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Sponsor / Company: Sanofi **Drug substance(s):** HOE490 (glimepiride)	**Study Identifiers:** NCT01459809, UTN Number U1111-1119-9984 **Study code:** GLIME_R_05809
Title of the study: A multinational, open label, randomized, active-controlled, 3-arm parallel group, 24-week study comparing the combination of glimepiride and metformin versus glimepiride and metformin alone in patients with type 2 diabetes	
Study center(s): A total of 54 centers were active, recruiting patients in 14 countries: Algeria, Colombia, Egypt, Guatemala, India, Iran, Lebanon, Mexico, Russia, South Africa, Tunisia, Turkey, United Arab Emirates, and Ukraine	
Study period: Date first patient enrolled: 14/Feb/2012 Date last patient completed: 28/Jan/2014	
Phase of development: Phase 3	
Objectives: The primary objective of the study was to demonstrate the superiority of the glimepiride + metformin free combination in comparison to glimepiride or metformin alone in terms of HbA_{1c} reduction, during a 24-week treatment period in patients with type 2 diabetes mellitus (T2DM). Secondary Objectives: To assess the effects of the free combination of glimepiride and metformin in comparison to glimepiride or metformin alone on: • Percentage of patients reaching HbA_{1c} <7%, • Percentage of patients reaching HbA_{1c} <6.5%, • Fasting Plasma Glucose (FPG), and • Safety and tolerability.	
Methodology: Multinational, active comparator-controlled, 3-arm parallel-group, randomized (1:1:1 ratio), open-label study. The study comprised 3 periods: • Up to 2-week screening period • 24-week treatment period: patients who meet eligibility criteria at the end of the screening period were randomized to one of the 3 following arms and were assessed at clinical visits. - Arm 1: glimepiride - Arm 2: metformin - Arm 3: glimepiride + metformin, in free combination Blood Glucose meter was provided by the Sponsor for Self-Monitored Plasma Glucose (SMPG). Patients were required to measure their FPG at least 3 times per week on 3 separate days during the main 24-week period for the adjustment of the treatment dose, and were advised to measure their FPG at least 3 times per week on 3 separate days during the main 24-week period in order to detect asymptomatic hypoglycemia.	

On-site visits: Visit 2: baseline, Week 0; Visit 3: week 2; Visit 4: Week 4; Visit 5: Week 6; Visit 8: Week 12; Visit 11: Week 24
Phone call visits: Visit 6: Week 8; Visit 7: Week 10; Visit 9: Week 16; Visit 10: Week 20

- 3-day safety follow-up: Visit 12 to assess if no new adverse event (AE) or hypoglycemia 3 days after the end of treatment (Phone call visit)

Number of patients**:** Planned: approximately 540 randomized patients (180 in each arm)

Randomized: 541

Treated: 538

Evaluated:

	Metformin	**Glimepiride**	**Glimepiride + Metformin**	**Total**
Randomized population	177	182	182	541
Modified-Intent-to-treat population (mITT)	175 (98.9%)	181 (99.5%)	179 (98.4%)	535 (98.9%)
Per Protocol (PP) population	169 (95.5%)	173 (95.1%)	172 (94.5%)	514 (95.0%)
Safety population	176	182[a]	180[a]	538[b]

Percentage calculated from Randomized population

Modified-Intent-to-treat population: all patients who were randomized, received at least one dose of investigational product, and had at least one post-baseline assessment during comparative period of any primary or secondary efficacy variables

Safety population: all randomized and treated patients (according to treatment actually received).

a One patient was randomized in glimepiride + metformin arm and received glimepiride only.

b Three patients were randomized but not treated.

Diagnosis and criteria for inclusion: Patients with T2DM, as defined by the World Health Organization (WHO), aged 18-78 years, not treated with hypoglycemic agent within the 3 months prior to study entry and with HbA_{1c} ≥7.6% and ≤9%, diagnosed within one year prior to the screening visit. The diagnosis of T2DM was based on the following: FPG ≥126 mg/dL (7 mmol/L) or 2 hours postprandial plasma glucose ≥200 mg/dL (11.1 mmol/L). The signed informed consent was obtained prior to any study procedure.

