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Sponsor / Company : sanofi-aventis **Drug Substance :** INSULIN GLARGINE		**Study Identifier :** NCT00562172 **Study Code :** LANTU_L_02193	
Title of the study:	Insulin Glargine vs Glimepiride as add-on Therapy in Type 2 Diabetic Patients Failing Metformin Monotherapy: Comparison of Effects on Beta-Cell function and Metabolic Profile		
Study Center(s):	9 clinical centers in Korea (single-country clinical trial)		
Study period: First Patient First Visit: 05-Sep-2007 Last Patient Last Visit: 28-Oct-2010		**Phase of development:** Phase 4	
Objectives:	**Primary Objective :** To compare the effects of insulin glargine and glimepiride on pancreatic beta-cell insulin secretion when given as add-on therapy in the early type 2 diabetes mellitus patients. **Secondary Objectives :** - To compare insulin resistance: HOMA-IR - To compare the change in blood glucose (HbA1C, Fasting Plasma Glucose FPG) values and lipid profiles - To compare the prevalence of hypoglycemia during the treatment period - To compare changes in body weight, waist circumference and waist/hip ratio		
Methodology:	A multi-center, single-country, phase 4, parallel-group, randomized, open-label, comparative study This is a multi-center, single-country, phase 4, parallel-group, randomized (1:1 randomization ratio), open-label, comparative study, consisting of a screening period (up to 4 weeks) and a 48-week treatment period. During the screening period, patients continued dietary and exercise therapy and their current therapy with metformin at a stable dose. Patients were also given an instruction on how to use a blood glucose meter provided by the sponsor for the study. Following screening assessments, eligible patients were randomized to receive either insulin glargine (once daily before breakfast) or glimepiride (once daily before breakfast) for 48 weeks. During the treatment period, patients continued treatment on a stable dose of metformin from screening period (at least 1,000 mg/day), and were prohibited from taking any other oral blood-glucose lowering agent, except study drugs. Patients received insulin glargine or glimepiride as add-on therapy before breakfast, and the dose was adjusted according to the protocol based on a fasting blood-glucose level. Patients in the insulin glargine group were given an instruction regarding blood glucose self-monitoring and insulin self-administration. The study consisted of a screening period of up to 4 weeks and a 48 week treatment period.		
Number of patients:	Planned: 74	Randomized: 75	Completed: 65
Evaluated:	Safety Population: 74	Intent To Treat (ITT) population: 72	Per Protocol (PP) population : 64

Diagnosis and criteria for inclusion:	**Inclusion Criteria** 1. Patients with type 2 diabetes mellitus for at least 6 months 2. Patients treated on metformin at least ≥ 1,000 mg/day for at least last 3 months prior to study entry; patients previously treated with sulfonylurea or insulin may be eligible for the study if they have not used such treatment within last 3 months before screening. 3. 7 % ≤ HbA1c ≤ 12 % 4. Patients aged between 18 and 75 years 5. Body Mass Index (BMI) < 35 kg/m^2 6. Patients who are able and willing to perform blood glucose self-monitoring using the glucose meter and to complete the patient diary. 7. Patients who have provided written informed consent before study entry.
	Exclusion Criteria 1. Patients with type 1 diabetes mellitus 2. Patients with liver dysfunction, as evidence by Alanine Aminotransferase (ALT) and/or Aspartate Aminotransferase(AST) greater than 3 times the upper normal range at study entry. 3. Patients with renal dysfunction at study entry: serum creatinine ≥ 1.5mg/dL(≥ 133μmol/L) for males, and ≥ 1.4mg/dL(≥ 124μmol/L) for females. 4. Patients who underwent photocoagulation or surgical treatment for active proliferative diabetic retinopathy within 6 months prior to study entry, or who have other unstable retinopathy (rapidly progressing) requiring photocoagulation or surgical intervention during the study period (results of fundoscopic exam performed within 2 years prior to study entry should be available). 5. Patients with a history of alcohol or other substance abuse. 6. Pregnant patients (women of childbearing potential should have a negative pregnancy test prior to study entry and should use medically acceptable contraceptives) 7. Patients who are breastfeeding 8. Patients with known hypersensitivity to study drug or drugs possessing a similar chemical structure 9. Patients who have used systemic corticosteroid or other drugs affecting blood glucose level within 3 months before study entry. 10. Patients with other disease which, in the opinion of the investigator may interfere with completion of the study according to the protocol or scientific analysis of study results. 11. Patients unlikely to comply with the protocol requirements. For example, uncooperative attitude, inability to return for follow-up visits and unlikelihood of completing the study
Investigational products:	**Insulin glargine (Lantus Inj. SoloSTAR ®) (hereafter, referred to as 'Metformin+Insulin Glargine')** Dose: Insulin glargine was administered once a day at the same time before breakfast each day, beginning with an initial dose of 0.2U/kg/day. The dose of insulin glargine was subsequently adjusted according to fasting glucose levels self-measured in the morning before breakfast using a glucose meter provided to patients at study entry. Dose adjustment continued until a fasting glucose level reaches 90 ~ 130 mg/dL, as measured using a self-monitoring glucose meter system. If a fasting glucose level was higher than the target range, the dose of insulin glargine was titrated by an increment of 2 U in every 3 day. Patients who achieved a fasting glucose level within a range of 90 and 130 mg/dL with insulin glargine dose of 8 U or less were discontinued insulin glargine. Administration: Subcutaneous injection once a day at the same time before breakfast each day

