These results are supplied for informational purposes only. *Prescribing decisions should be made based on the approved package insert in the country of prescription*			
Sponsor/company:	Sanofi-aventis	**ClinialTrials.gov Identifier:**	NCT00353691
		Study Code:	HOE490_4038
Generic drug name:	Glimepiride	**Date:**	27 July 2007

STUDY SYNOPSIS

Study number HOE490_4038

Title

Glimepiride versus Metformin as Monotherapy in Pediatric Subjects with Type 2 Diabetes Mellitus: A Single Blind Comparison Study

Investigator(s), study site(s)

Multinational (96 sites): US (47), Argentina (2), Brazil (10), Costa Rica (1), Mexico (9), Peru (4), Germany (3), Hungary (2), Poland (5), India (7), S. Korea (2), Taiwan (2), and S. Africa (2)

Sponsor's responsible medical officer: Aleksandra Vlajnic, MD

Study duration and dates

The first subject was enrolled on 11 October 2002, and the last subject completed the study on 15 November 2004

Phase IIIb

Objectives

Primary Objective:

To compare the change in glycemic control from baseline to endpoint (last available posttreatment assessment) as measured by hemoglobin A1c (HbA1c) in pediatric subjects with type 2 diabetes receiving either glimepiride or metformin as monotherapy

Secondary Objectives:

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

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.

Study design

This was a 26-week (2 weeks screening and 24 weeks treatment) multinational, randomized, single-blind (subject-blinded), parallel-group, active-treatment controlled study in pediatric subjects with type 2 diabetes who had not responded adequately to 2 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 (to 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.

Number of subjects planned

A total of 200 subjects were to be enrolled; at least 50% of the enrolled subjects were to be African-American, Native American, or Latino/Hispanic. (The protocol requirement stating that at least 25% were to be under 12 years of age was waived per FDA letter of 14 April 2004)

Inclusion criteria

Subjects 8 to 17 years of age at the time of randomization who had type 2 diabetes treated with diet and exercise only for at least 2 weeks prior to randomization, or who were previously or currently treated with an oral agent and had not responded to diet, exercise, and oral therapy for at least 3 months (documented by an HbA1c >7.5%).
Subjects who completed glimepiride pharmacokinetic Study HOE 490/4045 at preselected sites within 3 weeks prior to the screening period were also permitted to enroll. Subjects were required to be negative for islet cell antigen (ICA) and glutamic acid decarboxylase (GAD) autoantibodies and to have a C-peptide level at 90 minutes of ≥1.5 ng/mL. The HbA1c was required to be >7.1% at screening and <12.0% on the day of randomization.

Treatments

Subjects were assigned to 1 of 2 treatment arms:
Glimepiride group: 1 mg or 4 mg tablets encapsulated; subjects were started at 1 mg daily (1 capsule in the morning), and titrated at Weeks 4, 8, and 12, based on mean SMBG, to a maximum of 8 mg in the morning (2 capsules 4 mg glimepiride). To maintain subject blinding, placebo was taken in the evening, using the same number of capsules as taken for the morning dose of glimepiride.
Metformin group: 500 mg tablets; subjects were started at 500 mg (1 tablet) twice daily, and titrated once at Week 12, based on mean SMBG, to 1000mg (2 tablets) twice daily.

Efficacy data

The primary endpoint was change in HbA1c from baseline to Week 24 or last evaluable ontreatment 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 secondary endpoints were as follows:
Change in HbA1c from baseline to Week 12.
Responder rate, defined as the proportion of subjects with HbA1c< 7.0% at Week 24 or the last evaluable on-therapy observation.
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).
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.
Percent completers, which was defined by subjects who continued study medication until completion of all requirements of Visit 6 (Week 18).
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.
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.

Safety data

Safety data included adverse events reported by the subject or noted by the investigator, vital signs, and standard hematology, serum chemistry, and urinalysis. Safety data also included episodes of hypoglycemia. Female subjects were assessed for menstrual patterns and pregnancy as determined from urine pregnancy testing.

