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Sponsor/company:	sanofi-aventis	**ClinialTrials.gov Identifier:**	NCT00708578
		Study Code:	LANTU_L_02670
Generic drug name:	Insulin glargine	**Date:**	18/Jan/2011

Title of the study:	Comparison of efficacy and safety of glimepiride, metformin, or both in combination with insulin glargine in patients with type 2 diabetes: A randomized, controlled trial (LANTU_L_02670 – LOHAS)		
Investigator(s):	SungWoo Park, Kangbuk Samsung Hospital		
Study center(s):	5 centers in Korea		
Publications (reference):	none		
Study period: Date first patient enrolled: 20-May-2008 Date last patient completed: 18-Dec-2009		**Phase of development:** Phase IV	
Objectives:	-Primary objective: Comparison of efficacy of glimepiride, metformin or both in combination with insulin glargine by HbA1c level -Secondary objectives: The frequency of hypoglycemic events of regimen of OHA combined with insulin glargine		
Methodology:	randomized, prospective, open-label, parallel study		
Number of patients/subjects:	Planned: 99	Randomized: 99	Treated: 99
Evaluated:	Efficacy analysis (in the ITT population): 96		Safety: 99
Diagnosis and criteria for inclusion:	-Diagnosis: Type 2 Diabetes Mellitus (T2DM) patients failing glycemic control with MET/SU -Main inclusion criteria: 1) T2DM diagnosed for at least 6 months 2) 7.0 % ≤ HbA1c ≤ 11% 2) Patients who had taken MET/SU as equal or more than the dose of below, at least for 3 months before this trial - MET : maximum tolerable dose or ≥1000mg/day - SU : maximum tolerable dose or glimepiride ≥4mg/day or the equivalent dose of glimepiride ≥4mg/day		
Investigational product: Dose: Administration:	Insulin glargine Daily dose depends on patient's status, once-a-day subcutaneous		
Duration of treatment: 6 months		**Duration of observation:** 1 week	

Reference therapy:	NA
Criteria for evaluation:	
Efficacy:	Primary efficacy variable: Glycated haemoglobin (HbA1c) at the end of study Secondary efficacy variables: Fasting blood glucose (FBG), the proportion of patients who reached HbA1c<7%, the incidence of symptomatic hypoglycemia, lipid profile (total cholesterol, LDL, HDL, triglycerides, free fatty acid), microalbuminuria, hsCRP, adiponectin and quality of life (DSC-R)
Safety:	Safety variables: Hypoglycemia, adverse events, laboratory test (AST, ALT, ALP, gamma-GPT, bilirubin, BUN, creatinine), vital sign and physical examination
Statistical methods:	<u>Population for efficacy analysis</u> - ITT (Intention-to-treatment) population: All randomized subjects with at least one dose of study medication. Subjects of the ITT population should have the baseline and at least one data after the baseline concerning a primary variable. - PP(Per protocol) population: All subjects who belong to the ITT population, excluding subjects with major protocol violations. The following were considered major protocol violations: • Inclusion / exclusion criteria violations • Randomization error • Concomitant treatment not permitted during the study • Low compliance: discontinuation of insulin glargine more than 14 days, less than 80% of treatment compliance of OAD • Shift of treatment during the study period • Early drop-out before visit12 Primary analysis were mainly analyzed for the ITT population and analyzed for the PP population to confirm robustness. - Safety population: All randomized subjects who received at least one dose of study medication. All subjects were analyzed according to the study medication that they actually received. <u>Primary efficacy analysis</u> The primary efficacy analysis aimed at comparing the glycated haemoglobin, HbA1c, at the study endpoint among the three treatment arms. It was performed using ANCOVA (Analysis of Covariance) adjusted with baseline HbA1c as a covariate. When the difference among treatment arms was statistically significant, pair-wise comparison (1 vs. 2, 2 vs. 3, 1 vs. 3) was performed as a multiple comparison adjusting the significance level by the Bonferroni method.

Summary of Results:

Study population:

One hundred and twenty-two subjects entered the screening phase of the study. Ninety-nine subjects were randomized to one of the three treatment arms. The intention-to-treatment population included 96 patients (n=32, insulin glargine + metformin; n=32, insulin glargine + glimepiride; n=32, insulin glargine + metformin + glimepiride) excluding 3 subjects who did not evaluate efficacy. Nineteen subjects (n=6, insulin glargine + metformin; n=5, insulin glargine + glimepiride arm; n=8, insulin glargine + metformin + glimepiride) were considered as major protocol violations. The per protocol population retained for analysis consisted of 77 subjects, 26 randomized to insulin glargine + metformin, 27 randomized to insulin glargine + glimepiride and 24 randomized to insulin glargine + metformin + glimepiride. Subjects had a mean age of 55.76 years, 57.29 years and 56.81 years with a preponderance of male subjects (60.61%, 58.82%, 71.88%) in the insulin glargine + metformin arm, insulin glargine + glimepiride arm and insulin glargine + metformin + glimepiride arm, respectively. There were no differences in other baseline characteristics among treatment arms.

Efficacy results:

The statistical result of the primary efficacy variable, HbA1c at the endpoint of the study, is shown in the following table.