Investigational products:	**Glimepiride (Amaryl ®)(hereafter, referred to as 'Metformin+Glimepiride')** Dose: Patients in the glimepiride group received an initial dose of 1 mg in the morning before breakfast. After one week of treatment, dose was permitted to be increased to 2mg/day. The dose titration continued until a fasting glucose level at Week 3, 5 and 7 reached within a range of 90 and 130 mg/dL. The maximum daily dose of glimepiride was 8mg. Dose adjustment was made based on the investigator's judgment. Patients who achieved a fasting glucose level within a range of 90 and 130 mg/dL with glimepiride dose of 0.25mg or less were discontinued glimepiride. Administration: Oral administration in the morning before breakfast
Duration of treatment: Up to 48 weeks	**Duration of observation:** up to 49 weeks (48 weeks of treatment + 1 week of follow-up)
Criteria for evaluation:	
Efficacy :	**Primary Efficacy Endpoint** - C-peptide level as a measure of insulin secretion in a glucagon stimulation test at 0, 24 and 48 weeks of post-randomization. **Secondary Efficacy Endpoint** – Fasting serum proinsulin/insulin ratio at 0, 24 and 48 weeks post-randomization – Insulin resistance index (HOMA-IR) at 0, 24 and 48 weeks post-randomization: HOMA-IR: (FPI(mU/mL) X FPG(mg/dL))/405 – HbA1c value at screening and at 12, 24, 36 and 48 weeks – Fasting plasma glucose (FPG(0) at 0, 12, 24, 36 and 48 weeks post-randomization – Fasting lipid profiles at screening, and at 24 and 48 weeks (total cholesterol, HDL, LDL, triglyceride, apolipoprotein A1, apolipoprotein B, free fatty acid) – 3-point (before each meal) fasting blood glucose levels self-monitored continuously for 2 days before each visit (for both treatment groups) and blood glucose levels measured each time when a patient experiences symptoms of hypoglycemia – Hypoglycemic episodes (symptomatic hypoglycemia, severe hypoglycemia)
Safety :	Incidence of adverse event (including topical tolerability at the injection site, weight change, changes in waist circumference and waist/hip ratio, laboratory measurements, vital signs and physical examination)

