These results are supplied for informational purposes only.
Prescribing decisions should be made based on the approved package insert in the country of prescription

Sponsor/company:	sanofi-aventis	**ClinialTrials.gov Identifier:**	NCT00693771
		Study Code:	LANTU_L_02756
Generic drug name:	Insulin glargine	**Date:**	18/Jan/2011

Title of the study:	A prospective study to OPTIMZe insulin treAtment by Switching to Insulin Glargine in Type-2-Diabetic patients prevIously uncontrolled ON premixed insulin	
Investigator(s):	Prof. Wenying Yang, MD	
Study center(s):	19 centers	
Publications (reference):	None	
Study period: 15 months Date first patient enrolled: April 27, 2008 Date last patient completed: July 22, 2009		**Phase of development:** IV
Objectives:	Primary: -To show an improvement in HbA_{1c} control after 4 months of treatment with once daily insulin glargine in T2DM patients previously uncontrolled on twice daily premixed insulin (with or without OAD) Main Secondary: - Improvement of Fasting blood glucose (FBG) after 4 months treatment - % of patients with HbA_{1c} <7% or FBG<6.0mmol/L - Frequency of hypoglycemic episodes - Treatment satisfaction(DTSQ) - Adherence and compliance with new treatment	
Methodology:	Multicenter, national, single-arm, open label, Ph IV study	
Number of patients:	Planned: 310	Treated: 313
Evaluated:	Efficacy : 297(ITT); 293(PP)	Safety: 313
Diagnosis and criteria for inclusion:	Type 2 diabetes patients aged 35-75 years, HbA_{1c} 7.5% to 9.5%, FBG ≥ 6.7 mmol/L, diabetes duration < 10 years, and premix insulin daily dosage < 50 IU/Day at screening visit. Patient should have received twice daily premixed insulin (with or without OAD) treatment for at least 3 months.	
Investigational product:	Insulin glargine (Optiset 3mL/vial, 100IU/mL) during the 16-week treatment period	
Dose:	The dosage of insulin glargine should be individually adjusted and based on the recommendation of locally approved package insert. A specific proposal for a titration scheme (up-titrated by 2 IU / 3days to FBG < 6.0mmol/L) will be provided to each participating physician.	
Administration:	Once daily insulin glargine injected subcutaneously before bedtime, at the same time each day.	
Duration of treatment: 16 weeks		

Reference therapy:	NA
Criteria for evaluation:	
Efficacy:	Efficacy evaluations included HbA_{1c}, FBG, PBG, quality of life, insulin dose, hypoglycemia events. The primary efficacy measure was HbA_{1c} change from baseline to week 16.
Safety:	Safety evaluations included adverse events (AEs), vital signs, body weight, waist circumference, physical exam, electrocardiogram (ECG, 12-lead), hematology, blood chemistry and urinalysis.
Statistical methods:	The planned sample size of at least 155 patients provided the study with 90% power to detect a decrease of 0.33% from baseline level in mean HbA_{1c} with a type I error of 0.025(one-sided) in this single-arm study. The patient drop-out rate, etc was at most 10%. SAS® 9.1 was used for statistical analyses in this study. ITT set was used as the primary analyses for efficacy and safety population for safety analyses. The continuous data provided mean and standard deviation, with paired *t*-test or Wilcoxon signed rank sum test (QoL satisfaction scores) used to compare the change from baseline levels; ANOVA was used for between-group comparison of continuous data when grouping variables have more than two levels. The categorical data were described using frequency and percentage, with chi square test or Fisher's exact test to compare change in proportion. Stepwise Logistic regression was used to explore those influential factors of HbA_{1c} rate at $HbA_{1c}<7\%$ vs $\geq 7\%$ after 16-week on-study treatment.

Summary:

Patients population:

Among the 313 patients recruited in this study (safety analysis set), 18 patients (5.8%) did not complete the study treatment period. Drop out reasons were identified as adverse events (n=6), loss to follow up (n=6) and other reasons (n=6). For intention to targets population (ITT) including 297 patients, a total of 48.8% were male and 51.2% were female. Mean age was 56.1 and 57.8 years, and mean body mass index (BMI) was 25.9 and 25.3 kg/m^2 for males and females, respectively. 28.8% had at least one diabetic complication. Most of them (85.5%) were previously treated with premix human insulin and the others used premix insulin analogues for at least 3 months. Characteristics of the patients at the start of observation are summarized in **Table 1**.

Table 1

	All
Age (years, mean ± SD)	56.97 ± 8.31
Sex(male: female, n)	145:152
Weight (kg, mean ± SD)	69.72 ±11.40
Body mass index (kg/m^2, mean ± SD)	25.62 ±3.04
Diabetes duration (years, mean ± SD)	7.46 ±2.56
Any diabetic complications (n, %)	90(28.8%)
Diabetic retinopathy	48(15.3%)
Diabetic neuropathy	37(11.8%)
Diabetic nephropathy	18(5.8%)
Diabetes, cardiovascular disease	17(5.4%)
Diabetic peripheral vascular disease	9(2.9%)
Diabetes, cerebral vascular disease	6(1.9%)

Efficacy results:

After 16-weeks' treatment, the mean reduction of HbA_{1c} from baseline to week-16 was 0.51% (from 8.36 to 7.85%, P<0.001). A total of 19.2% (57 out of 297) and 42.1% (125 out of 297) of patients reached HbA_{1c} ≤7% and HbA_{1c} ≤7.5% respectively. FBG and 2h PBG level also decreased significantly, changes from baseline to week-16 were -2.92 mmol/L and -2.41mmol/L respectively (**table 2**).

