | | | | Interaction |
| Subgroup | Value | N | Mean | SE | N | Mean | SE | Mean | 95% CI | | SE | Prob | P-Value |
| Gender | Male | 44 | -1.01 | 0.376 | 44 | -0.72 | 0.380 | -0.28 | ( -1.1; | 0.6) | 0.425 | 0.5070 | 0.2142 |
| | Female | 88 | -0.48 | 0.346 | 87 | -0.85 | 0.332 | 0.37 | ( -0.2; | 1.0) | 0.300 | 0.2207 | |
| Age | < 12 years | 23 | -0.80 | 0.476 | 21 | -1.32 | 0.460 | 0.52 | ( -0.7; | 1.7) | 0.612 | 0.3969 | 0.5268 |
| | >= 12 years | 109 | -0.52 | 0.336 | 110 | -0.61 | 0.341 | 0.09 | ( -0.4; | 0.6) | 0.267 | 0.7228 | |
| Race | White | 17 | -0.88 | 0.652 | 21 | -1.02 | 0.603 | 0.13 | ( -1.2; | 1.4) | 0.654 | 0.8372 | 0.4109 |
| | African American | 29 | -0.25 | 0.576 | 27 | -1.07 | 0.574 | 0.82 | ( -0.2; | 1.9) | 0.534 | 0.1241 | |
| | Asian | 23 | -1.04 | 0.555 | 19 | -0.90 | 0.611 | -0.14 | ( -1.4; | 1.1) | 0.619 | 0.8168 | |
| | Hispanic | 52 | -0.55 | 0.490 | 52 | -0.72 | 0.491 | 0.17 | ( -0.6; | 0.9) | 0.389 | 0.6608 | |
| | Other | 11 | -0.74 | 0.687 | 12 | 0.32 | 0.661 | -1.07 | ( -2.7; | 0.6) | 0.830 | 0.2004 | |
| Obesity | BMI >= 30 kg/m**2 | 70 | -0.92 | 0.371 | 74 | -1.13 | 0.368 | 0.21 | ( -0.4; | 0.9) | 0.333 | 0.5265 | 0.9575 |
| | 25 < BMI < 30 kg/m**2 | 32 | -0.90 | 0.441 | 26 | -0.93 | 0.454 | 0.03 | ( -1.0; | 1.1) | 0.528 | 0.9602 | |
| | BMI <= 25 kg/m**2 | 29 | -0.34 | 0.441 | 31 | -0.50 | 0.422 | 0.16 | ( -0.8; | 1.2) | 0.513 | 0.7525 | |
| Baseline Insulin | < median baseline fasting serum insulin | 61 | -0.74 | 0.353 | 63 | -0.67 | 0.346 | -0.07 | ( -0.8; | 0.6) | 0.355 | 0.8499 | 0.3748 |
| | >= median baseline fasting serum insulin | 67 | -0.48 | 0.371 | 66 | -0.85 | 0.358 | 0.37 | ( -0.3; | 1.0) | 0.343 | 0.2777 | |
| Baseline C-Peptide | < median baseline c-peptide | 60 | -0.64 | 0.344 | 62 | -0.68 | 0.342 | 0.04 | ( -0.6; | 0.7) | 0.351 | 0.9068 | 0.4751 |
| | >= median baseline c-peptide | 69 | -0.88 | 0.357 | 67 | -1.27 | 0.351 | 0.39 | ( -0.3; | 1.0) | 0.332 | 0.2443 | |
| Baseline HbA1c | HbA1c < 7.5% | 37 | 0.21 | 0.538 | 37 | 0.37 | 0.559 | -0.16 | ( -1.1; | 0.7) | 0.456 | 0.7267 | 0.3250 |
| | 7.5% =< HbA1c < 8.5% | 36 | -0.12 | 0.443 | 28 | -0.79 | 0.477 | 0.67 | ( -0.3; | 1.6) | 0.495 | 0.1752 | |
| | 8.5% =< HbA1c =< 9.5% | 19 | -0.47 | 0.526 | 29 | -1.19 | 0.433 | 0.72 | ( -0.4; | 1.9) | 0.583 | 0.2178 | |
| | HbA1c > 9.5% | 40 | -2.18 | 0.593 | 37 | -1.88 | 0.596 | -0.31 | ( -1.2; | 0.6) | 0.455 | 0.5018 | |
| Titration Schedule | FPG target < 7.8 mmol/L (140 mg/dL) | 129 | -0.64 | 0.310 | 128 | -0.80 | 0.299 | 0.16 | ( -0.3; | 0.6) | 0.247 | 0.5266 | 0.8566 |
| | FPG target < 7.0 mmol/L (126 mg/dL) | 3 | -2.16 | 1.160 | 3 | -2.01 | 1.185 | -0.14 | ( -3.4; | 3.1) | 1.631 | 0.9306 | |
| Plasma/whole blood | Used 'plasma-like' results | 68 | -0.79 | 0.327 | 68 | -1.04 | 0.318 | 0.25 | ( -0.4; | 0.9) | 0.341 | 0.4620 | 0.6868 |
| | Used 'whole blood' results | 64 | -0.83 | 0.327 | 63 | -0.88 | 0.318 | 0.05 | ( -0.6; | 0.7) | 0.353 | 0.8802 | |
| Country (Pooled) | United States of America | 68 | -0.88 | 0.329 | 68 | -1.12 | 0.319 | 0.25 | ( -0.4; | 0.9) | 0.340 | 0.4701 | 0.5427 |
| | Argentina,Brazil,Costa Rica,Mexico,Peru | 35 | -0.96 | 0.400 | 37 | -1.38 | 0.386 | 0.42 | ( -0.5; | 1.3) | 0.467 | 0.3696 | |
| | Germany,Hungary,Poland | 7 | -0.76 | 0.775 | 6 | -0.35 | 0.849 | -0.41 | ( -2.6; | 1.8) | 1.103 | 0.7075 | |
| | India | 7 | -1.36 | 0.789 | 6 | -1.27 | 0.845 | -0.09 | ( -2.3; | 2.1) | 1.103 | 0.9357 | |
| | South Korea,Taiwan | 9 | 0.08 | 0.689 | 9 | -0.13 | 0.687 | 0.20 | ( -1.6; | 2.0) | 0.933 | 0.8283 | |
| | South Africa | 6 | -1.76 | 0.852 | 5 | 0.30 | 0.886 | -2.06 | ( -4.5; | 0.3) | 1.218 | 0.0920 | |