Statistical methods:	All statistical tests were performed at two-sided, 5% significance level. **Analysis Population:** Intent To Treat Population comprised patients who were randomized and received the study drug, orally or by injection, for at least 3 months. They were analyzed according to the treatment group to which they were randomized. Per Protocol Population comprised patients who were randomized and completed the study with no major protocol violation. Major protocol violations include: – Violation of inclusion/exclusion criteria – Early withdrawal (excluding early withdrawal due to insufficient efficacy) – Use of prohibited medication Safety population comprised patients who were randomized and received at least one dose of the study drug, orally or by injection. The safety analyses were conducted according to the treatment received actually. **Primary Efficacy Endpoint:** The change from baseline in C-peptide level, the primary efficacy endpoint, was compared between the two groups by ANCOVA(Analysis of Covariance) with a baseline C-peptide as a covariate. The efficacy was analyzed at 24 and 48 weeks, and a 95% confidence interval for the difference between the two groups with regard to the adjusted mean change from baseline in C-peptide level was determined. The primary population for efficacy is the ITT population, and a supportive analysis was also performed on the PP population to evaluate the robustness of the study results. **Secondary Efficacy Endpoints:** Mean changes from baseline in secondary efficacy endpoints were also evaluated at 24 and 48 weeks by ANCOVA using each baseline parameter as covariates, and the efficacy was compared between the two groups. With regard to hypoglycemic episodes (symptomatic hypoglycemia and severe hypoglycemia), the number and percentage of patients experiencing such episodes were summarized and Chi-square test or Fisher's exact test was performed. The mean frequency of hypoglycemia per patient was also presented and the difference between the two groups was compared. **Safety Analysis:** Safety was analyzed in the safety population. The number and percentage of adverse events occurring after initiation of treatment (Treatment Emergent Adverse Event) were summarized by treatment group, system organ class and preferred terms. Adverse events related to the study drug were also presented. - Overall adverse events - Adverse events of severe-to-greater intensity - SAE (Serious Adverse Events) - Adverse events leading to death - Adverse events leading to discontinuation of the study All other safety variables including vital sign (Systolic Blood Pressure/Diastolic Blood Pressure), physical examination and laboratory values are continuous variables and these continuous variables were summarized for each visit using descriptive statistics (mean, standard deviation, median, minimum and maximum).

Summary:

A total of 82 patients provided written consent to participate in the study, and 7 of them were withdrawn due to screening failure and 75 were randomized. Safety was analyzed in 74 patients who had at least one safety assessment. Of 74 patients in the safety population, two were excluded from the ITT due to missing post-baseline C-peptide data (one or more missing data), the primary efficacy endpoint, and thus, 72 patients were included in the ITT. A total of 64 patients in the ITT population who completed the study according to the protocol were included in the PP population. (Table 1)

Table 1. Patient disposition

	Metformin Insulin Glargine	Metformin +Glimepiride	No. of Patients	Percentage (%)
Screening			82	(100.00)
Screening Failure			7	(8.54)
Randomized	39	36	75	(91.46)
Early Withdrawal	5	5	10	(13.33)
Investigator's judgment	0	2	2	(20.00)
Violation of inclusion/exclusion criteria	1	0	1	(10.00)
Use of prohibited medication	1	0	1	(10.00)
Violation of protocol	1	1	2	(20.00)
Withdrawal of consent	2	1	3	(30.00)
Lost to follow-up	0	1	1	(10.00)
Treatment Completion	34	31	65	(79.27)
Failure to administer the study drug			1	(1.22)
Safety Population	38	36	74	(98.67)
Missing post-baseline efficacy measurement	0	2	2	(2.70)
ITT Population	38	34	72	(97.30)
Investigator's judgment	0	1	1	(1.39)
Violation of Inclusion/exclusion criteria	1	1	2	(2.78)
Use of prohibited medication	1	0	1	(1.39)
Violation of protocol	1	1	2	(2.78)
Withdrawal of consent	1	1	2	(2.78)
PP Population	34	30	64	(88.89)

The study involved 45 women (60.81%) and 29 men (39.19%), with an average age of 53.05±8.48 years. No statistically significant difference between the two treatment groups was noted with regard to the prevalence of diabetes complications, duration of the disease, previous medications, past illness or disease, concurrent disease, past surgical history, body weight, height, Body Mass Index, physical examination, concurrent medications, duration of treatment, and dosage of metformin, insulin glargine and glimepiride. Mean exposure to Insulin Glargine and Glimepiride group was 0.04 patient-years and 0.14 patient-years respectively. (Table 2)

