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Sponsor / Company : sanofi-aventis **Drug substance :** Glimepiride		**Study Identifier** : NCT00908921 **Study Code** : GLIME_L_04409	
Title of the study:	Efficacy and safety of Glimepiride as Oral Anti-Diabetic (OAD) first-line mono-therapy in Chinese Type 2 Diabetes Mellitus (T2DM)		
Study center(s):	18 centers, China		
Study period: Date first patient enrolled: 29-Apr-2009 Date last patient completed: 24-Sep-2010		**Phase of development:** IV	
Objectives:	Primary Objective: To investigate the HbA1c control of Glimepiride (AMARYL®) as OAD (Oral Anti-Diabetic) initiation mono-therapy in Type 2 Diabetic patients in China. Secondary Objectives: To evaluate: **1.**Change in FPG (Fasting Plasma Glucose), PPG (Post Prandial Glucose); **2.** Safety profile: hypoglycemia or other adverse event; **3.**HOMA-ß (ß-cell function), HOMA-IR (insulin resistance); **4.** Percentage of patients achieving HbA1c <7.0% of Glimepiride 1mg, 2mg, 4mg; **5.**Change in body weight ; **6.** Compliance.		
Methodology:	This is a 16-week, non-controlled, open-label, single-arm, multi-center study. The initiation dose of glimepiride was 1 mg/d, with titration to 2mg/d and 4mg/d according to the FBG (Fasting Blood Glucose) level measured at each visit. For patients who have received glimepiride 4mg/d for 4 weeks with FBG level >11.1mmol/L, metformin 500-2000mg/d can be added at the physician's discretion.		
Number of patients:	**Planned:** 403	**Randomized:** 391	**Treated:** 390
Evaluated:	**Efficacy:** 363 (Full analysis set) 356 (Per-protocol set)	**Safety:** 390	

Diagnosis and criteria for inclusion:	Type 2 Diabetes Mellitus (T2DM) (American Diabetes Association criteria for the diagnosis) inadequately controlled with diet and exercise or had taken oral antidiabetic medication irregularly and stopped treatment >1month ; 8.0mmol/L ≤ FBG ≤ 13.5mmol/L (continuous 2 times of 1-week interval, difference ≤1.8mmol/L).
Investigational product:	Glimepiride (AMARYL®), Metformin(Glucophage®)
Dose:	1-4mg, 500-2000mg
Administration:	PO,QD PO,QD-TID

Duration of treatment: 16 weeks	**Duration of observation:** 18 weeks

Criteria for evaluation:	
Efficacy:	Efficacy evaluations include HbA1c, Fasting Plasma Glucose, 2h Post Prandial Glucose, Percentage of patients achieving HbA1c <7.0%, HOMA-ß, HOMA-IR, Weight ,Waist, Patient's compliance; The primary efficacy measurement was Change in HbA1c from baseline to week16
Safety:	Safety evaluations included hypoglycemia episodes, medical history, adverse events (AEs), vital signs, body weight, physical exam, electrocardiogram (ECG, 12-lead), hematology, blood chemistry and urinalysis.
Statistical methods:	The primary efficacy variables (mean change in HbA1c from baseline to week 16) as well as other continuous variables of secondary efficacy variables were described using N, mean, standard deviation, geomean, median, minimum and maximum. Paired t-test or signed rank test was applied to compare the change from baseline while ANOVA or rank-based nonparametric test was used for between-group comparison of these continuous measures. Categorical variables (e.g. Percentage of patients achieving HbA1c <7.0%, proportions of hypoglycemic events) were presented by frequency distributions (N, %) and were tested using Chi-square or Fisher's exact test. The primary analysis was based on Full Analysis Set (FAS), which included patients who was administrated at least one dose of the study drug, had at least one measurement of primary endpoint post baseline and had no major protocol violation. Safety analyses were based on Safety Set (SS), which included all patients who was administrated at least one dose of the study drug. The significance level was set at 0.05 for all statistical tests (two-sided). Post hoc analyses for clear results were added as marked as * in the synopsis.

Summary:

Study population:

Totally 391 patients were enrolled. 27 patients were not included in FAS (Full Analysis Set) due to missing the primary efficacy endpoint value and 1 patient was not included in FAS due to no drug administration after screening. Totally 363 patients were in FAS. Another 2 patients were not included in Per-protocol set (PP) due to protocol deviation and 5 patients were not included in PP due to drop-out. Totally 356 patients were in PP. 1 patient was not included in SS (Safety Set) due to no drug administration after screening, 390 patients were in SS.