Study treatments

Investigational medicinal product(s): Glimepiride and metformin were provided by the Sponsor.

Formulation: Glimepiride: tablets that contain 1 mg; Metformin: tablets that contain 500 mg.

Route(s) of administration: Oral

Dose regimen: After randomization, the investigational medicinal product (IMP) doses were increased, every 2 weeks, according to FPG levels (obtained by the calculation of the average fasting SMPG assessments on 3 separate days within one week before visits). The goal of the dose adjustment was to achieve fasting SMPG values ≤130mg/dL (7.2 mmol/L) and >70 mg/dL (3.9 mmol/L) without symptomatic hypoglycemia. The dose increase was as follows:

Arm 1: From randomization (Visit 2) to Week 2 (Visit 3), patients received 2 mg/day of glimepiride or 1 mg/day of glimepiride if FPG at baseline (Visit 2) <180 mg/dL (10 mmol/L). From Week 2 (Visit 3), the daily dose was increased by 1 mg every 2 weeks up to the usual maximum effective dose of 4 mg daily. Glimepiride was taken in the morning, immediately before breakfast or before the first meal.

Arm 2: From randomization (Visit 2) to Week 2 (Visit 3): patients received 500 mg twice a day (BID) (1000 mg/day) of metformin. From Week 2 (Visit 3): the dose was increased by 500 mg every 2 weeks up to the usual maximum dose of 2000 mg daily. Metformin was taken once in the morning and once in the evening, during or after the meals.

Arm 3: From randomization (Visit 2) to Week 2 (Visit 3): patients received 2 mg/day of glimepiride or 1 mg/day of glimepiride if FPG at baseline (Visit 2) <180 mg/dL (10 mmol/L) and 500 mg BID (1000 mg/day) of metformin. From Week 2 (Visit 3), glimepiride daily dose was increased by 1 mg every 2 weeks up to 4 mg/day and metformin daily dose was increased by 500 mg every 2 weeks, up to 2000 mg/day. Glimepiride was taken once in the morning, immediately before breakfast or before the first meal and metformin was taken BID, in the morning and in the evening during or after the meals.

Duration of treatment: 24 weeks

Duration of observation: 27 weeks (2-week screening period followed by 24-week treatment period and 3-day safety follow-up period).

Criteria for evaluation:

Efficacy:

Primary Endpoint: Change in HbA_{1c} from baseline (Week 0) to the end of treatment.

Secondary Endpoints:

- Percentage of patients with HbA_{1c} <7% and <6.5% at the end of treatment.
- Change in FPG from baseline (Week 0) to the end of treatment.

Safety:

- Adverse events (AEs), serious adverse events (SAEs)
- Physical examination (including body weight), vital signs
- Frequency and incidence of hypoglycemia during the study period: asymptomatic hypoglycemia, documented symptomatic hypoglycemia, severe hypoglycemia, probable symptomatic hypoglycemia, relative (pseudo) hypoglycemia, and nocturnal hypoglycemia

Statistical methods:

The mITT population consisted of all patients who were randomized, received at least one dose of IMP, and had at least one post-baseline assessment of any primary or secondary efficacy variables, irrespective of compliance with the study protocol and procedures.

In order to control globally the type I error for both primary and secondary criteria described before due to multiplicity, a Bonferroni correction of the type I threshold (primary criterion) combined to a hierarchical step-down testing procedure (secondary criteria), described by Hochberg and Tamhan, was applied.

Efficacy analyses:

The primary analysis investigated the absolute change in HbA_{1c} from baseline to the end of treatment and was based on the mITT population. The end of treatment value was the last available HbA_{1c} value measured during the study treatment up to 14 days after the last dose.

