Safety and Efficacy of the Fixed-dose Combination Of Glimepiride-Metformin in Treating Type II Diabetes Mellitus (GLMET_L_05632): A Real World Experience

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Abstract

Introduction: Diabetes in the Philippines is a major and growing health issue. From its prevalence of 2.8 million in 2000, it was projected by the World Health Organization to reach 7.8 million by 2030. Glimepiride has been found to be effective and well-tolerated, as monotherapy and in combination with metformin, in managing glycemic levels among type II diabetes mellitus (T2DM) patients. This study aimed to assess the safety and efficacy of a sustained release (SR) fixed-dose combination (FDC) preparation of glimepiride and metformin in the treatment of Filipino patients with T2DM.

Methods: This open-label, observational, multicenter, post-marketing study, conducted from April 2012 to December 2013, included 20 to 75-year-old patients with T2DM, presenting with 7% to 11% HbA1c or 110-250 mg/dL fasting blood sugar, insulin-naive, and in consideration for management with a glimepiride-metformin FDC. Baseline data were collected. Patients were prescribed with glimepiride-metformin FDC SR 2/500 mg/tab for a six-month treatment period. Follow-up data were collected on the third and the sixth month of treatment. Patients who missed one follow-up were included in population for safety analysis. Patients who completed both follow-up schedules make up the per-protocol population for efficacy analysis. Adverse events (AEs) were reported in frequencies and percentages. Repeated measures analysis of variance (ANOVA) was used for efficacy analysis on HbA1c and FBG data.

Results: From 1,052 enrollees, 795 patients had sufficiently filled data forms and attended at least one follow-up schedule; this is the population whose data was analyzed for this study. Fifty-nine AEs were reported; only 21 incidents of hypoglycemia were assessed to be definitely, probably, or possibly related to the study drug. Repeated measure ANOVA showed that the mean ± SD HbA1c at month three (7.15 ± 1.22%) and month six (6.80 ± 1.17%) were significantly lower than baseline (8.67 ± 1.10%). The mean ± SD FBG at month three (133.20 ± 35.46 mg/dL) and month six (122.47 ± 29.34 mg/dL) were also significantly lower than baseline (176.85 ± 41.24 mg/dL). The differences in HbA1c and FBG changes between those with concomitant OAD and those without were non-significant.

Conclusion: Fixed-dose combination of glimepiride-metformin is a drug with a tolerable profile and favorable benefits in treating patients with T2DM.

Keywords: glimepiride, metformin, diabetes

Introduction

According to estimates by the World Health Organization (WHO), the prevalence of diabetes in the Philippines was at 2.8 million in the year 2000, and it was projected to reach 7.8 million by 2030.[1] In the seventh National Nutrition Survey (NSS) published in 2008, the prevalence of high fasting blood sugar (FBS: >125mg/dL) among adults increased to 4.8%, from 3.4% in 2003, while the prevalence of impaired fasting glucose (IFG) was at 2.7%.[2] These figures show that diabetes in the Philippines is a major and growing health issue. Timely and effective intervention is needed.

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Blood glucose control is a basic requirement in the management of diabetes. The United Kingdom Prospective Diabetes Study (UKPDS) and the Diabetes Control and Complications Trial (DCCT) showed that good glycemic control is associated with decreased risks for retinopathy, nephropathy, and neuropathy.[3-6] Although medical nutrition therapy, weight management, and lifestyle modifications such as exercise and smoking cessation form the cornerstones of diabetes management, pharmacologic therapies aid in the achievement of glycemic targets. Sulfonylureas help control blood sugar levels by enhancing insulin secretion, while biguanides suppress hepatic glucose output and improve peripheral insulin sensitivity.[8-10] The findings of Charpentier et al.[10] suggest that patients with type II diabetes mellitus (T2DM) require more than one drug to control their blood sugar levels.

The sulfonylurea glimepiride has been found to be an effective and well-tolerated glycemic control drug, even in

combination with the biguanide metformin, in T2DM patients. Evidence has shown that patients are adequately controlled by one to six milligrams of glimepiride daily.[11] Treatment with glimepiride was also associated with a lower incidence of hypoglycemia than the second-generation sulfonylurea glyburide.[12] Thus, a fixed-dose combination (FDC) of glimepiride and metformin can be an effective tool in allowing patients with T2DM to achieve their glycemic targets.

