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Sponsor / Company: Sanofi **Drug Substance:** Glimepiride		**Study Identifier:** NCT 00957060 **Study Code:** GLIME_L_04140	
Title of the study:	Multicenter open, randomized study to evaluate the superiority of glimepiride over sitagliptin in naïve type 2 Diabetes patients (T2DM) in a 24-week treatment period.		
Study Center(s):	Five active centers in Guatemala and thirty-four in Mexico		
Study period: Date first patient/subject enrolled: 09-Jul-2009 Date last patient/subject completed: 28-Oct-2010		**Phase of development:** Phase IV	
Objectives:	**Primary** • Determine the superiority of glimepiride over sitagliptin in terms of HbA1c reduction after 24 weeks of treatment **Secondary** Evaluate the effect of glimepiride compared to sitagliptin after 24 weeks of treatment on: • Fasting blood glucose • Post-prandial blood glucose • Percentage of patients with HbA1c < 7% and ≤ 6.5 % • Symptomatic hypoglycemia • Body weight changes • Percentage of withdrawal from protocol and percentage of patients with rescue therapy Evaluate the safety of glimepiride compared to sitagliptin: Adverse Events (AE) and Serious Adverse Events (SAE), hypoglycemia, vital signs and laboratory results during the whole study.		
Methodology:	A multicenter, comparative, two-arm, randomized (1:1), open, 24-week period study. Eligible patients were randomized to receive either glimepiride (started at 2mg q.d. and titrated as needed up to 6 mg q.d.) or sitagliptin (dose 100 mg q.d.). Randomization was centralized and performed by means of envelopes sent to centers.		
Number of patients/subjects:	Planned: 400	Randomized: 400	Treated: 400

Evaluated:	306 patients* *Per Protocol (PP) population, defined as all individuals meeting the inclusion criteria and having HbA1c measures at baseline, week 12 and week 24.	• Weight and height at each visit • Blood pressure at each visit • HbA1c at baseline, weeks 12 and 24 • Central glucose at baseline • Fasting and postprandial glucose (average self-monitoring) on weeks 0, 2, 4 and 12. • Lipid profile at baseline visit
Diagnosis and criteria for inclusion:	1. Subjects with type 2 Diabetes Mellitus 2. Men or women between 18 and 70 years old. 3. Subjects *naïve* to treatment with antidiabetes agents 4. Subjects with HbA1c > 8.5% up to 11% 5. Subjects under therapy for lipid reduction, antihypertensive therapy, hormone replacement, thyroid replacement and/or contraceptive hormones were admitted as long as they are kept at a stable dosing during the 24 week treatment 6. Subjects granting their written informed consent and agree to follow the procedures described in the protocol	
Investigational product:	**Glimepiride:** Amaryl® 2 and 4 mg (treatment group 1) **Dose:** Glimepiride administered once a day with a starting dose of 2 mg, then titrated up to 6mg as needed **Administration:** Oral	
Duration of treatment: 24 weeks per patient		**Duration of observation:** 24 weeks per patient
Reference Therapy:	In the present study design, **sitagliptin** 100 mg (treatment group 2) is the reference therapy to which glimepiride is compared. **Dose:** 100 mg / day **Administration:** Oral	

Criteria for evaluation:	
Efficacy/Pharmacodynamics: Safety:	Efficacy data, analyzed in the Intention-to-Treat (ITT) population, defined as patients recruited for study and who received at least one dose of the investigational/reference drug, was obtained by measuring the following: • Mean HbA1c change between baseline and weeks 12 and 24 • Mean Blood Glucose changes from baseline visit to end of treatment (week 24) • Mean fasting blood glucose (FBG) and mean postprandial blood glucose (self-monitoring) changes from baseline visit to end of treatment (week 24) Throughout the entire study and in the ITT population (defined above): Safety was measured by hypoglycemia and severe hypoglycemia events, adverse events, serious adverse events according to global pharmacovigilance definitions, vital signs and laboratory results. Hypoglycemia was defined as a blood glucose value ≤70 mg/dL (3.9 mmol/L) with or without symptoms and severe hypoglycemia defined as a blood glucose value ≤50 mg/dL (2.8 mmol/L).

