*These results are supplied for informational purposes only.*
*Prescribing decisions should be made based on the approved package insert in the country of prescription.*

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| **Sponsor / Company:** Sanofi<br>**Drug substance(s):** HOE4900 | **Study Identifiers:** NCT01699932, UTN U1111-1120-0058<br>**Study code:** GLMET_R_05823 |
| **Title of the study:** A multinational, open-label, non-comparative, 24-week study to evaluate the blood glucose lowering efficacy and safety of a fixed dose combination of glimepiride and metformin in patients with inadequately controlled type 2 diabetes | |
| **Study center(s):** A total of 13 centers were active, recruiting patients in 3 countries: Lebanon, Russian Federation, and Ukraine. | |
| **Study period:**<br>Date first patient enrolled: 26/Sep/2012<br>Date last patient completed: 17/Apr/2014 | |
| **Phase of development:** Phase 3 | |
| **Objectives:**<br>Primary objective: To demonstrate the efficacy of a fixed combination of glimepiride + metformin in terms of glycated hemoglobin ($HbA_{1c}$) reduction, during a 24-week treatment period in patients with inadequately controlled type 2 diabetes mellitus (T2DM).<br>Secondary objectives: To assess the effects of the fixed combination of glimepiride and metformin at Week 24 on:<br>• Percentage of patients reaching HbA1c <7%;<br>• Percentage of patients reaching HbA1c <6.5%;<br>• Fasting Plasma Glucose (FPG);<br>• Safety and tolerability. | |
| **Methodology:** Multinational, non-comparative, 24-week, open-label study.<br>The study is comprised of 3 periods:<br>• 2-week screening period (Visit 1, Week 2),<br>• 24-week treatment period: Patients who met eligibility criteria at the end of the screening period received the investigational medicinal product (IMP): fixed combination of glimepiride and metformin.<br>Blood glucose meter kit was provided by the Sponsor for self-monitoring of fasting plasma glucose (SMFPG). Patients were asked to measure their SMFPG at least 3 times on 3 separate days the weeks prior to visits for the treatment dose adjustment.<br>On-site visits: baseline, Week 2, Week 4, Week 6, Week 12, and Week 24. Phone call visits: Week 8, Week 10, Week 16, and Week 20.<br>• 3-day safety follow-up: Visit 12 to assess if no ongoing or new adverse event (AE) within 3 days after the end of treatment (phone call). | |

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| **Number of** patients**:** | Planned: 150<br>Treated: 167 |
| **Evaluated:** | Efficacy: Modified intent-to-treat (mITT): 167<br>Per protocol population (PP): 159<br>Safety: 167 |

**Diagnosis and criteria for inclusion:** Adult patients with T2DM inadequately controlled despite a treatment, stable for at least 12 weeks, with sulfonylurea (SU) alone, or metformin alone, or a free combination of metformin and SU prior to study entry and with $HbA_{1c}$ ≥7% and <11%. The signed informed consent was obtained prior to any study procedure.

**Study treatments**

**Investigational medicinal product(s):** Fixed dose combination (FDC) of glimepiride and metformin (Amaryl M® 2/1000 and Amaryl M® 4/1000).

Formulation: Amaryl M® 2/1000: divisible tablet: containing a fixed combination of 2 mg of glimepiride and 1000 mg of metformin.

Amaryl M® 4/1000: divisible tablet: containing a fixed combination of 4 mg of glimepiride and 1000 mg of metformin.

Route(s) of administration: Oral

Dose regimen:

Starting dose:

- Starting dose of Amaryl M® 2/1000 once daily in case of previous monotherapy with glimepiride (or other SU alone), with metformin alone or treatment with an association of metformin and glimepiride <3 mg/day (or other SU equivalent dose).
- Starting dose of Amaryl M® 2/1000 twice daily (BID, 4/2000) in case of previous treatment with an association of metformin and glimepiride ≥3 mg/day (or other SU equivalent dose).

Maximum dose: Amaryl M® 4/1000 BID (8 mg of glimepiride and 2000 mg of metformin, daily).

Dose adjustment: After receiving the starting dose of IMP, doses were increased every 2 weeks, according to the average SMFPG levels calculated on 3 separate days within 1 week before visits. The goal of the dose adjustment was to achieve SMFPG values ≤130 mg/dL (7.2 mmol/L) and >70 mg/dL (3.9 mmol/L) without symptomatic hypoglycemia.