This study aimed to assess the safety and efficacy of a sustained-release (SR) fixed-dose combination preparation of glimepiride and metformin in the treatment of Filipino patients with T2DM. Its primary objectives were to determine the rate of symptomatic hypoglycemic events and to obtain spontaneously reported adverse events (AEs) for glimepiride-metformin. Its secondary objectives were to identify efficacy endpoints in terms of changes in HbA1c and fasting plasma glucose from baseline to the end of follow-up.

Methods

This is an open-label, observational, multicenter, real world experience study conducted from April 2012 to December 2013. Patients included in the study were Filipinos aged 20–75 years diagnosed with T2DM and presenting with poor glycemic status (HbA1c within 7% to 11%) or fasting blood sugar (110–250 mg/dL); either currently taking or previously treated with oral anti-diabetes drugs (OADs) or are drug-naïve; insulin-naïve; and in consideration for management with a glimepiride-metformin FDC. Pregnant women, patients with an acute illness that required hospitalization in the past two months, and patients with active liver disease, impaired renal or hepatic functions, or known hypersensitivity to metformin, glimepiride, other sulfonylureas, other sulfonamides, or any other excipients of Solosamet® SR were excluded from the study.

Patient data were collected using a paper data collection form (DCF). Patients were prescribed with glimepiride-metformin FDC SR 2/500 mg/tab, to be taken orally either once or twice daily (depending on the physician's judgement in consideration of the patient's baseline and target blood glucose levels), during the six-month treatment period. Titration of the study drug was done based on blood glucose monitoring, with a fasting blood sugar of less than 100 mg/dl. Patients who were already on FDC glimepiride + metformin were shifted to the study drug Solosamet® SR. Determination of HbA1c was done at baseline and at three-month intervals. Patients were followed up at three and six months post-baseline. Data were recorded in the case report form (CRF) monthly during the six-month observation period. Patients who had sufficient data for both the third month and sixth month visit became part of the per protocol (PP) population, which was used to evaluate the efficacy criteria. Patients who missed one of the follow-up schedules were included in the intention-to-treat (ITT) population, which was analyzed to describe the safety profile of glimepiride-metformin (Solosamet® SR). At the last follow-up visit, the patients' and the physician's assessment of treatment were recorded using the global assessment of the treatment of diabetes form.

The study sponsor collected the completed DCFs from the sites (through professional sales representatives), encoded the data using MS Excel, and performed manual validation. Data rectification forms (DRFs) were sent to physicians for clarification. Query resolutions were used to update the clinical database. Missing data were treated as absent information, and statistical computations and analysis were based only on information that was provided.

The data for the safety analysis were solicited and reported using the safety report form. Adverse events (AEs) were reported in frequencies and percentages and were summarized by severity and relation to study treatment. Adverse drug reactions (ADRs; AEs that were assessed as related to the use of Solosamet® SR) were recorded on the ADR data collection form. We used the last observation carried forward (LOCF) method for handling missing data. If the ADR was assessed as serious, it was recorded and reported to Sanofi-Aventis Philippines using the Serious Adverse Drug Reaction Report form within 24 hours of the physician's first knowledge of event. Safety was evaluated on the basis of ADRs.

For the efficacy analysis, a per-protocol analysis was done, which included those with complete efficacy data. Comparison of changes between visits (i.e., baseline and month three, baseline and month six, month three and month six) used a two-tailed t-test to determine whether there was a statistically significant difference in the changes of the variables (i.e., HbA1c, fasting blood glucose). Demographic variables were summarized using means and SDs for continuous parameters and frequencies, and percentages for categorical parameters. The global assessments at the