Statistical methods:

Sample size calculation:

Table 1. Sample size estimation scenarios

Scenarios	I	II	III	IV	V
Difference (%)	0.31	0.33	**0.35**	0.37	0.39
Alfa	0.05	0.05	**0.05**	0.05	0.05
Beta	0.20	0.20	**0.20**	0.20	0.20
Desv. Estándar (%)	1.3	1.3	**1.3**	1.3	1.3
N (each group)	271	239	**212**	190	171
N Total	542	478	**424**	380	342
N Total + 15%	624	550	**488**	438	394

Scenario V from Table 1, was applied for the present study, with a sample size of 342 patients, increased to 394 patients (rounded 400) based on a dropout rate of 15%, an alpha of 5% and a power of 80% to detect an absolute difference of 0.39% in HbA1c.
Patients registered on the study and in www.clinicaltrials.org were 400.

Statistical Methods

1. To compare discrete variables, several methods of Analysis of Frequency Data were used (relative frequency distribution, frequency tables and polygons, etc).

To compare proportions and determine the degree of association among them, independence Chi square test and its variations were used when appropriate (Pearson Chi Square and maximum similarity tests of independence).

For variables showing percentage units of magnitude.
a) Pearson Chi Square and Maximum similarity tests of independence.
b) Z (two proportions).

2. To compare mean values of the variables analyzed in the study, between the two study groups, t-Student tests were used, according to the following plan:

a) Intra-group comparison: t - student test for dependent or paired samples.
b) Inter-group comparison: t - student test for independent samples.
c) Levene and Brown - Forsythe tests to evaluate the homogeneity of the samples.
d) Arithmetic mean, median and standard deviation, maximum and minimum values.

3. The following tests were used to compare both treatment groups:

a. Variance Analysis (one and two factors) were used to determine significant differences between HbA1c and fasting and postprandial glucose mean values in both groups of treatment (baseline *versus* week 24).
b. Tukey's test - Multiple comparisons were used to define difference between HbA1c values in baseline *versus* week 24 in both treatment groups.

All test results were considered statistically significant when the significance level or p value reported for the test was less than 5%.

Summary

A total of 400 randomized patients (200 per treatment group) were registered. There were 306 analyzable patients and 94 withdrawals due to different causes, i.e., the subject was lost to follow up, did not wish to continue in the study, protocol violation, non-compliance with treatment procedures, pregnancy or discontinuation of contraception in the intention of becoming pregnant, does not meet the lab criteria and hypoglycemia; and 29 patients were excluded because they did not have HbA1c values recorded at week 24.Fig. 1 shows the study population distribution:

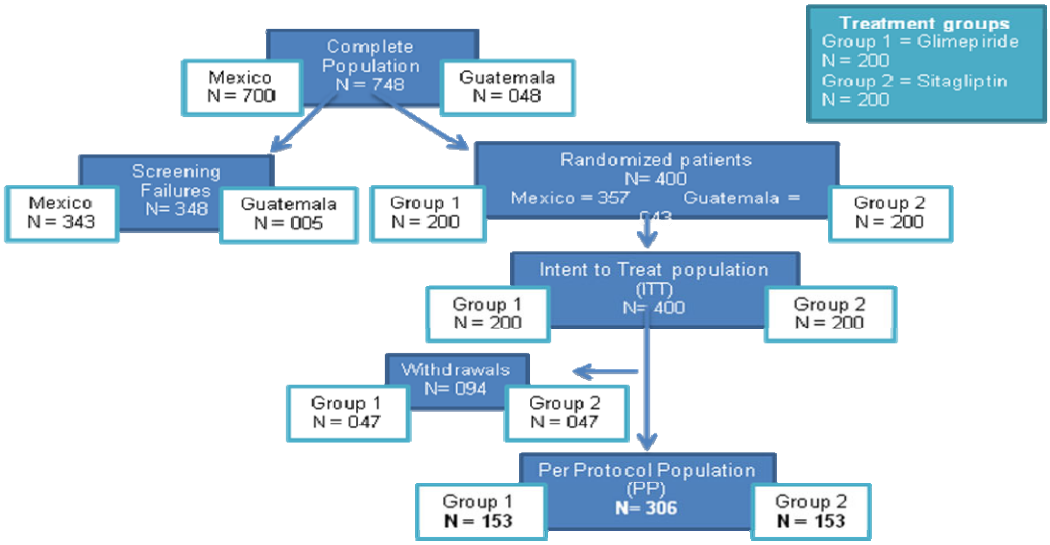

Fig. 1. Population distribution

Results:

Table 2. Baseline characteristics per treatment group

	Group 1 (glimepiride) N=200			Group 2 (sitagliptin) N=200		
	Mean	**SD**	**Median**	**Mean**	**SD**	**Median**
Age [Years]	49.5	10.5	50.6	48.6	11.7	49.1
Weight [kg]	79.1	16.6	77.1	80.0	18.8	78.1
BMI [kg/m²]	24.5	4.4	23.9	24.5	5.0	23.6
HbA1c [%]	9.6	0.9	9.6	9.6	0.8	9.7
Fasting blood glucose [mg/dl]	210.3	72.4	201.0	201.9	68.9	197.0
Creatinine [mg/dl]	0.74	0.22	0.71	0.75	0.20	0.75
AST [U/L]	31.5	16.3	26.0	31.9	17.1	27.0
ALT [U/L]	37.6	26.2	30.0	36.8	22.1	30.0
Cholesterol [mg/dl]	196.4	48.9	195.0	195.1	39.3	191.0
HDL [mg/dl]	36.2	14.8	34.0	35.2	8.0	34.0
LDL [mg/dl]	116.9	34.0	119.0	114.1	31.5	117.0
Triglycerides [mg/dl]	241.5	191.5	193.0	265.6	249.1	196.5

Baseline characteristics in the ITT population are shown in Table 2. There is no statistical difference between the two treatment groups.

Summary

Primary objective:
The primary objective was to determine the superiority of glimepiride over sitagliptin in reducing HbA1c after 24 weeks of treatment.

The per protocol statistical analysis showed no superiority of glimepiride versus sitagliptin in terms of HbA1c reduction. After 24 weeks of treatment, there was no statistically significant difference between the mean HbA1c in both groups baseline (p=0.705; week 24: p=0.138). An intra-group analysis showed statistically significant differences in the mean HbA1C from baseline to week 24 (p <0.000001 for glimepiride and p <0.000001 for sitagliptin) (Table 3).

Table 3. Mean reduction in HbA1c, per protocol

PP population	HbA1c %		
Treatment group	**Visit**	**Mean ± SD**	**% Reduction**
Group 1 (glimepiride) N=153	Baseline Week 24	9.84 ± 0.74 7.78 ± 1.90	2.06
Group 2 (sitagliptin) N=153	Baseline Week 24	9.81 ± 0.71 8.12 ± 2.08	1.69

The trend in the efficacy of glimepiride was absolute reduction difference 0.37% (2.06% reduction of HbA1c with glimepiride less 1.69% reduction of HbA1c with sitagliptin) *versus* a hypothesis of superiority of 0.39% (see table 1).

The percentage of patients that achieved HbA1c levels ≤7%, ≤6.5 was not statistically significant different between the treatment groups.

Table 4. Rate of patients achieving HbA1c levels < 7% and < 6.5% at week 24

PP population	HbA1c %					
Treatment group	**Visit**	**≥ 7.1%**	**%**	**≤ 7% (group ≤6.5% included)**	**%**	**≤ 6.5%**	**%**
Group 1 (glimepiride) N = 153	Week 24	**78**	51.0	**75**	49.0	**46**	30.1
Group 2 (sitagliptin) N = 153		**88**	57.5	**65**	42.5	**47**	30.7

The analysis of HbA1c changes by glimepiride titration (per doses) are shown in Table 5, and statistically significant differences in mean HbA1c were observed among the different glimepiride doses (p < 0.000001; F = 18.48).

Summary

Table 5. Mean HbA1c per glimepiride administered doses

PP population	HbA1c				
Group 1: glimepiride doses	**Visit**	**N**	**Mean (SD +/-)**	**Median**	**Range**
2 mg	Week 24	27	6.25 ± 0.92	6.1	4.40
4 mg		16	6.79 ± 1.12	6.50	3.80
6 mg		110	8.30 ± 1.91	7.85	8.9

Secondary objectives - Evaluate the effect of glimepiride compared to sitagliptin in:

1. **Fasting blood glucose.** In the Per Protocol population, the reduction of Fasting Blood Glucose in glimepiride group at week 24 was 27.54 mg/dL and in sitagliptin 22.28 mg/dL, with no statistically significant differences between the 2 groups (p = 0.234).

