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Sponsor / Company: sanofi-aventis **Drug substance(s):** Glimepiride and Metformin	**Study Identifier:** NCT00924573 **Study code:** EFC10846
Title of the study: A multi-center, randomized, double-blind, placebo-controlled, parallel-group, 24-week administration study to investigate the efficacy and safety of HOE490 O (glimepiride/metformin) compared with placebo in Type 2 diabetes mellitus patients who have inadequately controlled blood sugar with a fixed dose of glimepiride.	
Study center(s): Multi-center (Japan, 36 centers)	
Study period: Date first patient enrolled: 11-May-2009 Date last patient completed: 18-Mar-2010	
Phase of development: Phase III	
Objectives: **Primary objective:** To investigate the efficacy of HOE490 O (glimepiride/metformin) in comparison with the control of glimepiride in combination with placebo, with hemoglobin A1C (HbA1C) degradation as an indicator. **Secondary objective:** To investigate the safety of HOE490 O (glimepiride/metformin) in comparison with the control of glimepiride in combination with placebo.	
Methodology: Multi-center, randomized, double, blind, placebo-controlled, parallel-group, 24-week administration	
Number of patients: **Planned:** 180 (90 in each group) **Randomized:** 189 (glimepiride + placebo (G + P) group: 93, glimepiride + metformin (G + M) group: 96) **Administered:** 189 (G + P group: 93, G + M group: 96)	
Diagnosis and criteria for inclusion: **Study population:** Patients with type 2 diabetes mellitus **Inclusion criteria:** • Patients with type 2 diabetes mellitus currently taking a fixed dose of Amaryl® tablets in addition to diet and exercise • Patients from whom documented consent was obtained **Main exclusion criteria:** • Patients whose HbA1C at -6 weeks and -2 weeks was less than 7.0% or over 11.0% (centralized measurement of the National Glycohemoglobin Standardization Program : NGSP) • Patients who, at the start of screening, were taking a low dose (less than 2 mg/day) of Amaryl® tablets or a high dose (over 6 mg/day) of Amaryl® tablets. • Patients who had been administered a hypoglycemic agent other than Amaryl® tablets within 8 weeks prior to screening or who had been administered a hypoglycemic agent other than the study drug between screening and inclusion. • Type1 diabetes mellitus patients Note) Subjects whose C-peptide at -6 weeks was lower than 0.5 ng/ml were to be excluded since they had type 1 diabetes mellitus. • Patients aged less than 20 or over 75 years of age at the time of consent • Patients whose laboratory test values at -6 weeks were as follows: - ALT and/or AST over 3 times the upper limit of normal - Neutrophil count less than 1 000/mm3 and/or platelet count less than 100 000/mm3 - Hemoglobin less than 11 g/dl - Creatinine over 1.3 mg/dl (males) or over 1.0 mg/dl (females) • Other patients considered by the principal investigator or sub-investigator to be unsuitable for participation in this study.	

Investigational product:

Test drug: glimepiride tablets and metformin tablets

Control drug: placebo

Dose: Glimepiride tablets

- 1 mg tablet: tablet formulation containing 1 mg glimepiride
- 3 mg tablet: tablet formulation containing 3 mg glimepiride

Metformin tablets or placebo tablets

- 250 mg metformin tablet: tablet formulation containing 250 mg metformin
- Placebo tablet: tablet formulation not containing metformin but with an identical appearance to the 250 mg tablet

Administration:

Glimepiride was started as oral administration from -6 weeks.
From Week 0, a 250 mg tablet metformin or placebo tablet was administered twice daily postprandially morning and evening as well as glimepiride. If, at Week 12, glycemic control was still poor, the dose was increased to 750 mg metformin (500 mg morning, 250 mg evening) or 3 placebo tablets (2 tablets morning, 1 tablet evening).

Duration of treatment: Maximum 32 weeks

- Screening period: 6 weeks ± 1 week
- Administration period: 24 weeks ± 1 week

Criteria for evaluation:

Efficacy:

Primary endpoint

- HbA1C change from Week 0 to Week 24 (or final evaluation)

Secondary endpoints

- At Week 24 (or final evaluation) the proportion of subjects with HbA1C of less than 7.0% and less than 6.5%
- Change in fasting plasma glucose (FPG) from Week 0 to Week 24 (or final evaluation)
- Change in lipid metabolism parameters (total cholesterol, HDL-cholesterol, LDL-cholesterol, neutral fat) from Week 0 to Week 24 (or final evaluation)
- Change in weight, BMI, HOMA-IR, HOMA-β, adiponectin, TNF-α, IRI, and C-peptide from Week 0 to Week 24 (or final evaluation)

Safety:

Adverse events, adverse events for which a causal relationship with the investigational drug cannot be ruled out, hypoglycemia, laboratory test values, potentially clinically significant abnormalities (PCSA) and vital signs (blood pressure)

Statistical methods:

Intent to treat (ITT) population:

The ITT population (i.e. patients who had received at least once, during this study, combined administration of the study drug and for whom data were collected for primary endpoints at least once at the start of combined administration (Week 0) and after the start of combined administration), was the efficacy analysis population. In addition, an analysis was also carried out on the PP population (i.e. patients from the ITT population with no major protocol deviations). The safety analysis population consisted of patients who had received combined administration of the study drug at least once during the study. However, patients with "a record of unconfirmed inclusion criteria" (i.e. protocol deviation) were excluded from the efficacy and safety analyses.