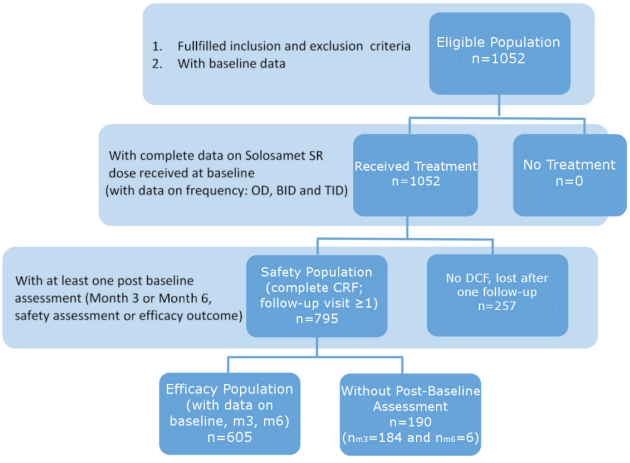

Figure 1. Patient disposition from start of study to end of follow-up

Table I. Patients baseline characteristics

	Status of concomitant OAD		Total
	Without	With	
Total Number of Patients	198	597	795
Male	96	261	367
Female	102	336	428
Demographics	**(Mean ± SD)**		
Age (years)	71±23	70±18	70±20
Weight (kg)	52±11	55±11	54±11
Height (cm)	162±7	161±7	161±7
BMI (kg/m^2)	27.15±8.2	26.91±6.4	26.97±6.9
SBP (mm Hg)	123.79±10.93	131.75±16.15	129.77±15.41
DBP (mm Hg)	80±8	82±10	82±10
Duration of diabetes (years)	4±3	5±5	5±5
HbA1c (%)	8.56±1.06	8.68±1.16	8.65±1.13
FBG (mg/dL)	171.62±45.9	177.09±39.68	175.8±41.29
Concomitant diseases			
Hypertension	198	596	794
Dyslipidemia	194	583	777
Stroke	198	591	789
Mycardial infarction	198	585	783
Angina	197	587	784
Peripheral vascular disease	193	580	773
Others	198	597	795

end of treatment follow-up were described using frequencies and percentages. All statistical tests carried out on efficacy and safety evaluations were two-sided, with 0.05 level of significance.

Results

A total of 1,052 subjects were enrolled in the study. From these, 86.5% had complete follow-up attendance (i.e., they returned for follow-up on month three and month six). An additional 7.9% came for third-month follow-up but did not come on the 6th month, while 0.6% came for the sixth-month follow-up although they missed the third month. At the end of the study, 13% were lost to follow-up. One of the limitations in this trial is the high number of drop outs. The study was terminated early because of the local Food and Drug Agency (FDA) guidance of disallowing post marketing surveillance studies, thus the decreased number of subjects.

Table I shows that most of the population whose data we used for the safety and efficacy analyses had concomitant AODs (75%). Most were female (78.5%). Mean age was 70 ± 20 years. Between the group with concomitant OADs and those without, there were no statistically significant differences in BMI (26.97 ± 6.9 kg/m^2, p=0.711); HbA1c (8.65 ± 1.13%, p=0.224); and FBG (175.8 ± 41.29 mg/dL, p=0.169). Patients with concomitant OADs had significantly higher systolic blood pressures (131.75 ± 16.15 vs. 123.79 ± 10.93 mm Hg, p<0.0001) and a significantly longer mean duration of diabetes (5±5 vs. 4±3 years, p<0.0001).

Table II. Concomitant OADs taken with glimepiride+metformin

Concomitant medication	Frequency	Percentage
OAD		
Biguanide	177	22.26%
DPP4 inhibitor	93	11.70%
Thiazolidinedione	48	6.04%
Sulfonylurea	43	5.41%
FDC (biguanide + DPP4)	20	2.52%
FDC (thiazolidinedione + biguanide)	14	1.76%
FDC (sulfonylurea + biguanide)	7	0.88%
FDC (glimepiride + metformin)	2	0.25%
Non-OAD		
Angiotensin receptor blocker	7	0.88%
Calcium channel blocker	1	0.13%
FDC (losartan + amlodipine)	1	0.13%
FDC (metformin + sitagliptin)	1	0.13%
FDC (telmisartan + amlodipine)	1	0.13%
Others	24	3.02%

OAD, oral antidiabetic drug; DPP4, dipeptidylpeptidase 4; FDC, fixed-dose combination

Table III. Non-serious AEs and their relationship to glimepiride-metformin therapy

Non-serious AE n (%)	Definitely related	Probably related	Possibly related	Unrelated	No data
Fever	-	-	-	1 (0.13%)	-
Cough	-	-	-	1 (0.13%)	-
URTI	-	-	-	1 (0.13%)	-
Hypoglycemia	2 (0.25%)	13 1.64%)	6 (0.75%)	13 (1.64%)	21 (2.64%)

Table II lists the concomitant OADs and the non-OAD medications taken by the study population. Biguanides were the most frequently taken concomitant medication, reported by 177 (22.26%) of the total study population; these were followed by DPP4 inhibitors, reported by 93 (11.7%), and thiazolidinediones, reported by 48 (6.04%). Biguanide-DPP4 was the most commonly reported concomitant combination drug, reported by 20 (2.52%).

Of the 597 patients with concomitant OAD medications, 572 (96%) received the study drug once a day, while 25 (4%) received it twice. Of the 198 with no concomitant OADs, 196 (99%) received the glimepiride-metformin dose once a day, while two (1%) received it twice a day.

