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

Sponsor / Company: Sanofi Drug substance(s): AMARYL M (1/250 mg) / HOE490	Study Identifiers: NCT01457911, U1111-1121-6792 Study code: EFC11761
Title of the study: A multicenter, randomized, open-label, 2-arm parallel group, 20-week study comparing the efficacy and safety of fixed-dose combination of 1 mg glimepiride and 250 mg metformin (AMARYL M 1/250 mg) versus glimepiride (AMARYL®) in Chinese type 2 diabetes patients inadequately controlled with metformin.	
Study center(s): Multicenter (22 centers in China)	
Study period: Date first patient enrolled: 28/Oct/2011 Date last patient completed: 05/Feb/2013	
Phase of development: Phase 3	
Objectives: Primary: To evaluate the efficacy of fixed-dose combination (FDC) of 1 mg glimepiride and 250 mg metformin (AMARYL M 1/250 mg) in comparison with glimepiride (AMARYL) alone in terms of glycemic control as reflected by HbA_{1c} during a 20-week treatment period in patients with type 2 diabetes mellitus (T2DM) inadequately controlled with metformin. Secondary: • To evaluate the percentage of patients reaching HbA_{1c} <7% or HbA_{1c} ≤6.5% of FDC of 1 mg glimepiride and 250 mg metformin (AMARYL M 1/250 mg) in comparison with glimepiride (AMARYL) alone at Week 20. • To evaluate the effect on Fasting Plasma Glucose (FPG) of FDC of 1 mg glimepiride and 250 mg metformin (AMARYL M 1/250 mg) in comparison with glimepiride (AMARYL) alone at Week 20. • To assess the safety and tolerability of FDC of 1 mg glimepiride and 250 mg metformin (AMARYL M 1/250 mg).	
Methodology: This was a randomized, open-label, active-controlled, 2-arm parallel group, multicenter, 20-week study.	
Number of patients: Planned: 240 Randomized: 244 Treated: 243 Evaluated: Efficacy: 243 Safety: 243	
Diagnosis and criteria for inclusion: Chinese patients with type 2 diabetes mellitus, as defined by World Health Organization (WHO) diagnosed for at least 1 year at the time of screening visit and inadequately controlled with metformin; age ≥18 and <80 years at screening; HbA_{1c} ≥7% and ≤10% at screening.	

Study treatments

Investigational medicinal product(s):

Tested drug: AMARYL M (1/250 mg)

Control drug: AMARYL

Formulation:

AMARYL M (1/250 mg): A tablet containing active ingredients of 1 mg of glimepiride and 250 mg of metformin hydrochloride.

AMARYL: A tablet containing active ingredient of 1 mg of glimepiride.

Route(s) of administration: Oral.

Dose regimen:

Either AMARYL M (1/250 mg) or AMARYL was taken once daily during a breakfast or twice daily during breakfast and dinner.

Dose Titration:

The recommended initial daily dose for AMARYL M (1/250 mg) was 1 tablet (glimepiride 1 mg / metformin 250 mg) and for AMARYL was 1 mg of glimepiride according to labeling.

During the first 8-week titration period, based on the average of fasting self-monitoring of plasma glucose (SMP), the Investigational Medicinal Product (IMP) dose was titrated to the next higher dose level with increment of AMARYL M (1/250 mg) 1 tablet or AMARYL 1 mg, respectively, every week or every two weeks as considered appropriate by the Investigator.

The maximum daily dose for AMARYL M (1/250 mg) was 6 tablets (glimepiride 6 mg / metformin1500 mg) and for AMARYL was 6 mg.

Dose Maintenance

During the remaining 12-week dose maintenance period, AMARYL M (1/250 mg) or AMARYL was maintained at the same dosing regimen as established at the end of the titration period.

Duration of treatment: 20 weeks (An 8-week dose titration period + a 12-week dose maintenance period).

Duration of observation: Up to 23 weeks (An up to 2-week screening period + a 20-week open-label, active controlled treatment period + a 3-day safety follow-up period).

Criteria for evaluation:

Efficacy:

Primary endpoint:

- Absolute change of HbA_{1c} from baseline to Week 20.

Secondary endpoints:

- Percentage of patients reaching HbA_{1c} <7% or HbA_{1c} ≤6.5% at Week 20, respectively.
- Absolute change in FPG from baseline to Week 20.