Table 2. Demographic factors

		Metformin+Insulin Glargine		Metformin+Glimepiride		Total		p-value
	Total	38	(51.35)	36	(48.65)	74	(100.00)	
Sex		n	(%)	n	(%)	n	(%)	
	Male	12	(31.58)	17	(47.22)	29	(39.19)	0.1683
	Female	26	(68.42)	19	(52.78)	45	(60.81)	
Age	mean±std (years)	51.26	± 8.12	54.94	± 8.56	53.05	± 8.48	0.0616
	median	51.00		55.50		53.00		
Diabetes Mellitus duration	mean±std (months)	78.95	± 59.90	97.97	± 71.97	88.20	± 66.28	0.2195
	median	60.50		84.00		72.00		
Diabetic complication	Yes	12	(31.58)	13	(36.11)	25	(33.78)	0.6803
	No	26	(68.42)	23	(63.89)	49	(66.22)	
	Diabetic Retinopathy	5	(41.67)	7	(53.85)	12	(48.00)	overlap
	Diabetic Neuropathy	7	(58.33)	6	(46.15)	13	(52.00)	
	Diabetic Nephropathy	1	(8.33)	2	(15.38)	3	(12.00)	
	CVD(Angina/MI/CHF/Stroke)	1	(8.33)	2	(15.38)	3	(12.00)	
	PVD(other diabetic vascular disorder)	1	(8.33)	0	(0.00)	1	(4.00)	
Weight	mean±std (kg)	62.68	± 9.06	65.28	± 11.39	63.94	± 10.27	0.2803
	median	64.20		64.45		64.45		
Height	mean±std (cm)	160.22	± 7.78	160.48	± 7.02	160.34	± 7.37	0.8785
	median	159.15		159.05		159.10		
BMI	mean±std (kg/m2)	24.37	± 2.65	25.26	± 3.68	24.80	± 3.20	0.2329
	median	24.45		25.35		24.95		
Treatment duration	n(%)	38	(51.35)	36	(48.65)	74	(100.00)	
metformin	mean±std (months)	18.92	± 6.96	21.71	± 17.07	20.01	± 12.87	0.4670
	median	16.50		15.00		16.00		
comparative drug	mean±std (months)	10.42	± 2.13	10.19	± 2.55	10.31	± 2.33	0.6786
	median	11.00		11.00		11.00		

The dose of drug for treatment by group was as follows. The mean dose of metformin at baseline was 1,365.13 ± 448.0 mg in Metformin+Insulin Glargine and 1,411.12 ± 455.93 mg in Metformin+Glimepiride. (p= 0.6631). (Table 3)

Table 3. Mean dose of comparative drug by visit

		insulin Glagine (U) (Metformin+Insulin Glargine)	Glimepiride(mg) (Metformin+Glimepiride)
		n (%)	n (%)
Week 0	n(%)	38 (51.35)	36 (48.65)
	mean±std *	12.24 ± 1.90	1.03 ± 0.17
	median	12.00	1.00
Week 12	n(%)	37 (50.00)	34 (45.95)
	mean±std *	21.03 ± 10.94	3.82 ± 2.04
	median	20.00	4.00
Week 24	n(%)	35 (47.30)	32 (43.24)
	mean±std *	21.69 ± 9.20	3.88 ± 2.21
	median	20.00	4.00
Week 36	n(%)	34 (45.95)	31 (41.89)
	mean±std *	22.76 ± 9.36	4.29 ± 2.33
	median	22.00	4.00

At the last study visit, in the Metformin+Insulin Glargine, there were 3 patients (8.11%) with dose increase, 1 patient (2.70%) with dose reduction, and 33 patients (89.19%) with no dose change; while, in the Metformin+Glimepiride, there were 2 patients (5.41%) with dose increase, 0 patient with no dose reduction, and 33 patients (89.19%) with no dose change. There was no significant difference between the two groups (p=1.0000). (Table 4)

Table 4. Status of dose change

	Metformin+Insulin Glargine n (%)	Metformin+Glimepiride n (%)	Total n (%)	p-value
Increased	3 (8.11)	2 (5.41)	5 (6.94)	1.0000
Reduced	1 (2.70)	0 (0.00)	1 (1.39)	
Unchanged	33 (89.19)	33 (89.19)	66 (91.67)	
Total	37 (51.39)	35 (48.61)	72 (100.00)	

Efficacy results:

These results are summarized mean change from baseline within treatment period in both group for C-peptide, fasting serum proinsulin/insulin ratio, HOMA-IR, HbA1c, FPG and lipid profile. (Table 5)