Adverse events

Thirty-seven patients reported AEs. Two events were directly related to the investigational product. (Figure 1)

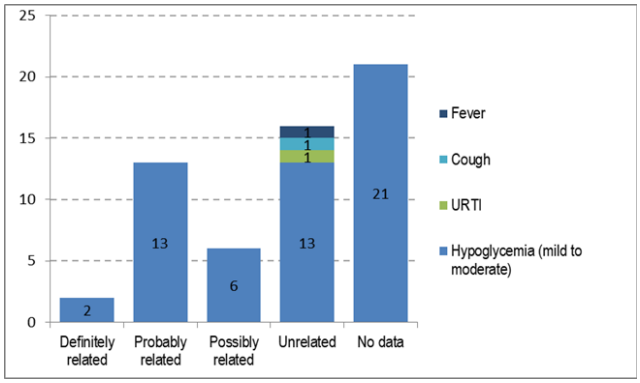

Figure 2. Adverse events reported in the use of glimepiride-metformin combination

Thirty-six patients reported 58 incidences of non-serious AEs, specifically, 55 mild-to-moderate hypoglycemic episodes, one upper respiratory tract infection (URTI), one cough, and one fever. In total, 21 of the 59 reported AEs (35.6%) were assessed to have some relationship with the study drug (Table III). A serious adverse event was reported that of a fatal myocardial infarct in a 69-year-old female patient who was obese, and a 14-year history of diabetes, with a previous history of myocardial infarction, known hypertension and dyslipidemia. The patient had the following medications on board, on top of Solosamet® SR: insulin glargine, sitagliptin, valsartan, atorvastatin, pentoxifylline, denosumab, and clopidogrel. An investigator confirmed that the serious AE was unrelated to the study drug.

Changes in HbA1C

Repeated measure ANOVA showed that the mean ± SD HbA1c at month three (7.15 ± 1.22%) and month six (6.80 ± 1.17%) were significantly lower than baseline (8.67 ± 1.10%) (Table IV). Statistically significant mean changes in HbA1c level were observed between baseline and month three (0.71 ± 1.04% 95% CI 1.25–1.51 $p<0.0001$), between baseline and month six (0.74 ± 1.17% 95% CI 1.64–1.91 $p<0.0001$), and between month three and month six (0.20 ± 0.75% 95% CI 0.27–0.57 $p<0.0001$).

Table V compares mean HbA1c values and mean changes between those with concomitant OADs and those without. We found that those with concomitant OADs had significantly higher mean HbA1c levels at baseline and month three than those without concomitant OADs, but the difference in OAD levels between the two groups became non-significant at month six. There was no statistical significance found in the difference in HbA1c change between the two groups from baseline to month three, baseline to month six, and month three to month six of follow-up.

Changes in FBG

Table VI shows that the mean ± SD FBG at month three (133.20 ± 35.46 mg/dL) and month six (122.47 ± 29.34 mg/dL) were significantly lower than baseline (176.85 ± 41.24 mg/dL). The changes between baseline and month three (44.92 ± 39.77 mg/dL 95% CI 40.95–48.89 $p<0.0001$), baseline and month six (56.28 ± 45.87 mg/dL 95% CI 51.98–60.59 $p<0.0001$) and month three and month six (12.86 ± 28.96 mg/dL 95% CI 9.07–16.65 $p<0.0001$) were statistically significant.

Table VII shows that there were statistically significant differences in the mean FBGs between patients with concomitant OADs and those without, at baseline (180.59 vs. 174.76 mg/dL, $p=0.038$), month three (157.56 vs. 129.89 mg/dL, $p<0.0001$), and month six (135.68 vs 121.91 mg/dL, $p=0.027$). On the other hand, the differences in amount of change in FBG between the two groups were non-significant.

Changes in weight, BMI, and blood pressure

There were no significant differences in mean ± SD weight of the patients at baseline (70.31 ± 18.91 kg 95% CI 69.171.46), month three (70.75 ± 21.06 kg 95% CI 69.272.22) and month six (68.95 ± 18.22 kg 95% CI 67.500.40) ($p=0.213$).