Statistical procedures

The per-protocol population was the primary population for which all efficacy analyses were performed. Prespecified 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. Statistical tests on continuous variables for the secondary objectives were also analyzed using ANCOVA; categorical variables were analyzed by the Cochran Mantel Haenszel procedure, controlling for pooled countries, and by logistic regression, controlling for pooled countries and Tanner stage stratum.

Interim analysis
No interim analysis was performed.

Results - Study subjects and conduct
A total of 536 pediatric subjects with diabetes type 2 were enrolled and screened, and 285 subjects were randomized. One subject randomized to metformin withdrew before treatment, resulting in 284 subjects in the safety population. A total of 263 (132 glimepiride and 131 metformin) constituted the ITT, 218 (107 glimepiride and 111 metformin) constituted the completer, and 162 (81 glimepiride and 81 metformin) constituted the per-protocol population. The mean age was 14 years and 33% were males. About 40% were Hispanic, 21% African-American, 15-17% Asian, and 13-15% White. Subjects tended to be at higher Tanner stage, with about 40% at Tanner stage 5. For the safety population, the mean dose of glimepiride at last visit was 3.6 mg daily; 42% used 1 mg daily as their maximum dose and 31% used 8 mg daily as their maximum dose. The mean dose of metformin was 1373 mg; 60% used 1000 mg daily as their maximum dose and 39% used 2000 mg daily as their maximum dose.

Results – Efficacy
The per-protocol population was used for the primary analyses, in response to a FDA written request. The results of the ITT analyses followed the same general pattern as the results of the per-protocol analyses. Some of the ITT results are discussed in the body of the report; additional results and data are presented in the end-of-text listings and figures and in the appendices.

Results of the analysis of the per-protocol population:
Primary variable: Decreases from baseline in HbA1c at Week 24 were significant for both the glimepiride group *(P = 0.0034)* and the metformin group *(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 $\leq$ 7.0%, or the time to achieve this endpoint. Because the upper limit of the 95% CI exceeded the predefined limit of 0.3%, the non-inferiority criterion was not met. One possible explanation for not meeting the non-inferiority criterion may be insufficient power due to the fact that the standard deviations of the mean changes in HbA1c for both treatment groups in the per-protocol analysis were much larger (approximately 2.0) than that used in the estimation of the sample size (1.2), such that the power of the study was only 40%.

Secondary variables: Decreases in fasting SMBG from baseline were statistically significant at all visits, except at Weeks 4 and 24 for glimepiride; there was no significant difference between the 2 groups. 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.
Total cholesterol increased by a mean of 0.206 mmol/L at Week 24 with glimepiride; although clinically a small increment, this increase was statistically significant *(P = 0.0123)*. Total cholesterol did not change significantly with metformin. There was no significant difference between treatment groups in their change in total cholesterol from baseline.
No significant changes from baseline in HDL cholesterol were observed in either treatment group.
A nonsignificant increase from baseline in mean LDL was observed with glimepiride and a nonsignificant decrease was observed with metformin.
The difference between the 2 treatments in changes in LDL from baseline was statistically significant *(P = 0.0415).* Increases from baseline in triglycerides were not significant with glimepiride but were statistically significant *(P = 0.0368)* with metformin. The difference between the 2 treatment groups in change from baseline was not significant.
There was no significant difference between treatments in their change in BMI from baseline at week 24 for the per-protocol subjects.

Results – Safety

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.
Serious adverse events were reported for 15 subjects; the event occurred before glimepiride treatment was initiated in 1 of these subjects and during the screening phase before randomization for 2 screen failure subjects. Treatment-emergent serious adverse events occurred for 7/142 (4.9%) glimepiride subjects and for 5/142 (3.5%) metformin subjects. The incidence of serious adverse events was similarly low (ä5%) in both treatment groups. The incidence of discontinuations from study medication was also similarly low for the 2 groups.
Hypoglycemic episodes occurred in 16% of glimepiride and 13% of metformin subjects. One subject in each group had a severe episode
No clinically important changes were observed in vital signs, and menstrual patterns. Subjects grew a mean of 1 cm in both groups during the study, and a mean weight increase of 1.3 kg was statistically significant in the glimepiride group

Date of report

04-Mar-2005