Baseline data(FAS):

The mean age was 53.1±10.3years, median Diabetes Mellitus duration was 2 months (range:0-214months), mean Body Mass Index (BMI) was 25.5±3.1kg/m^2, mean HBA1c, FPG, 2hPPG was 8.6±1.6%, 9.8±2.2mmol/L and 16.8±4.1mmol/L respectively (Table 1).

Drug exposure:

The mean exposure in the study to glimepiride =(the average daily dose in the study x number of treated subjects)/1 patient-year *=2.93x 390/2x 365=1.57patient-year

Number of patients exposed to study drugs for 1 year based on the average daily dose = (the average daily dose in the study x number of treated subjects x 16weeks x 7days) /1 patient-year* =(2.93x 390 x 16 x 7)/(2x 365)= 175.84

*1 patient-year = Defined Daily Dose(DDD) x365, DDD for glimepiride as set by WHO is 2 mg

Table 1:patients baseline characteristics (mean±SD, FAS)

	All n=363	Male n=217	Female n=146
Age(yrs)	53.1±10.3	51.4±9.9	55.8±10.4
Diabetes Mellitus duration(month) Median(Min, Max)	2.0(0.0,214.0)	2.0(0.0,214.0)	3.0(0.0,205.0)
Weight(kg)	70.5±11.7	74.9±11.1	64.0±9.2
BMI(kg/m^2)	25.5±3.1	25.7±3.0	25.2±3.1
HbA1c（%）	8.6±1.6	8.8±1.6	8.3±1.47
FPG（mmol/L)	9.8±2.2	9.8±2.2	9.8±2.2
2hPPG（mmol/L)	16.8±4.1	16.7±4.2	16.8±4.1
Waist circumstance(cm)	88.7±9.5	91.1±8.4	85.1±9.8

Efficacy results:

After 16-weeks Glimepiride treatment, HbA1c reduced significantly, the reduction was 1.7%(from baseline 8.6±1.6％ to 6.9±0.9％， *P*<0.001,). The reduction of FPG and 2hPPG were 2.3mmol/L and 4.4mmol/L respectively, reduced from baseline 9.8±2.2mmol/L to endpoint 7.5±1.6mmol/L for FPG and from baseline16.8±4.1 mmol/L to 12.4±3.6mmol/L for 2hPPG （ both *P*<0.001 baseline vs endpoint ）;Insulin secretion increased significantly, HOMA-ß increased from 20.8±20.8 to 39.9±46.1; HOMA-IR decreased from 2.5±2.3 to 2.2±1.9， *P*＝0.009 . Mean weight increase 0.4kg at the study endpoint and waist circumstance has no significant change during the treatment (Table 2). Patient's compliance is 99.1% from baseline to endpoint [actual dose(mg）/planned dose（mg）×100%].

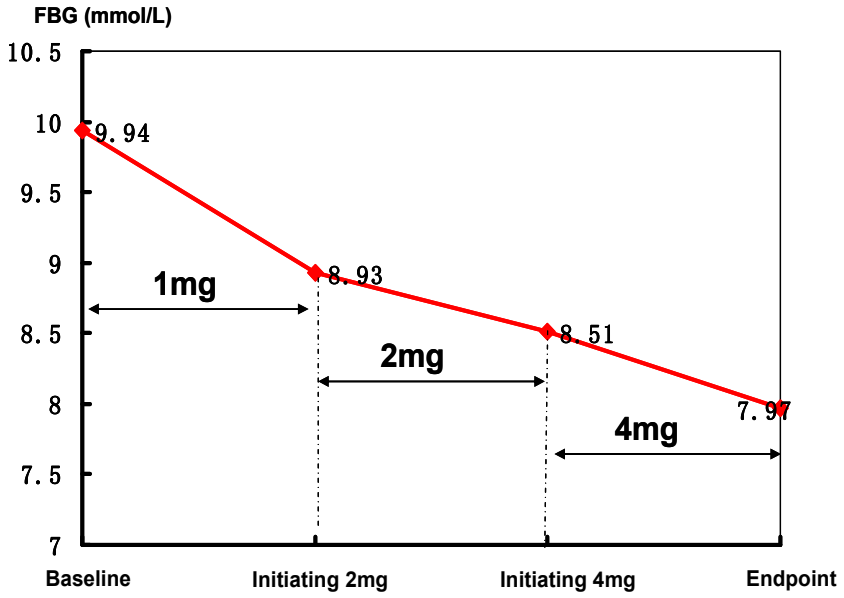
The percentage of HbA1c <7% at the study endpoint was 60.9% for total 363 population. Percentage of patients achieving HbA1c <7.0% of Glimepiride 1mg, 2mg, 4mg was 92.4%,76.3%,45.1% respectively.(table 3).