There were no significant differences in mean ± SD BMI of the patients at baseline (26.91 ± 6.77 kg/m^2 95% CI

Table IV. Mean HbA1c level at each clinic visit

Visit	N	Mean (%)	SD	95% CI	*p*-value
Baseline	793	8.67	1.10	8.60–8.75	<0.0001
Month 3	667	7.15	1.22	7.06–7.24	
Month 6	524	6.80	1.17	6.70–6.90	

*SD, standard deviation; CI, confidence interval

Table V. Mean HbA1c level at each clinic visit in patients with and without concomitant OAD medications

HbA1C	Concomitant OAD medications				*p*-value
	Without		With		
	n	Mean (%)	N	Mean (%)	
Baseline	480	8.56	313	8.85	
Month 3	587	7.07	80	7.73	<0.0001
Month 6	502	6.78	22	7.36	0.140
Change from baseline to month 3	276*	-1.33	38*	-1.82	0.085
Change from month 3 to month 6	416*	-0.39	4*	-0.03	0.653
Change from baseline to month 6	252*	-1.68	10*	-1.5	0.282

* Difference between the two parameters

Table VI. Mean FBG level at each clinic visit

Visit	N	Mean (%)	SD	95% CI	*p*-value
Baseline	930	176.85	41.24	174.20–179.50	<0.0001
Month 3	735	133.20	35.46	130.64–135.76	
Month 6	566	122.47	29.34	120.06–124.89	

SD, standard deviation; CI, confidence interval

Table VII. Mean FBG level at each clinic visit in patients with and without concomitant OAD medications

FBG	Number of patients				*p*-value
	Without OADs		With OADs		
	n	Mean (mg/dL)	N	Mean (mg/dL)	
Baseline	596	S174.76	334	180.59	0.038
Month 3	647	129.89	88	157.56	<0.0001
Month 6	543	121.91	23	135.68	0.027
Change from baseline to month 3	363*	-44.22	39*	40.33	0.562
Change from month 3 to month 6	464*	-10.66	5*	6.32	0.717
Change from baseline to month 6	302*	-56.20	6*	67.23	0.577

* Difference between the two parameters

26.49–27.33), month three (27.17 ± 7.43 kg/m^2 95% CI 26.62–27.70), and month six (26.56 ± 6.68 kg/m^2 95% CI 26.69–27.65) (p=0.229). Mean ± SD SBP was noted to be significantly higher at baseline (130 ± 15 mmHg 95% CI 129–130) than at month three (124 ± 11 mmHg 95% CI 123–125) and month six (123 ± 10 mmHg 95% CI 122–124) (p<0.0001). The changes in mean SBP were statistically significant between baseline and month three (<0.0001) and baseline and month six (p<0.0001) but not between month three and month six (p=0.081).

Mean ± SD DBP was noted to be significantly higher at baseline (82 ± 10 mmHg 95% CI 82–83) than at month three (80 ± 8 mmHg 95% CI 79–80) and month six (79 ± 9 mmHg 95% CI 77–80) (p<0.0001). The changes in mean DBP were statistically significantly between baseline and month three (<0.0001) and baseline and month six (p<0.0001) but not between month three and month six (p=0.163).

Discussion

This study analyzed data from 795 patients, where 37 reported a total of 59 AEs: 55 mild-to-moderate hypoglycemic incidents, one URTI, one fever, one cough, and one serious AE, a fatal myocardial infarction that occurred before the patient could attend the third-month follow-up. Among these, the investigator assessed that 21 of the hypoglycemia incidents were related to glimepiride-metformin; all the other reported AEs were assessed to be unrelated to the study drug.

The risk of hypoglycemia is the most common concern with combined therapy.[12] In most cases, the risks associated with poor blood glucose control greatly outweigh the risk for hypoglycemia.[14] Appropriate blood glucose monitoring contributed in preventing hypoglycemic complications. The efficacy of Solosamet® SR was evaluated with respect to HbA1c endpoints and FBG. Repeated measures ANOVA demonstrated that, during glimepiride-metformin (Solosamet® SR) treatment, the HbA1c levels of patients were significantly lower at month three and month six, and the changes between baseline and month three, baseline and month six and month three and month six were statistically significant. Similar results were seen for FBG.

Tight control of diabetes with reduction of HbA1c from 9.1% to 7% has been shown to reduce the risk of microvascular complications better than conventional therapy (mostly diet alone). Cardiovascular complications have not been noted for any particular therapy; metformin treatment alone reduced the risk of macrovascular disease (myocardial infarction, stroke). Epidemiologic analysis by the UKPDS suggested that every one percent decrease in the HbA1c achieves an estimated reduction of 37% for microvascular complications, 21% for diabetes-related end point and death related to diabetes, and 14% for myocardial infarction.[5,6]

Conclusion

In conclusion, we found that the FDC of glimepiride-metformin is a drug with a tolerable profile and favorable HbA1c and FBG management benefits for treating patients with T2DM.

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