2. **Postprandial glucose (after breakfast, lunch and dinner).** In the PP, changes (week 2 vs. week 24) showed a reduction in both groups; 33.26 mg/dL in average for glimepiride and 28.59 mg/dL for sitagliptin. No statistically significant differences between the 2 groups were observed after: breakfast p> 0.73; lunch p <0.620788, or dinner p> 0.88.

3. **Percentage of patients at week 24 with HbA1c ≤ 6.5 %** was 30.1 for group 1 and 30.7 for group 2. **Percentage of patients with HbA1c ≤ 7 %, including those who are ≤ 6.5** was 18.9 for group 1 and 11.8 for group 2.

4. **Body weight.** The mean change in body weight was -0.27% (-0.216kg) in glimepiride group and -1.12% (-0.892kg) in sitagliptin group. Differences between baseline and week 12 in both groups are no statistically significant (p = 0.695).

5. **Percentage of withdrawal from protocol and percentage of patients with rescue therapy.** During the course of the study, 42 dropouts were reported: those patients were evenly distributed between both treatment groups and did not show statistical differences (p = 0.66). Two patients in sitapliptin group received rescue therapy, and none from glimepiride group.

Summary	**Safety results:** Safety was measured in the ITT population by the presence of Adverse Events (AEs) and Serious Adverse Events (SAEs), hypoglycemia, significant changes in vital signs and laboratory tests results. **Adverse Events and Serious Adverse Event** A statistically significant difference between the 2 treatment groups was observed (Chi square = 31.58, p <0.0000001). Table 6. Incidence of AEs and SAEs

	Adverse Events and Serious Adverse Events							
Treatment group	**N***	**%**	**Adverse Events reports**	**%**	**N***	**%**	**Serious Adverse Events**	**%**
Group 1 (glimepiride) N = 200	**66**	37.07	**143**	65.89	**13**	**7.3**	**23**	69.69
Group 2 (sitagliptin) N = 200	**60**	33.33	**74**	34.10	**6**	**3.33**	**10**	30.30
Total	**126**		**217**	**100**	**19**		**33**	**100**

*N= Only patients who have experienced at least one AEs and SAEs.

Symptomatic hypoglycemia

Results showed a statistically significant difference between the 2 treatment groups, in patients who developed hypoglycemia events (Chi Square = 29.0, p <0.000001). See Table 7.

Table 7. Incidence of symptomatic hypoglycemia

	Symptomatic hypoglycemia (blood glucose ≤ 70 mg/dL)					
Treatment group	**N***	**%**	**Hypoglycemia reports**	**%**	**Symptomatic hypoglycemia reports**	**%**
Group 1 (glimepiride) N = 200	**71**	39.88	**236**	80.54	**94**	88.67
Group 2 (sitagliptin) N = 200	**25**	13.96	**57**	19.45	**12**	11.32
Total	**96**		**293**		**106**	

*N= Only patients who have experienced at least one hypoglycemia event.

Is important to mention that patients in the glimepiride group went through a titration period (2, 4 and 6 mg), which was not the case with sitagliptin. The incidence of hypoglycemic events had an average of 3.32 events for patient in the glimepiride group and 2.28 events for patient in the sitagliptin and showed a statistically significant difference (p <0.001).

Severe Hypoglycemia

Results showed a statistically significant difference in patients who developed hypoglycemia events between the 2 treatment groups (Chi Square = 29.0, p <0.000001). The sitagliptin group did not report any severe hypoglycemia events (Table 8). No fatal events were reported in either of the groups.

Table 8. Incidence of severe hypoglycemia

	Severe hypoglycemia (Glucose ≤ 50 mg/dL)					
Treatment group	**N***	**%**	**Severe Hypoglycemia**	**%**	**Symptomatic hypoglycemia**	**%**
Group 1 (glimepiride) N = 200	**7**	3.93	**8**	100	**94**	88.67
Group 2 (sitagliptin) N = 200	**0**	0	**0**	0	**12**	11.32
Total	**7**		**8**		**106**	

*N= Only patients who have experienced at least one severe hypoglycemia event.

Systolic and diastolic blood pressure (SBP and DBP)

The comparison of the mean systolic and diastolic blood pressures in the PP population (N=306) did not show a statistically significant difference between treatment groups. No changes were found from baseline to week 24 in SBP, DBP and pulse rate.

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