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Prescribing decisions should be made based on the approved package insert in the country of prescription.

Sponsor / Company: Sanofi	**Study Identifiers:** NCT01204580, U1111-1116-8173
Drug substance(s): Glimepiride and Metformin (Amaryl-M)	**Study code:** GLMET_L_04735

Title of the study: Adiponectin and ADMA Level in Type-2 Diabetes Patients After 12 Weeks of Treatment with Glimepiride and Metformin Fixed Dose Combination

Study period:

Date first subject enrolled: 21 December 2010

Date last subject completed: 21 March 2012

Phase of development: IV

Objectives:

The primary objective of this Clinical Trial was to evaluate the change in plasma levels of adiponectin and Asymmetric Dimethylarginine (ADMA) in type 2 diabetes mellitus (T2DM) patients after 12 weeks of treatment with Amaryl-M

Secondary objectives:

- To assess the role of Amaryl-M in the change of plasma levels of adiponectin and ADMA in type 2 diabetes patients after 8 weeks of therapy
- To evaluate the brachial-ankle pulse wave velocity (baPWV) change after 8 and 12 weeks of therapy with Amaryl-M
- To evaluate the efficacy of Amaryl-M in the improvement of patients glycemic level (FBG and HbA1c)
- To evaluate the change of TNF-Alfa after 12 weeks of therapy with Amaryl-M
- To evaluate the HOMA-IR change after 12 weeks of therapy with Amaryl-M
- To evaluate the HOMA-β change after 12 weeks of therapy with Amaryl-M
- To evaluate the relationship between adiponectin and ADMA level with FBG or HbA1c level

Methodology:

Pre-post study comparison design

Duration: 12 weeks.

Number of subjects:
Planned: 40
Randomized: 40
Treated: 40

Evaluated:
Efficacy: 35
Safety: 40

Diagnosis and criteria for inclusion:

- **Inclusion Criteria**
  - Aged from 40 to 60 years inclusively
  - Type 2 diabetes mellitus patients
  - Patients with HbA1c ≥ 7.0% and < 10.0%
  - Patients not currently treated with any oral antidiabtic drugs (OADs)
  - Patients have been informed of the Clinical Trial procedure and have given their written informed consent
  - Willingness and ability to comply with the Clinical Trial protocol

- **Exclusion Criteria**
  - Participation in other investigational Clinical Trial
  - Current temporary insulin treatment: gestational diabetes, pancreas cancer, surgery etc.
  - Women who are pregnant or lactating
  - Type 1 diabetes mellitus patients
  - Treatment with antihypertensive ACE-Inhibitors and/or ARB or has just stopped treatment for less than two months
  - Treatment with lipid lowering agent statins or has just stopped treatment for less than two months
  - Known hypersensitive to any of the excipients of Amaryl-M, sulphonylureas, sulfonamides or biguanide
  - Patients with active smoking or history of smoking cessation less than 2 months
  - Patients with history of severe hepatic dysfunction
  - Patients with serum creatinine ≥ 1.5 mg/dL (male) and ≥ 1.4 mg/dL (female)
  - Patients with congestive heart failure requiring pharmacologic treatment
  - Treatment with antifungal agent especially Miconazole

Study treatments

Investigational medicinal product(s): Amaryl-M 1/250 mg film coated tablets

Formulation: Glimepiride 1 mg and metformin 250 mg

Route(s) of administration: Oral

Dose regimen: One tablet per day

Duration of treatment: 12 weeks

Duration of observation: 12 weeks

Criteria for evaluation:

Efficacy: The primary efficacy variables were the mean changes in serum adiponectin and ADMA between baseline and week 12 in type 2 diabetes patients after 12 weeks treatment with Amaryl-M

Secondary efficacy variables:

- Comparison of mean serum adiponectin change between baseline and week 8
- Comparison of mean serum ADMA change between baseline and week 8
- Comparison of the mean brachial-ankle pulse wave velocity (baPWV) change between baseline, week 8, and week 12
- Comparison of the mean TNF-Alfa change between baseline and week 12
- Comparison of the mean reduction of FBG between baseline and week 12
- Comparison of the mean reduction of HbA1c between baseline and week 12
- Comparison of t the mean HOMA-IR change between baseline and week 12
- Comparison of t the mean HOMA- β change between baseline and week 12
- Correlation between adiponectin and ADMA level with FBG or HbA1c level

Criteria for evaluation (cont'd):

Safety:

- Hypoglycemia (mild to moderate or severe): the number of patients experiencing these events was calculated during the study period.
- Vital signs (body weight and waist circumference): the mean variation between the value at baseline (visit 1) and the last measurement at endpoint (visit 5) was calculated.
- Adverse events: treatment emergent adverse events were analyzed: adverse events beginning or worsening during the study period.

Statistical methods: All values were expressed as the mean ± SD. Statistical analyses was performed using the Student's paired t-test (two-tailed) or Wilcoxon test, depending on the distribution of the data; values of $p < 0.05$ was considered to indicate statistical significance. The sample size was estimated to be half of the increase of adiponectin in the Japanese T2DM population.

$$n = \frac{SDd2\ (Z\alpha + Z\beta)2}{D2}$$

$$n = \frac{42\ (1.96 + 0.842)2}{1.822} = 39$$

Therefore 40 was decided to be the total number of patients to be enrolled in this study.

Summary:

Population characteristics:

Forty subjects were recruited for this study; they consisted of 24 females and 16 males. The mean ±SD age of the subject was 51.3 +/- 5.5 years with 62.5% of them aged older than 50 years. The majority of subjects were not relying on anti diabetic drug before the study; around 42.5% of subjects used sulphonylurea as their main anti diabetic drug before switching to Amaryl-M. One patient was discontinued for this study due to adverse reaction, three patients due to poor compliance and one patient due to out migration. Therefore 35 patients were evaluated in this study.

Efficacy results:

Adiponectin was not affected by the administration of Amaryl-M after a 3-month treatment period, it decreased in 57.1% and increased in 42.9% of patients. ADMA was increased (68.6%), while fasting blood glucose and HbA1C were decreased (42.8 mg/dl and 1.1%) following the treatment by Amaryl-M. Brachial-ankle pulse wave velocity and HOMA-IR were decreased (48.6% and 67.5%), while HOMA-β showed an increase (67.5%).

Safety results:

No death reported among the subjects after being observed for a 12-week period. Edema palpebra, elevated ALT, nausea and dermatological reaction were found in 3 of 40 patients (7.5%), and recovered without any discontinuation of this study. However a case (2.5%) of thrombotic infarct has occurred in this study and was reported to be unrelated to the study procedure/drug. The event outcome was reported to be recovery with sequel.

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