Safety:

Endpoints assessed for safety: Hypoglycemia events (asymptomatic hypoglycemia, documented symptomatic hypoglycemia, severe hypoglycemia, probable symptomatic hypoglycemia, relative hypoglycemia, and nocturnal hypoglycemia); adverse events (AEs) and serious adverse events (SAEs); vital signs; safety laboratory tests.

Statistical methods:

Efficacy: The efficacy analyses were based on the modified intent-to-treat (mITT) population, corresponding to all randomized patients who received at least one dose of IMP after or on randomization and had a baseline value assessment of efficacy variables, irrespective of compliance with the study protocol and procedures.

For the efficacy analysis, the baseline was defined as the last available value prior to the first dose of IMP after or on randomization. The missing values for all efficacy variables were imputed from the baseline value using the baseline value carried forward (BVCF) procedure.

The primary efficacy endpoint (absolute change in HbA_{1c} from baseline Week 20) was analyzed using an analysis of covariance (ANCOVA) model with treatment, strata of HbA_{1c} at screening (<8.5%, ≥8.5%) and pre-randomization metformin dose (low dose, high dose) as fixed effects and using the baseline HbA_{1c} value as a covariate. The difference between AMARYL M (1/250 mg) group and AMARYL alone group and its corresponding 95% confidence interval (CI) were estimated within the framework of ANCOVA.

The secondary efficacy endpoint of percentage of patients with HbA_{1c} <7% and ≤6.5% at week 20 was analyzed using the Cochran-Mantel-Haenszel test stratified by the randomization strata of screening HbA_{1c} (<8.5, ≥8.5%) and pre-randomization metformin dose (low dose, high dose).

The secondary efficacy endpoint of absolute change in FPG from baseline to Week 20 was analyzed using a similar ANCOVA model with treatment, strata of HbA_{1c} at screening (<8.5%, ≥8.5%) and pre-randomization metformin dose (low dose, high dose) as fixed effects and using the baseline FPG value as a covariate. Difference between AMARYL M (1/250 mg) group and AMARYL alone group and its corresponding 95% CI were estimated within the framework of ANCOVA.

Safety: The safety population was defined as all randomized patients who received at least one dose of IMP after or on randomization. The review of safety and tolerance were performed on the safety population. The safety analyses were based on the reported hypoglycemia events, AEs, and other safety information (clinical laboratory evaluations and vital signs). The summaries of safety results were presented for each treatment group (AMARYL M [1/250 mg] and AMARYL).

Summary:

Population characteristics:

A total of 368 patients were screened and 244 patients were randomized in 22 centers in China to 1 of 2 treatment groups (122 patients in the AMARYL M group, 122 patients in the AMARYL group). One patient was randomized twice in the AMARYL group. Of the 244 randomized patients, 243 patients were exposed to the study treatment and were included in the mITT population and the safety population. One patient who was randomized to the AMARYL group received AMARYL M by dispensation error for 4 weeks after randomization, and then was switched to the correct treatment group (AMARYL). During the on-treatment period, 4 patients (3.3%) in the AMARYL M group and 12 patients (9.8%) in the AMARYL group prematurely discontinued the study treatment.

The demographic and other baseline characteristics were generally similar between the 2 treatment groups. Disease characteristics, including diabetic history, were generally comparable between the 2 treatment groups. The use of metformin at screening and at baseline was generally similar between the 2 treatment groups. Baseline efficacy variables (HbA1c and FPG) were generally comparable between the 2 treatment groups.

Efficacy results:

Superiority of AMARYL M compared with AMARYL was demonstrated, based on the pre-specified primary analysis of the least square mean (LS mean) change in HbA_{1c} from baseline to Week 20 (BVCF) (-0.91% and -0.29% in the AMARYL M and AMARYL groups, respectively with observed margins). The LS mean difference for AMARYL M versus AMARYL was statistically significant (-0.62%; 95% CI: -0.853, -0.390; p<0.0001).

At Week 20, the percentage of HbA_{1c} responders (pre-specified as patients reaching HbA_{1c} <7% or ≤6.5%, respectively) was also significantly higher in the AMARYL M group (49.6% or 25.6%, respectively) versus the AMARYL group (20.5% or 9.8%, respectively) (p<0.0001 or p = 0.0013, respectively).

The LS mean change in FPG from baseline to Week 20 (BVCF) was -0.88 mmol/L and -0.22 mmol/L in the AMARYL M and AMARYL groups, respectively with observed margins. The LS mean difference between the 2 treatment groups was statistically significant (-0.66 mmol/L; 95% CI: -1.151, -0.164; p = 0.0092).