In order to test the hypothesis that there is no difference between the treatment arms, an analysis of covariance (ANCOVA) was performed, using change from baseline to last on-treatment measurement, with treatment and group of countries as fixed effect and the corresponding baseline value as a covariate.

Secondary HbA_{1c} summaries and analyses were based on the mITT population.

Glycated hemoglobin response rates, assessed as the percentage of patients who reach the targets of HbA_{1c} <7% and HbA_{1c} <6.5%, were summarized descriptively at each visit (Week 12 and Week 24) and at the end of treatment, by treatment group and overall. Comparison between treatments (combination - glimepiride / combination - metformin) in HbA_{1c} response rates at end of treatment was performed using Pearson's chi-square test, conditionally to the global control of the type I error. In the event of an expected frequency of less than 5 patients falling into a category within a treatment group, then Fisher's exact test had to be used.

FPG summaries and analyses were based on the mITT population. Fasting plasma glucose was summarized descriptively at each visit (Week 0, Week 12, and Week 24) and at end of treatment, by treatment group and overall. Change from baseline in FPG at end of treatment was analyzed and compared using an ANCOVA model with a fixed effect for treatment and a covariate for baseline, conditionally to the global control of the type I error.

Safety analyses:

All safety analyses were based on the safety population (all randomized and treated patients).

The number and percentage of patients with treatment-emergent adverse events (TEAEs), serious TEAEs, possibly treatment-related TEAEs, TEAEs leading to treatment discontinuation, and deaths were described.

Analyses were conducted on the frequency of patients with hypoglycemia using Pearson chi-square or Fisher's exact test (depending on the number of events) and on the number of hypoglycemic episodes per patient-year of exposure, using a generalized linear model based on a Poisson, negative binomial, zero-inflated Poisson, or zero-inflated negative binomial distributions.

Change from baseline in body weight at end of treatment was analyzed and compared using an ANCOVA model with a fixed effect for treatment and baseline as a covariate.

Summary:

Population characteristics:

A total of 996 patients were screened, 541 were randomized, 538 were randomized and exposed to the study treatment, 1 patient was exposed to study treatment without being randomized, and 454 patients (45.6%) were screening failures. The main reason for screening failures was an HbA_{1c} out of required range (exclusion criterion: HbA_{1c} <7.6% or >9%).

A total of 513 patients (95.4% of the randomized and treated population) completed the study: 169 (96.0%) in the metformin arm, 177 (97.8%) in the glimepiride arm and 167 (92.3%) in the glimepiride + metformin arm. Twenty-five patients (4.6%) prematurely discontinued the study treatment: 7 patients (4.0%) in the metformin arm, 4 patients (2.2%) in the glimepiride arm, and 14 patients (7.7%) in the glimepiride + metformin arm. Four patients discontinued for AEs (further described in the safety results section below).

Demographics and baseline characteristics were similar between treatment arms. Nearly half of the patients from the randomized population were male (49.4 %); the mean (±SD) age was 50.9 (±10.0) years. Mean body weight was 78.8 (±13.9) kg and body mass index was 29.1 (±4.1) kg/m². Median time since diagnosis of diabetes was 2.3 months (mean 3.4 months). The starting dose of metformin was 1000 mg for nearly all the patients (173 [98.3%] in the metformin arm and 176 [97.8%] in the glimepiride + metformin arm).The starting dose of glimepiride was 1 mg in the majority of the patients (158 [86.8%] in the glimepiride arm and 152 [84.4%] in the glimepiride + metformin arm). At the end of the study, the mean (±SD) dose of metformin was 1645 (±457.0) mg in the metformin arm and 1314 (±442.3) mg in the glimepiride + metformin arm; the mean (±SD) dose of glimepiride was 2.4 (±1.2) mg in the glimepiride arm and 1.9 (±1.1) mg in the glimepiride + metformin arm.