Table 5. Mean change from baseline within treatment period by group

			Metformin+Insulin Glargine		Metformin+Glimepiride		
C-peptide (ng/ml)			mean	± std	mean	± std	p value
	Baseline	Week 0	2.44	± 0.92	2.39	± 0.94	
		Week 24	2.59	± 0.89	2.60	± 1.22	0.8501
		Week 48	2.60	± 1.13	2.58	± 0.94	0.9505
		Difference(Week 24-Week 0)	0.13	± 0.83	0.19	± 0.99	0.8501
		Difference(Week 48-Week 0)	0.13	± 1.27	0.17	± 0.72	0.9505
	After 6min	Week 0	4.83	± 1.89	4.75	± 1.96	
		Week 24	4.84	± 2.01	5.03	± 2.58	0.6235
		Week 48	5.19	± 2.15	5.40	± 2.31	0.6144
		Difference(Week 24-Week 0)	0.01	± 1.84	0.24	± 1.91	0.6235
		Difference(Week 48-Week 0)	0.36	± 2.10	0.61	± 1.90	0.6144
	After 6min-Baseline	Week 0	2.39	± 1.29	2.37	± 1.39	
		Week 24	2.30	± 1.45	2.43	± 1.65	0.7298
		Week 48	2.60	± 1.35	2.81	± 1.56	0.4732
		Difference(Week 24-Week 0)	-0.05	± 1.57	0.05	± 1.45	0.7298
		Difference(Week 48-Week 0)	0.23	± 1.18	0.44	± 1.44	0.4732
Fasting serum proinsulin/insulin ratio		Week 0	2.19	± 1.55	2.16	± 1.81	
		Week 24	2.36	± 1.77	2.11	± 1.60	0.5498
		Week 48	2.04	± 1.20	2.57	± 2.52	0.2619
		Difference(Week 24-Week 0)	0.16	± 1.93	-0.05	± 2.38	0.5498
		Difference(Week 48-Week 0)	-0.18	± 1.99	0.50	± 2.89	0.2619
HOMA-IR (mUxmg/mLxdL)		Week 0	3.75	± 2.10	3.51	± 2.28	
		Week 24	3.06	± 1.72	3.14	± 1.92	0.5043
		Week 48	3.41	± 2.38	2.81	± 1.17	0.2764
		Difference(Week 24-Week 0)	-0.72	± 2.30	-0.34	± 1.68	0.5043
		Difference(Week 48-Week 0)	-0.32	± 2.77	-0.73	± 2.53	0.2764
HbA1C (%)		Screening	8.76	± 1.23	8.94	± 1.33	
		Week 24	6.95	± 0.53	6.95	± 0.62	0.9385
		Week 48	6.86	± 0.53	7.01	± 0.83	0.3674
		Difference(Week 24-Screening)	-1.79	± 1.32	-1.88	± 1.12	0.9385
		Difference(Week 48-Screening)	-1.91	± 1.23	-1.73	± 1.23	0.3674
FPG (mg/dl)		Week 0	168.30	± 44.68	168.88	± 38.85	
		Week 24	131.77	± 20.98	136.22	± 20.60	0.3335
		Week 48	132.56	± 22.61	138.90	± 21.20	0.2039
		Difference(Week 24-Screening)	-33.79	± 42.63	-29.06	± 33.74	0.3335
		Difference(Week 48-Screening)	-33.45	± 43.48	-24.84	± 37.82	0.2039
Lipid profile							
	Total Choresterol (mg/dl)	Screening	167.47	± 38.68	166.65	± 30.73	
		Week 24	160.94	± 32.97	157.50	± 29.27	0.3835
		Week 48	165.21	± 30.71	163.00	± 31.18	0.2461
		Difference(Week 24-Screening)	-3.94	± 21.51	-8.53	± 23.66	0.3835