Efficacy analysis:

Primary analysis

For the ITT population, based on change in the response variable HbA1C in the G + M group and G + P groups, the explanatory variable of the administration group, and the analysis of covariance (ANCOVA) for the covariation of the HbA1C baseline value for Week 0 to Week 24 (or final evaluation), the superiority of the G + M group over the G + P group was confirmed.

Secondary analysis

- The point estimation and 95% two-sided confidence interval was calculated for change in HbA1C at each timepoint from Week 0 to Week 24 (or final evaluation)
- Changes in the proportion of subjects whose HbA1C was less than 7.0% and less than 6.5% from Week 0 to Week 24 (or final evaluation) were compared.
- Changes in FPG from Week 0 to Week 24 (or final evaluation) were compared.
- Changes in lipid metabolism parameters (total cholesterol, HDL-cholesterol, LDL-cholesterol, neutral fat) from Week 0 to Week 24 (or final evaluation) were compared.
- Changes in weight and BMI from Week 0 to Week 24 (or final evaluation) were investigated.
- Changes in HOMA-IR, HOMA-β, adiponectin, TNF-α, IRI, and C-peptide from Week 0 to Week 24 (or final evaluation) were investigated.

Safety analysis:

・ Adverse events including abnormal changes in laboratory test values were grouped by diagnosis (or symptom), and the incidence rate calculated.

・ Hypoglycemia levels were grouped, and the incidence rate and number of incidences per month per patient were calculated. The incidence of hypoglycemia in patients who had achieved HbA1C of less than 7% was evaluated.

・ The incidence of laboratory test values corresponding to PCSAs was investigated.

Summary:

Efficacy results:

The amount of change in HbA1C from Week 0 to the final evaluation was 0.29 ± 0.79% in the G + P group (mean value ± standard deviation) and 0.48 ± 0.72% in the G + M group. The inter-group variation (G + M group – G + P group) of the adjusted mean of the amount of variation in HbA1C from Week 0 to the end of evaluation and the 95% two-sided confidence interval were -0.75% (-0.961 - -0.536), and the superiority of the G + M group in comparison with the G + P group was shown ($p<0.0001$).

Change in FPG from Week 0 to the final evaluation was 14.9 ± 29.8 mg/dl in the G + P group and -6.6 ± 27.4 mg/dl in the G + M group. The inter-group variation of the adjusted mean of the amount of variation in FPG from Week 0 to the end of evaluation and the 95% two-sided confidence interval were -20.3 mg/dl (-27.86 - -12.81), and a significant difference between the G + M group and the G + P group was found ($p<0.0001$).

Concerning changes in lipid metabolism parameters from Week 0 to the final evaluation, total cholesterol and LDL-cholesterol were significantly lower in the G + M group compared to the G + P group ($p = 0.0001$ and $p = 0.0006$).

Concerning changes in HOMA-β from Week 0 to the final evaluation, there was a significant increase in the G + M group compared to the G + P group ($p = 0.0443$).

Concerning changes in weight and BMI from Week 0 to the final evaluation, no significant differences were found ($p = 0.0713$ and $p = 0.0598$).

Safety results:

The incidence rate of treatment emergent adverse events (TEAE) was 59.8% (55/92 patients) in the G + P group and 64.6% (62/96 patients) in the G + M group. The TEAEs (preferred term) with the incidence rate over 3% higher in the G + M group than in the G + P group were “upper respiratory inflammation” (G + P group 4.3% (4/92 patients), G + M group 11.5 % (11/96 patients), “hypoglycemia” (G + P group 3.3% (3/92 patients), G + M group 8.3 % (8/96 patients) and “abdominal discomfort” (G + P group 0.0% (0/92 patients), G + M group 3.1 % (3/96 patients)). The severity of all TEAEs in the G + M group was mild or moderate.

The incidence rate of TEAEs for which a causal relationship with the study drug could not be ruled out was 8.7% (8/92 patients) in the G + P group and 19.8% (19/96 patients) in the G + M group. The TEAEs (preferred term) for which a causal relationship with the study drug could not be ruled out and which had an incidence rate of over 3% higher in the G + M group than in the G + P group were “hypoglycemia” (G + P group 3.3% (3/92 patients), G + M group 8.3 % (8/96 patients) and “constipation (G + P group 1.1% (1/92 patients), G + M group 5.2 % (5/96 patients)).

There were no deaths. Also, the incidence rate of severe TEAEs was 4.3% (4/92 patients) in the G + P group and 1.0% (1/96 patients) in the G + M group, and a causal relationship between these severe TEAEs and the study drug was ruled out.

The incidence rate of TEAEs leading to the study treatment discontinuation was 2.2% (2/92 patients) in the G + P group and 5.2% (5/96 patients) in the G + M group. Also, although there were no TEAEs leading to study treatment discontinuation for which a causal relationship with the study drug was found in the G + P group, there were 3.1 % (3/96) in the G + M group, with 1 case each of “constipation”, “fatigue” and “abnormal liver function test”.

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