Efficacy results:

At baseline, mean (±SD) HbA_{1c} was 8.2% (±0.4%) in the mITT population, similar in all treatment arms. At Week 12, mean HbA_{1c} was 6.8% (±0.8%) in both metformin and glimepiride arms and 6.6% (±0.8%) in the glimepiride + metformin arm. At Week 24 as well as at end of treatment, mean HbA_{1c} was 6.8% (±0.9%) in both metformin and glimepiride arms and 6.7% (±1.0%) in the glimepiride + metformin arm.

The adjusted mean change in HbA_{1c} from baseline to end of treatment was -1.37% in the metformin arm, -1.36% in the glimepiride arm and -1.50% in the glimepiride + metformin arm. The adjusted mean difference (±SE) was -0.13% (±0.10%) (p=0.175) between the glimepiride + metformin arm and the metformin arm and -0.14% (±0.10%) (p=0.145) between the glimepiride + metformin arm and the glimepiride arm. The superiority of the combination glimepiride + metformin compared to metformin or glimepiride alone was not demonstrated. Similar results were obtained on the PP population.

In the mITT population, 59.3% of the patients treated with metformin, 64.6% of the patients treated with glimepiride and 71.1% of the patients treated with glimepiride + metformin reached an HbA_{1c} level <7% at the end of the treatment period. They were 30.8%, 31.5%, and 45.7%, respectively to reach an HbA_{1c} <6.5%.

At baseline, mean (±SD) FPG was 150 (±32) mg/dL in the mITT population, similar in all treatment arms. A mean decrease in FPG was observed in all treatment arms, with an adjusted mean change (±SE) in FPG from baseline to end of treatment of -25 (±2.4) mg/dL in the metformin arm and in the glimepiride + metformin arm and 20 (±2.3) mg/dL in the glimepiride arm.

In the 3 treatment arms, mean self-monitored fasting plasma glucose (SMFPG) decreased from Week 2 to Week 12 and remained at a similar level from Week 12 to Week 24. Overall, mean (±SD) SMFPG was 135.1 (±27.7) mg/dL at Week 2, 121.3 (±20.6) mg/dL at Week 12, and 123.8 (±20.9) mg/dL at Week 24.

Safety results:

The proportion of patients experiencing at least one TEAE was similar in the 3 treatment arms. During the study treatment period, 15 patients (2.8%) experienced at least one SAE: 3 (1.7%) in the metformin arm, 5 (2.7%) in the glimepiride arm, and 7 (3.9%) in the glimepiride + metformin arm. No serious hypoglycemia and no deaths were reported during the treatment period.

Four patients had to permanently discontinue the study treatment due to AEs: 2 patients (1.1%) in the metformin arm due to TEAEs related to treatment (1 patient presenting with dehydration [SAE], abdominal pain, diarrhea, nausea, and vomiting, and 1 patient presenting with gastritis) and 2 patients (1.1%) in the glimepiride + metformin arm due to pregnancy in both cases.

Overview of Treatment emergent adverse events – Safety population

Number (%) of patients with at least one	Metformin (N=176)	Glimepiride (N=182)	Glimepiride + Metformin (N=180)
any TEAE	47 (26.7%)	53 (29.1%)	55 (30.6%)
Any TEAE possibly related to glimepiride	0	4 (2.2%)	5 (2.8%)
Any TEAE possibly related to metformin	14 (8.0%)	0	10 (5.6%)
Any serious TEAE	3 (1.7%)	5 (2.7%)	7 (3.9%)
Any fatal TEAE	0	0	0
Any TEAE leading to permanent treatment discontinuation	2 (1.1%)	0	2 (1.1%)

TEAE: treatment-emergent adverse event

Mean blood pressure and heart rate remained stable in all treatment arms. The adjusted mean (±SE) change in weight from baseline to the end of treatment was -1.63 (±0.21) kg in the metformin arm, 0.17 (±0.20) kg in the glimepiride arm and 0.16 (±0.21) kg in the glimepiride + metformin arm. Between baseline and end of treatment, a weight decrease of more than 5% was observed for 14 patients (8.2%) in the metformin arm, 6 patients (3.4%) in the glimepiride arm, and 10 patients (5.7%) in the glimepiride + metformin arm, and a weight increase of more than 5% was observed for 2 patients (1.2%), 7 patients (3.9%), and 14 patients (8.0%), respectively.