Table 2:Summary of efficacy results (FAS)

variable	Week0	Week 16	Week 16-Week0	P value
HbA1c (%)	8.6±1.6	6.9±0.9	-1.7±1.6	<0.001
FPG(mmol/L)	9.8±2.2	7.5±1.6	-2.3±2.2	<0.001
2hPG(mmol/L)	16.8±4.1	12.4±3.6	-4.4±4.4	<0.001
HOMA-ß	20.8±20.8	39.9±46.1	19.1±39.4	<0.001
HOMA-IR	2.5±2.3	2.2±1.9	-0.3±2.1	0.009
Weight(kg)	70.5±11.7	70.8±11.7	0.4±2.5	0.007
Waist(cm)	88.7±9.4	88.9±8.8	0.2±4.2	0.308

Table 3: Percentage of patients achieving HbA1c <7.0% (FAS)

Last dose of study drug	n(%)
1mg	73(92.4%)
2mg	58(76.3%)
4mg	79(45.1%)
4mg+metformin	11(33.3%)
overall	221(60.9%)

Efficacy results:	Totally there were 175 patients whose last dose of glimepiride was titrated to 4mg, during the 16 weeks treatment, FBG decreased significantly with the dose increasing, FBG (mean ±SD)at baseline and the visits of titration to 2mg, 4mg Glimepiride and study endpoint were 9.94 ±1.46 mmol/L, 8.93 ±1.46 mmol/L, 8.51±1.29 mmol/L, 7.97 ±1.53 mmol/L for this175 patients (figure 1).* ***Figure 1:FBG trend for the patients whose last dose was 4mg glimepiride**** 

Safety results

The percentage of patients with Treatment Emergent Adverse Events (TEAEs) was 32.8% (128/390)

TEAEs leading to discontinuation of study medication were reported in 6/390 (1.54%) patients: 1 chest pain, 1 rash, 1 herpes, 1 coronary disease, 1 hyperlipidemia, 1 upper respiratory tract infection

Adverse Events (AEs) considered by investigators as related to study drug were reported in 57/390(14.6%) patients: hypoglycaemia 51/390 (13.08%), skin disorders 3/390(0.77%), hepatic disorder 2/390 (0.51%), gastroenteric disorder 2/390 (0.51%) are the most common .

4 patients reported Treatment Emergent Serious Adverse Events (TESAEs) during the study.: 1 gastroenteritis, 1 osteoarthritis, 1coronary disease and 1 herpes; non of these Serious Adverse Events (SAEs) considered by investigators as related to study drug.

AEs with patient's percentage>1% were hypoglycemia, dislipidemia and upper respiratory tract infection. No death reported during the study (Table4).

Table 4:Summary of AE and SAE(SS)

	Case no.	Subjects no. (%)
All AE	239	128(32.8)
AE considered by investigators as related to study drug	101	57(14.6)
Discontinuation due to AE	6	6(1.54)
All SAE	4	3(0.8)
SAE considered by investigators as related to study drug	0	0(0.0)
Death	0	0(0.0)

The incidence of all symptomatic hypoglycemia was 14.87 %(58/390) and the incidence of confirmed hypoglycemia (confirmed by BG≤3.9mmol/L) during the study was 3.08%*(12/390). The incidence of nocturnal hypoglycemia was 0.77%(3/390, 1 case of nocturnal hypoglycaemia is severe hypoglycaemia) and 3 patients reported 3 cases of severe hypoglycemia (Table 5). The incidence of hypoglycemia in patients with different last dose was summarized in table 6.

Safety results	***Table 5:Summary of hypoglycemia(SS)***

	Case no.	Subjects no. (%)
All Hypoglycemia	105	58(14.87)
Hypoglycemia considered by investigators as related to study drug	91	51(13.08)
All severe hypoglycemia	3	3(0.77)
All nocturnal hypoglycemia	3	3(0.77)
Confirmed hypoglycemia by BG≤3.9mmol/L*	14	12(3.08)

Table 6:Summary of hypoglycemia in patients with different last dose (SS)

	Case no.	Subjects no. (%)
Last dose 1mg glimepiride (n=91)		
All Hypoglycemia	29	14(15.4)
Confirmed hypoglycemia by BG≤3.9mmol/L*	7	6(6.6)
Last dose 2mg glimepiride(n=81)		
All Hypoglycemia	20	15(18.5)
Confirmed hypoglycemia by BG≤3.9mmol/L*	0	0
Last dose 4mg glimepiride(n=183)		
All Hypoglycemia	41	21(11.5)
Confirmed hypoglycemia by BG≤3.9mmol/L*	4	4(2.2)
Last dose 4mg glimepiride+metformin (n=35)		
All Hypoglycemia	11	7(20)
Confirmed hypoglycemia by BG≤3.9mmol/L*	3	2(5.7)

**Post hoc analysis.*

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