**Duration of treatment:** 24 weeks.

**Duration of observation:** Up to 27 weeks: up to 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 to end of treatment.

Secondary endpoints:

- Percentage of patients with $HbA_{1c}$ <7% at end of treatment;
- Percentage of patients with <6.5% at end of treatment;
- Change in FPG from baseline to end of treatment.

Safety:

- Occurrence of AEs: treatment-emergent adverse events (TEAEs), serious adverse events (SAEs).
- Incidence and rate per patient-year of hypoglycemia during the study period: documented symptomatic hypoglycemia and severe hypoglycemia.
- Body weight, vital signs (heart rate [HR], systolic blood pressure [SBP] and diastolic blood pressure [DBP]), standard hematological and biochemical parameters.

**Statistical methods:** The mITT population consisted of all patients who received at least 1 dose of IMP, and had at least 1 post-baseline assessment of any primary or secondary efficacy variables, irrespective of compliance with the study protocol and procedures. The PP population was a subset of the mITT population, which excluded all patients who had major protocol violations. The Safety population consisted of all treated patients.

In order to control globally the type I error for both primary and secondary criteria, a hierarchical step-down testing procedure (secondary criteria), described by Hochberg and Tamhane, was applied.

**Efficacy analysis:**

Primary efficacy endpoint: absolute change in $HbA_{1c}$ from baseline to the end of treatment on the mITT population. The end of treatment value was the last available $HbA_{1c}$ value measured during the study treatment phase up to 14 days after last dose (Last Observation Carried Forward [LOCF] method). In order to test the treatment time effect and the baseline effect on $HbA_{1c}$ change, a repeated measures analysis of covariance (ANCOVA) was performed. In case of strong violation of normal assumption, a non-parametric analysis had to be performed on the rank transformation of the $HbA_{1c}$ changes.

Secondary efficacy endpoints: HbA1c response rates and change in FPG from baseline to the end of treatment on the mITT population. Glycated hemoglobin response rates, assessed as the percentage of patients who reached the targets of $HbA_{1c}$ <7% and the percentage of patients who reached $HbA_{1c}$ <6.5% were summarized descriptively at each visit (Week 12 and Week 24) and at the end of treatment. Baseline characteristics associated with $HbA_{1c}$ response rate targets ($HbA_{1c}$ <7% and $HbA_{1c}$ <6.5%) were investigated using a stepwise logistic regression.

Fasting plasma glucose (FPG) was summarized descriptively at each visit (Week 0, Week 12, and Week 24) and at end of treatment (the end of treatment value was the last available value measured during the study period up to 1 day after the last dose). Time effect or baseline level in the FPG change was analyzed using a mixed ANCOVA linear model for repeated measures. The mean of SMFPG values and the within patient variability (standard deviation of the 3 separate days within 1 week before visits for each patient) were summarized descriptively at each visit and at the end of treatment (the end of treatment value was the last available mean SMFPG measured during the study treatment phase up to 1 day after last dose).

**Safety analysis:**

Safety analyses were based on the Safety population except for body weight based on the mITT population.

The number and percentage of patients with TEAEs, TEAEs related to IMP, serious TEAEs, TEAEs leading to death, and TEAEs leading to permanent treatment discontinuation were described.

The numbers of patients who experienced at least 1 episode of symptomatic hypoglycemia, severe symptomatic hypoglycemia, day-time symptomatic hypoglycemia and nocturnal symptomatic hypoglycemia were described. For each type of symptomatic hypoglycemia, the rate per patient per year was calculated.

Changes from baseline in body weight at each visit and at the end of treatment were described. Time effect or baseline level on body weight change were analyzed using a mixed ANCOVA linear model for repeated measures.

Laboratory parameters and vital signs were analyzed using descriptive statistics and incidence of the potentially clinically significant abnormalities (PCSAs).

**Summary:**

**Population characteristics**: A total of 237 patients were screened, 167 patients were treated (safety population and mITT population), 160 patients completed the study (95.8% of the treated patients).

Seven patients (4.2%) prematurely discontinued the study treatment, among whom 2 patients discontinued for AEs (1 patient presenting with ischemic stroke leading to death and 1 presenting with diarrhea).