# 4 FINDINGS IN SUBGROUPS AND SPECIAL POPULATIONS

## 4.1 SEX, RACE AND AGE

There is no evidence of any interaction of treatment effect by predefined baseline variables (such as age, sex, race) on the change in HbA1c to endpoint for the per- protocol and ITT subjects (Table 17 and Table 18, respectively). The results were directly taken from Applicant's report (per-protocol: T-42, p. 192, and ITT: T-43, p.194).

# 5 SUMMARY AND CONCLUSIONS

## 5.1 STATISTICAL ISSUES AND COLLECTIVE EVIDENCE

No major statistical issues were identified after reviewing this pediatric supplement. However there are two issues that I would like to address in this review. One is on the quality of data provided by the applicant and the other is on the choice of study population used in the primary efficacy analysis. These issues were minor that can easily be address by conducting post-hoc analysis and by data management.

The quality of data provided by the applicant can definitely be improved. This can be accomplished by making the data definition clearer (e.g. provide a clear definition of the criteria used in categorizing subjects as "Valid") and by making the "variable" (e.g. LOCF-imputed data) used in the analysis available in the dataset. Although recoding the data is not difficult, it would have saved me time in trying to manage the data.

Although the Applicant analyzed the data using the intent-to-treat and completer populations, using per-protocol population as the primary study population may not be the most ideal choice. I believe the closest to the definition of Intent-to-Treat is the sponsor-defined "Safety" population. Nonetheless, the conclusion resulting from the analysis using the Safety Population is not different from the analysis using per-protocol population.

## 5.2 CONCLUSIONS AND RECOMMENDATIONS

Glimepiride and metformin were both effective in achieving glycemic control from baseline to endpoint in pediatric subjects with type 2 diabetes mellitus, as demonstrated by statistically significant decreases in HbA1c. However, glimepiride was not shown to be non-inferior to metformin according to the criterion specified in the protocol with or without excluding the protocol violators.

In terms of the secondary outcome variables, there was no significant difference between treatments in mean decreases in fasting SMBG from baseline to each visit. There was no significant difference between treatment groups in changes from baseline for total cholesterol, HDL cholesterol, and triglycerides. A statistically significant difference was observed between glimepiride and metformin in their changes in LDL cholesterol from baseline. However, the change from baseline within each group was not significant; a non-significant increase from baseline was observed with glimepiride and a non-significant decrease was observed with metformin. A small and non-significant increase from baseline in was observed at Week 24 in the glimepiride (per-protocol, ITT and safety) subjects, and a decrease in BMI that was statistically significant was observed in the metformin (per-protocol, ITT and safety) group. However, no significant difference between treatments for changes in BMI from baseline to Week 24 was observed for the per-protocol subjects, while there appears to be a statistically significant difference between treatments for the ITT and safety subjects.

# 6 LABELLING

## 6.1 ORIGINAL VERSION

(b) (4)

## 6.2 CORRECTED VERSION

(b) (4)

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/s/
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Joan Buenconsejo
9/14/2005 01:23:39 PM
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Todd Sahlroot
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BIOMETRICS

S. Edward Nevius
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Concur with review.