Hypoglycemia episodes (of any type) were mainly reported in patients treated with glimepiride: 17.6% of the patients treated with glimepiride alone and 23.9% of the patients treated with glimepiride + metformin. Only 5.1% of the patients treated with metformin alone reported hypoglycemic episodes. A total of 5 patients (0.9%) reported severe hypoglycemia: 1 patient (0.5%) in the glimepiride arm and 4 patients (2.2%), in the glimepiride + metformin arm.

Episodes of hypoglycemia – Safety population

	Metformin (N=176)	Glimepiride (N=182)	Glimepiride + Metformin (N=180)	p-value	
				(Gli + Met) vs Met	(Gli + Met) vs Gli
Patients with at least one episode of:	**n (%) [97.5% CI]**	**n (%) [97.5% CI]**	**n (%) [97.5% CI]**		
Hypoglycemia	9 (5.1%) [2.5%; 10.2%]	32 (17.6%) [12.2%; 24.8%]	43 (23.9%) [17.5%; 31.7%]	<0.001 (C)	0.139 (C)
Asymptomatic and/or symptomatic hypoglycemia confirmed by PG ≤70 mg/dL	6 (3.4%) [1.4%; 8.0%]	18 (9.9%) [6.0%; 16.0%]	38 (21.1%) [15.1%; 28.7%]	<0.001 (C)	0.003 (C)
Asymptomatic hypoglycemia	4 (2.3%) [0.5%; 6.3%]	5 (2.7%) [0.7%; 6.9%]	14 (7.8%) [3.9%; 13.5%]	0.018 (C)	0.032 (C)
Symptomatic hypoglycemia	5 (2.8%) [1.1%; 7.2%]	28 (15.4%) [10.3%; 22.3%]	33 (18.3%) [12.8%; 25.6%]	<0.001 (C	0.454 (C)
Symptomatic hypoglycemia confirmed by PG ≤70 mg/dL	2 (1.1%) [<0.1%; 4.5%]	14 (7.7%) [3.9%; 13.3%]	28 (15.6%) [10.0%; 22.6%]	<0.001 (C)	0.020 (C)
Severe symptomatic hypoglycemia	0 [0%; 2.5%]	1 (0.5%) [<0.1%; 3.5%]	4 (2.2%) [0.5%; 6.1%]	0.123 (F)	0.214 (F)
Nocturnal symptomatic hypoglycemia	1 (0.6%) [<0.1%; 3.6%]	3 (1.6%) [0.3%; 5.3%]	3 (1.7%) [0.3%; 5.3%]	0.623 (F)	1.000 (F)
Nocturnal symptomatic hypoglycemia confirmed by PG ≤70 mg/dL	0 [0%; 2.5%]	0 [0%; 2.4%]	3 (1.7%) [0.3%; 5.3%]	0.248 (F)	0.122 (F)
Nocturnal severe symptomatic hypoglycemia	0 [0%; 2.5%]	0 [0%; 2.4%]	1 (0.6%) [<0.1%; 3.5%]	1.000 (F)	0.497 (F)

No missing data; Met=metformin; Gli=glimepiride
(C) Chi-square test; (F) Fisher's exact test; Alpha level (α) = 2.5% (significant if p<0.025).

The adjusted mean rate (±SE) of hypoglycemia per patient-year was 0.16 (±0.05) in the metformin arm, 0.86 (±0.21) in the glimepiride arm, and 1.89 (±0.42) in the glimepiride + metformin arm.

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