Treated patients (58.1% female, 41.9% male) had a mean age (±standard deviation [SD]) of 57.57 (±9.42) years [range: 30-78]. The mean body weight (±SD) was 86.58 (±12.67) kg and mean body mass index (BMI, ±SD) was 30.96 (±3.09) kg/$m^2$.

Mean (±SD) time since diagnosis of diabetes was 6.52 (±5.33) years. At baseline, mean (±SD) $HbA_{1c}$ was 8.58 (±0.99) % and mean (±SD) FPG was 164.4 (±36.6) mg/dL. Nearly half of the patients (90 patients, 53.9%) had diabetic late complications, among which the most frequent were diabetic neuropathy (53 patients, 31.7%), coronary artery disease (49 patients, 28.8%), diabetic retinopathy (32 patients, 19.2%), and heart failure (29 patients, 17.2%). The majority of the patients were previously treated with a combination of metformin and SU (122 patients). The other patients were treated with metformin alone (35 patients) or SU alone (10 patients).

The starting dose of glimepiride/metformin FDC was 2 mg/1000 mg (2/1000) daily for 84 patients (50.3%) or 4 mg/1000 mg (4/2000) daily for 83 patients (49.7%). At the end of the study, 23 patients (13.8%) were taking the daily FDC of 2/1000, 56 patients (33.5%) the daily FDC of 4/2000, 26 patients (15.6%) the daily FDC of 6/2000 and 62 patients (37.1%) the daily FDC of 8/2000.

Efficacy results: In the mITT population, the mean (±SD) change from baseline to end of treatment in HbA1c (LOCF method) was -1.01 (±1.12)%, with a 95% confidence interval (CI) (-1.19;-0.84). In the ANCOVA model, the adjusted mean change (± standard error [SE]) from baseline at Week 12 in $HbA_{1c}$ was -1.22 (±0.06)% with a 95% CI (-1.35;-1.10) and the adjusted mean change (±SE) from baseline at Week 24 in $HbA_{1c}$ was -1.01 (±0.08)% with a 95% CI (-1.16;-0.85). Ranked mixed ANCOVA linear model for repeated measures was done due to non adequacy of the parametric model. Both p-value of the change from baseline to Week 24 in the ranked mixed ANCOVA linear model and parametric model for repeated measures were similar ($p<0.001$). Similar results were obtained on the PP population.

At the end of treatment, 50 patients (30.7%) reached $HbA_{1c}$ <7% and 23 patients (14.1%) reached $HbA_{1c}$ <6.5% in the mITT population. Two parameters were statistically significantly associated with HbA1c <7%: previous antidiabetic treatments and level of $HbA_{1c}$ at baseline. At the end of treatment, mean (±SD) change from baseline in FPG was -17.03 (±41.86) mg/dL with a 95% CI (-23.55;-10.52) (LOCF method). In the ANCOVA repeated measures analysis at Week 24, the adjusted mean change (±SE) from baseline was -16.69 (±2.90) mg/dL with a 95% CI (-22.41;-10.97).

Mean (±SD) SMFPG decreased from Week 2 (154.31 [±39.37] mg/dL) to Week 12 (130.17 [±25.47] mg/dL) and remained stable to the end of treatment (137.49 [±32.16] mg/dL). The variability of SMFPG was similar between each time point.

**$HbA_{1c}$ (%) - Change from baseline (End of treatment, W12, W24) - mITT population**

| | Total (N=167) |
|---|---|
| **Change from baseline (End of treatment, LOCF method)** | |
| n | 163 |
| Mean (SD) | -1.01 (1.12) |
| 95% CI (mean) | [-1.19;-0.84] |
| Median | -1.00 |
| 95% CI (median) | [-1.2;-0.7] |
| Q1 ; Q3 | -1.70 ; -0.30 |
| Min. ; Max. | -4.4 ; 2.8 |
| Missing data | 4 |
| **Change from baseline - ANCOVA linear model for repeated measures** | |
| Week 12 | |
| Number of patients | 163 |
| Raw mean (SD) | -1.22 (1.00) |
| Adjusted mean (SE) | -1.22 (0.06) |
| 95% CI of adjusted mean | [-1.35 ; -1.10] |
| p-value (*) | <0.001 |
| p-value (**) | <0.001 |
| Week 24 | |
| Number of patients | 158 |
| Raw mean (SD) | -1.02 (1.13) |
| Adjusted mean (SE) | -1.01 (0.08) |
| 95% CI of adjusted mean | [-1.16 ; -0.85] |
| p-value (*) | <0.001 |
| p-value (**) | <0.001 |