HbA1c in the intention-to-treatment population

HbA1c(%)		Insulin glargine + metformin (N=32)	Insulin glargine + glimepiride (N=32)	Insulin glargine + metformin + glimepiride (N=32)
Baseline	Mean (95% CI)	8.46 (8.13, 8.79)	8.44 (8.09, 8.79)	8.71 (8.38, 9.03)
End point	Mean (95% CI)	7.71 (7.42, 7.99)	7.74 (7.27, 8.22)	7.29 (7.07, 7.51)
	LSMean (95% CI)	7.74 (7.43, 8.05)	7.78 (7.47, 8.09)	7.22 (6.91, 7.53)
Change	Mean (95% CI)	-0.75 (-1.14, -0.36)	-0.70 (-1.15, -0.26)	-1.41 (-1.67, -1.16)
	LSMean (95% CI)	-0.80 (-1.10, -0.49)	-0.76 (-1.07, -0.45)	-1.32 (-1.63, -1.01)
p-value (paired t-est)		0.0004	0.0028	<0.0001
p-value (ANCOVA)		0.0223		

Mean changes in HbA1c from baseline to the endpoint of the study in the ITT population were -0.75%, -0.70% and -1.41% in Insulin glarginee + metformin arm, Insulin glarginee + glimepiride arm and Insulin glarginee + metformin + glimepiride arm, respectively (p=0.0004, 0.0028, <0.0001 vs baseline).

There was a statistically significant difference among the treatment groups in HbA1c at the endpoint of the study with adjusting baseline HbA1c (p=0.0223, ANCOVA). Thus pair-wise comparison was performed as a multiple comparison at the 0.017 significance level adjusted by the Bonferroni method.

Multiple comparisons of least square mean change in HbA1c from baseline to the endpoint of the study

Pair-wise comparison	LSMean (95% CI)	p-value (ANCOVA)
Insulin glargine+metformin vs Insulin glargine+glimepiride	-0.04 (-0.55, 0.47)	0.8831
Insulin glargine+metformin vs Insulin glarginee +metformin+glimepiride	0.49 (0.16, 0.82)	0.0046
Insulin glargine+glimepiride vs Insulin glargine+metformin+glimepiride	0.59 (0.13, 1.05)	0.0129

In comparison between Insulin glargine + metformin arm and Insulin glargine + metformin + glimepiride arm, there was a significantly greater decrease as much as 0.49% of least square mean HbA1c in the Insulin glarginee + metformin + glimepiride arm (p=0.0046). In the comparison between Insulin glargine + glimepiride arm and Insulin glargine + metformin + glimepiride arm, there was a significantly greater decrease as much as 0.59% of least square mean HbA1c in the Insulin glargine + metformin + glimepiride arm (p=0.0129).

Further analyses of secondary variables showed no statistically significant differences among the treatment arms in fasting blood glucose (FBG), the proportion of patients who reached HbA1c<7%, the incidence of symptomatic hypoglycemia, lipid profile (total cholesterol, LDL, triglycerides, free fatty acid), microalbuminuria, hsCRP and adiponectin. There was no treatment effect and interaction effect of visit and treatment groups in global score of quality of life evaluated by DSC-R. There was a statistically significant difference in lipid profile (HDL) at the endpoint of the study (p=0.0357) as shown in the following table. Thus pair-wise comparison was performed as a multiple comparison. However, there was no significant difference between each two arms at the 0.017 significance level.

HDL in the intention-to-treatment population

HDL		Insulin glargine + metformin (N=32)	Insulin glargine + glimepiride (N=32)	Insulin glargine + metformin + glimepiride (N=32)
Baseline	Mean (95% CI)	43.56 (39.43,47.70)	42.88 (39.17,46.58)	44.00 (39.86,48.14)
End point	Mean (95% CI)	42.37 (39.10,45.64)	44.03 (40.62,47.45)	41.55 (37.99,45.12)
	LSMean (95% CI)	42.18 (40.47,43.90)	44.45 (42.73,46.16)	41.32 (39.57,43.06)
Change	Mean (95% CI)	-0.70 (-2.70,1.30)	1.80 (-0.52,4.12)	-1.59 (-3.58,0.40)
	LSMean (95% CI)	-0.63 (-2.34,1.09)	1.64 (-0.08,3.35)	-1.49 (-3.24,0.25)
p-value (paired t-est)		0.4789	0.1236	0.1139
p-value (ANCOVA)		0.0357		

Safety results:

The percentage of subjects reporting adverse events during the treatment phase was 36.36%, 47.06% and 34.38% in the Insulin glargine + metformin arm, Insulin glargine + glimepiride arm and Insulin glargine + metformin + glimepiride arm, respectively, and there was no significant difference among the treatment arms (p=0.5217, chi-square test). Upper respiratory tract infections were the most commonly reported events. Most of treatment-emergent adverse events were considered to be of mild or moderate intensity. A possible relationship to the study medication was seen in 2 subjects.

During the treatment phase, serious adverse events occurred in 1 subject in the Insulin glargine + metformin arm, 3 subjects in the Insulin glargine + glimepiride arm and 1 subject in the Insulin glargine + metformin + glimepiride arm, and there was no significant difference among the treatment arms (p=0.6146, Fisher's exact test). There was no serious adverse drug reaction. There was no subject who permanently discontinued the study or died due to adverse events.

There were no difference in the proportion of subjects with non-symptomatic, diurnal symptomatic and nocturnal symptomatic hypoglycaemic episode among the treatment arms (p=0.7700, 0.6904, 0.5832, chi-square test or Fisher's exact test). There was no subject with severe symptomatic hypoglycaemic episode.

Date of report: 17-Nov-2010