	Difference(Week 48-Screening)	2.68	± 22.40	-4.26	± 20.24	0.2461
HDL(mg/dl)	Screening	50.75	± 11.43	49.13	± 8.89	
	Week 24	50.29	± 12.33	48.74	± 9.88	0.9966
	Week 48	47.42	± 9.48	50.25	± 8.70	0.0219
	Difference(Week 24-Screening)	-0.63	± 7.70	-0.08	± 9.45	0.9966
	Difference(Week 48-Screening)	-3.06	± 7.77	0.98	± 6.45	0.0219
*LDL(mg/dl)	Screening	92.03	± 34.01	92.08	± 27.77	
	Week 24	87.09	± 28.96	83.50	± 29.40	0.2637
	Week 48	90.02	± 29.53	89.34	± 30.43	0.3668
	Difference(Week 24-Screening)	-1.75	± 19.07	-7.59	± 22.22	0.2637
	Difference(Week 48-Screening)	2.95	± 22.28	-2.48	± 17.69	0.3668
Triglycerides(mg/dl)	Screening	123.47	± 55.90	127.18	± 74.29	
	Week 24	117.80	± 57.50	126.28	± 77.09	0.6804
	Week 48	138.82	± 66.26	117.06	± 46.46	0.0589
	Difference(Week 24-Screening)	-7.77	± 59.31	-4.31	± 78.58	0.6804
	Difference(Week 48-Screening)	13.91	± 63.39	-13.77	± 64.15	0.0589
Apolipoprotein A1(mg/dl)	Screening	142.58	± 26.49	141.44	± 17.26	
	Week 24	146.49	± 28.56	142.72	± 25.22	0.6708
	Week 48	141.59	± 20.04	151.68	± 19.53	0.0191
	Difference(Week 24-Screening)	3.29	± 23.08	1.69	± 24.32	0.6708
	Difference(Week 48-Screening)	-0.12	± 22.76	9.94	± 17.91	0.0191
Apolipoprotein B(mg/dl)	Screening	74.42	± 22.41	78.35	± 19.98	
	Week 24	71.63	± 22.54	68.22	± 18.27	0.0835
	Week 48	74.88	± 21.17	70.74	± 20.87	0.0200
	Difference(Week 24-Screening)	-1.94	± 17.35	-10.13	± 16.11	0.0835
	Difference(Week 48-Screening)	2.79	± 15.75	-7.71	± 15.42	0.0200
Free fatty acid(mg/dl)	Screening	578.03	± 221.73	538.85	± 175.65	
	Week 24	595.34	± 255.34	591.09	± 264.11	0.8166
	Week 48	595.21	± 221.31	600.26	± 264.41	0.8378
	Difference(Week 24-Screening)	20.49	± 215.57	55.66	± 312.11	0.8166
	Difference(Week 48-Screening)	17.38	± 338.33	63.97	± 240.83	0.8378

*LDL=Cholesterol-(TG/5+HDL)

There was no significant difference in the change of C-peptide for glucagon stimulation test, fasting serum proinsulin/insulin ratio, HOMA-IR and FPG in both group. And there was no significant difference in the change of lipid profile except HDL cholesterol, apolipoprotein A1 and apolipoprotein B after 48 weeks in both group. (HDL cholesterol p=0.0197, apolipoprotein A1 : p=0.0359, apolipoprotein B : p=0.0144)

With regard to 3-point before each meal, there was no statistically significant in both group at any point and difference from 24 weeks and 48 weeks. (prebreakfast: p=0.7603,p=0.0547), (prelunch: p=0.5527, p=0.3958), (predinner: p=0.7957, p=0.3076)

With regard to hypoglycemia, A total of 10 patients (26.32%) in the Metformin+Insulin Glargine and 19 patients (55.88%) in the Metformin+Glimepiride experienced symptomatic hypoglycemia and the difference between the two groups was statistically significant (p=0.0107). With regard to the frequency of symptomatic hypoglycemic episodes, there was 10 episodes in the Metformin+Insulin Glargine and 19 episodes in the Metformin+Glimepiride, and the difference between the two groups was not statistically significant (p=0.3552). There was no episode of severe hypoglycemia in the two groups. (Table 6)

Table 6. Hypoglycemia

		Metformin+Insulin Glargine		Metformin+Glimepiride		Total		p-value[1]
		n	(%)	n	(%)	n	(%)	χ^2-test
Symptomatic Hypoglycemia	Yes	10	(26.32)	1	(5.8)	29	(40.28)	0.0107
	No	28	(73 68)	15	(44.12)	43	(59.72)	
	Total	38	(100.00)	34	(53.97)	72	(100.00)	
Severe Hypoglycemia (random plasma glucose < 36mg/dL)	Yes	0	(0.00)	0	(0.00)	0	(0.00)	
	No	38	(100.00)	34	(00.00)	72	(100.00	
	Total	38	(100.00)	34	100 00)	72	(100.00)	

1 p-value for difference in proportions between the two groups

Safety results:

In this study, severe adverse events were reported total 7 events, and there was not statistically significant in both groups. (p=1.000) Adverse drug reactions which the causality to the study drug could not be ruled out were reported total 13 events, and there was not statistically significant between both groups. (p=0.2003) Also, adverse event was not significant difference. (p=0.6418) (Table 7)

Table 7. Incidence of Adverse Events

			total	Metformin +Insulin Glargine	Metformin +Glimepiride	p-value
	Subject	n	74	38	36	
AE	Number of Events	n	84	38	46	0.6418
	Incidence rate	n(%)	37(50.00)	18 (47.37)	19(52.78)	
ADR[1]	Number of Events	n	13	9	4	0.2003
	Incidence rate	n(%)	6 (8.11)	5(13.16)	1(2.78)	
SAE	Number of Events	n	7	4	3	1
	Incidence rate	n(%)	7(9.46)	4(10.53)	3(8.33)	

With regard to blood pressure for vital sign, there was no statistically significant in both group. With regard to physical examination, there was a statistically significance for mean change of body weight in the Metformin+Insulin Glargine. (from baseline to 24 weeks : p=0.0017)(from baseline to 48weeks p=0.0621). Other results for physical examination were not statistically significant. With regard serum creatinine level, there was a statistically significant difference between the two groups with regard to the change from screening to Week 48 (p=0.0439). (Table 8)

Table 8. Change of blood pressure, physical examination and laboratory results

		Metformin+Insulin Glargine		Metformin+Glimepiride		
		mean	± std	mean	± std	p-value
SBP	Week 0	125.08	± 13.92	123.11	± 12.84	0.5299
	Week 24	125.49	± 13.91	125.50	± 13.52	0.9966
	Week 48	123.42	± 12.47	122.78	± 15.81	0.8460
	Difference(Week 24-Screening)	0.00	± 12.90	0.78	± 11.13	0.7924
	Difference(Week 48-Screening)	-2.24	± 12.13	-0.39	± 12.86	0.5267
DBP	Week 0	75.18	± 8.84	72.89	± 8.40	0.2564
	Week 12	76.81	± 9.65	74.41	± 9.56	0.2968
	Week 48	74.61	± 8.21	74.36	± 9.30	0.9049
	Difference(Week 24-Screening)	-0.80	± 8.89	-2.53	± 9.52	0.4445
	Difference(Week 48-Screening)	-0.45	± 9.76	-2.42	± 8.88	0.3677
Weight	Week 0	62.48	± 8.43	65.06	± 11.43	0.2720
	Week 24	63.65	± 9.20	66.63	± 11.70	0.2487
	Week 48	64.21	± 9.27	65.10	± 10.71	0.7007
	Difference(Week 24-Week 0)	1.43	± 2.49	0.74	± 2.16	0.2335
	Difference(Week 48-Week 0)	1.72	± 2.70	0.04	± 3.13	0.0158
Waist circumference	Week 0	84.77	± 7.87	86.49	± 9.48	0.4017
	Week 24	85.85	± 7.53	87.57	± 9.33	0.4076
	Week 48	85.02	± 8.01	87.40	± 8.56	0.2208
	Difference(Week 24-Week 0)	1.35	± 3.74	0.23	± 2.52	0.1559
	Difference(Week 48-Week 0)	0.27	± 3.39	0.92	± 4.23	0.4728
Hip circumference	Week 0	94.59	± 5.10	95.71	± 7.35	0.4504
	Week 24	95.55	± 5.34	96.53	± 7.69	0.5507
	Week 48	94.82	± 5.85	96.18	± 6.77	0.3631
	Difference(Week 24-Week 0)	1.27	± 2.83	0.33	± 3.36	0.2254
	Difference(Week 48-Week 0)	0.31	± 3.03	0.24	± 2.82	0.9188
Waist/Hip	Week 0	0.90	± 0.06	0.90	± 0.05	0.6136
	Week 24	0.90	± 0.06	0.91	± 0.05	0.5865
	Week 48	0.90	± 0.06	0.91	± 0.05	0.3876
	Difference(Week 24-Week 0)	0.00	± 0.04	0.00	± 0.03	0.6626
	Difference(Week 48-Week 0)	0.00	± 0.03	0.01	± 0.04	0.3899

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