(*) p-value of the ANCOVA linear model for repeated measures
(**) p-value of the sensitivity non-parametric analysis – Ranked mixed ANCOVA linear model for repeated measures

**Safety results:**

In the safety population, a total of 68 patients (40.7%) experienced at least 1 TEAE, 4 patients (2.4%) experienced at least 1 serious TEAE, 1 patient (0.6%) died from an ischemic stroke, and 2 patients (1.2%) experienced a TEAE leading to permanent study discontinuation.

The most frequent TEAEs were body weight increase (7 patients, 4.2%), influenza (7 patients, 4.2%), nasopharyngitis (5 patients, 3.0%) and hypertension (4 patients, 2.4%).

Four (4) SAEs, considered as not related to the study treatment by the Investigators, were reported in 4 patients (2.4%): ischemic stroke of severe intensity which led to permanent discontinuation of the study treatment and death of the patient, pneumonia of severe intensity, coronary artery disease of mild intensity and wrist fracture of severe intensity.

**Overview of treatment emergent adverse events – Safety population**

| | Total (N=167) |
|---|---|
| Any TEAE | 68 (40.7%) |
| Any possibly related to study treatment TEAE | 7 (4.2%) |
| Any serious TEAE | 4 (2.4%) |
| Any fatal TEAE | 1 (0.6%) |
| Any TEAE leading to permanent treatment discontinuation | 2 (1.2%) |

n (%) = number and percentage of patients with at least one adverse event
TEAE: Treatment emergent adverse event

Most patients experienced TEAEs of mild or moderate intensity.

Seven patients (4.2%) experienced TEAEs possibly related to the IMP: body weight increase (3 patients, 1.8%), hyperglycemia, diarrhea, drug ineffectiveness, and non-serious accidental overdose (1 patient each, 0.6%).

The 2 TEAEs leading to permanent discontinuation of the study treatment (2 patients, 1.2%) were the serious ischemic stroke of severe intensity (considered as not related to IMP and which led to death of the patient) and a non-serious diarrhea of mild intensity (considered as related to IMP by the Investigator).

Episodes of symptomatic hypoglycemia were reported by 31 patients (18.6%). One patient (0.6%) reported at least 1 event of severe symptomatic hypoglycemia. Eight patients (4.8%) reported at least 1 episode of nocturnal symptomatic hypoglycemia.

**Episodes of hypoglycemia - Safety population**

| | Total (N=167) |
|---|---|
| Patients with at least one episode of symptomatic hypoglycemia | 31 (18.6%) |
| Patients with at least one episode of documented symptomatic hypoglycemia | 29 (17.4%) |
| Patients with at least one episode of severe symptomatic hypoglycemia | 1 (0.6%) |
| Patients with at least one episode of nocturnal symptomatic hypoglycemia | 8 (4.8%) |
| Patients with at least one episode of day-time symptomatic hypoglycemia | 29 (17.4%) |

No missing data

The rates of episodes of hypoglycemia were low with 1.6 events of symptomatic hypoglycemia per patient-year, 0.01 events of severe symptomatic hypoglycemia per patient-year and 0.2 events of nocturnal symptomatic hypoglycemia per patient-year.

The adjusted mean change (±SE) in body weight from baseline to Week 24 was 0.46 (±0.20) kg (p-value =0.026). At the end of treatment, 11 patients (6.7%) experienced an increase of their body weight from baseline higher than 5%. Conversely, 2 patients (1.2%) had a decrease of their body weight from baseline higher than 5% at the end of treatment.

potentially clinically significant abnormalities were reported for biochemistry parameters: increase of alanine transaminase (ALT) >3 times the upper limit of normal range (ULN, 1 patient, 0.6%), creatinine change above 100% from baseline (2 patients, 1.2%) and creatinine clearance in [30-50 mL/min] (2 patients, 1.2%). One PCSA was reported for 1 patient (0.6%) having heart rate ≤50 bpm and a decrease from baseline ≥20 bpm. No PCSAs were reported hematological parameters.

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