Safety results:

The number of any hypoglycemia events that occurred during the on-treatment period was 67 in the AMARYL M group compared with 14 in the AMARYL group. The number of documented symptomatic hypoglycemia events that occurred during the on-treatment period was 26 in the AMARYL M group compared with 3 in the AMARYL group. The mean event rate of any hypoglycemia (events/patient years) was higher in the AMARYL M group (2.39) compared with the AMARYL group (0.40). The mean event rate of documented symptomatic hypoglycemia was also higher in the AMARYL M group (0.74) compared with the AMARYL group (0.06). The incidence rate of any hypoglycemia was higher in the AMARYL M group (30.3%) compared with the AMARYL group (10.7%). The incidence rate of documented symptomatic hypoglycemia was also higher in the AMARYL M group (14.8%) compared with the AMARYL group (2.5%). The difference in the incidence of hypoglycemia events between the 2 treatment groups occurred mainly during the dose titration period. No severe hypoglycemia occurred during the on-treatment period, ie no treatment-emergent adverse event (TEAE) of severe symptomatic hypoglycemia, was reported during the on-treatment period.

The incidence of TEAEs was 35.2% (43/122) in the AMARYL M group compared with 27.9% (34/122) in the AMARYL group. The difference was mainly attributable to the difference in the events coded under the infections and infestations system organ class (SOC) (13.1% in the AMARYL M group versus 4.9% in the AMARYL group), particularly the events coded under the upper respiratory tract infections HLT (9.0% in the AMARYL M versus 4.1% in the AMARYL group). The most frequently reported TEAE by SOC was infections and infestations in the 2 treatment groups (13.1% and 4.9% in the AMARYL M and AMARYL groups, respectively). The most commonly reported TEAE by preferred term (PT) in the AMARYL M group was nasopharyngitis (4.9% and 0.8% in the AMARYL M and AMARYL groups, respectively), followed by upper respiratory tract infection (4.1% and 3.3%, respectively). The most commonly reported TEAE by PT in the AMARYL group was upper respiratory tract infection, followed by intentional overdose (0% and 2.5% in the AMARYL M and AMARYL groups, respectively).

No patients died during the study. A total of 7 patients had 7 SAEs during the on-treatment period: 2 patients (1.6%) in the AMARYL M group compared with 5 patients (4.1%) in the AMARYL group. Of these, 2 SAEs in the AMARYL group (spinal osteoarthritis and diabetic ketoacidosis) led to permanent treatment discontinuation. None of the SAEs were considered as related to study treatment by the Investigator. Most patients with SAEs recovered from the events without sequelae after corrective treatments were given, except for 1 patient with cerebral infarction in AMARYL M group who recovered from the event with sequelae.

No patients in the AMARYL M group had TEAE that led to permanent discontinuation of study treatment; 4 patients (3.3%) in the AMARYL group had 6 TEAEs that led to permanent discontinuation of study treatment. Among the 6 TEAEs, 2 TEAEs were reported as SAEs; the other 4 TEAEs were non-serious and occurred in 2 patients, each patient had 2 TEAEs. All 4 patients with TEAEs leading to permanent treatment discontinuation, recovered from the events without sequelae.

A total of 3 patients (2.5%) in the AMARYL M group had alanine aminotransferase (ALT) values >3 upper limit normal (ULN). All events of ALT increase were observed at the end of treatment visit. These events were reported as adverse events of special interests (AESIs) of ALT increase, which were coded to the PTs of liver injury (2 patients) and hepatic steatosis (1 patient). None of these events were considered as related to the IMP by the Investigator.

In total, 4 patients in the AMARYL group took the IMP at a dose at least twice of the intended dose during the study. These events were reported as AESIs of overdose by the Investigator, which were all coded to the PT of intentional overdose. No symptoms or hypoglycemia were reported from the 4 overdose patients.

The overall incidence of potentially clinically significant abnormalities (PCSAs) for clinical laboratory parameters was low in the 2 treatment groups. Among the TEAEs reported for the PCSAs, 3 TEAEs in the AMARYL M group were reported as AESIs of ALT increase (non-serious events); no SAEs or AEs leading to permanent treatment discontinuation were reported. No other safety issues or signals were identified in the review of laboratory data.

The vital signs data did not reveal any specific safety concerns.

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