Table 2

	Baseline	Endpoint	Change	P-value
HbA_{1c} (%)	8.36(0.57)	7.85(1.04)	-0.51(0.98)	<0.001
FPG (mmol/L)	9.5(2.1)	6.58(2.07)	-2.92(2.81)	<0.001
2h-PPG (mmol/L)	15.07(3.97)	12.66(3.8)	-2.41(4.52)	<0.001
2h C-peptide (nmol/L)	1.32±0.64	1.28±0.68	-0.05±0.55	0.114
Weight (kg)	69.71(11.43)	69.76(11.4)	0.06(2.09)	0.6357

After 16-week treatment, the mean daily dose of insulin glargine was 27.61U, which was lower than that of previous premix insulin (**table 3**). The mean daily insulin glargine dosage at 0-2w, 2-4w, 4-8w, 8-12w and 12-16w are 21.6 IU, 25.0 IU, 26.6 IU, 27.7 IU and 28.4 IU respectively. Also the relationship between titration of insulin glargine and FBG change was assessed during study period (**figure 1**). From baseline to week 16, the percentage of patients receiving 2 OADs was slightly changed from 15% to14.4%; the usage of metformin was decreased from 70.3% to 53.7%, whereas acarbose or repaglinde usage was increased from 31.9% to 39.3% and from 7.0% to 12.8% respectively (**table 4**).

Table 3

	Number	Mean daily dose, U(SD)
Previous premix human insulin	265	33.54(9.80)
Previous premix insulin analogue	48	32.98(9.59)
Endpoint insulin Glargine	313	27.61 (10.63)

Figure 1

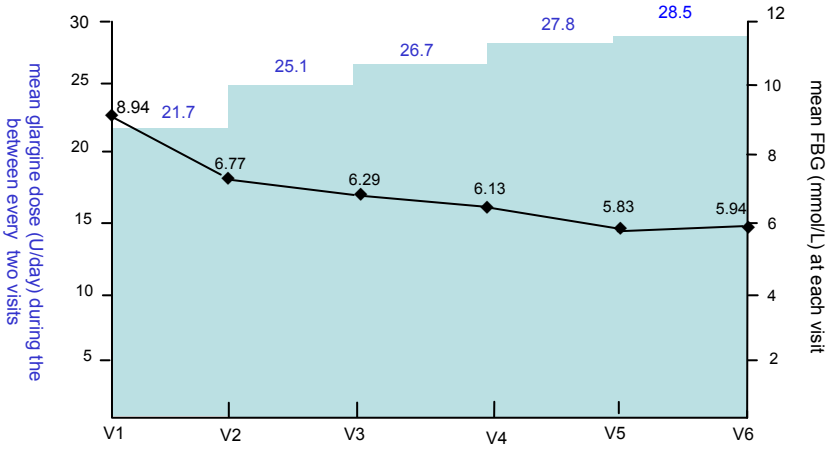

Table 4

	Baseline		**Endpoint**	
	N(%)	Mean daily dose (mg)	N(%)	Mean daily dose (mg)
Any OAD	310(99.0%)		310(99.0%)	
Metformin	220(70.3%)	1074.0	168(53.7%)	1166.6
Acarbose	100(31.9%)	142.1	123(39.3%)	202.3
Repaglinide	22(7.0%)	2.5	40(12.8%)	2.9
Glimepiride	4(1.3%)	2.5	7(2.2%)	2.1
Glipizide	4(1.3%)	7.5	10(3.2%)	11.8
Nateglinide	<1%	-	5(1.6%)	370.0
Dual combination	47(15.0%)	-	45(14.4%)	-
Acarbose +Metformin	23(7.3%)	-	21(6.7%)	-
Metformin+Repaglinide	11(3.5%)	-	6(1.9%)	-
Acarbose+ Repaglinide	<1%	-	6(1.9%)	-

Diabetes Treatment Satisfaction Questionnaire (8 questions, 0-6 points) was used to assess the patients' satisfaction to treatments. The scores at baseline and 16-week endpoint show that each item is much better than previous treatment (all P<0.001). These results showed that the patients were more satisfied with once daily insulin glargine plus OADs therapy (**table 5**).

Table 5

Questions	Mean change of scores	P value
1. How satisfied are you with your current treatment?	1.84	<0.001
2. How often have you felt that your blood sugars have been unacceptably high recently?	-1.83	<0.001
3. How often have you felt that your blood sugars have been unacceptably low recently?	-0.42	<0.001
4. How convenient have you been finding your treatment to be recently?	1.77	<0.001
5. How flexible have you been finding your treatment to be recently?	1.69	<0.001
6. How satisfied are you with your understanding of your diabetes?	1.65	<0.001
7. Would you recommend this form of treatment to someone else with your kind of diabetes?	1.70	<0.001
8. How satisfied would you be to continue with your present form of treatment?	1.69	<0.001

Overall hypoglycemic episodes including all categories of hypoglycemia during 16-week treatment are 257and patients incidence is 32.9%; majorities are mild-moderate hypoglycemia, only 2 episodes are severe hypoglycemia (0.6%). Incidence of treatment emergent adverse events (TEAE) excluding hypoglycemia is 28.1%, most of which are mild or moderate. Only 4 severe TEAE episodes excluding hypoglycemia were identified and corresponding incidence is 1.3% (**table 6**). Body weight was assessed both at baseline and week-16, there was no change (69.71 vs.69.76kg, P=0.636) after change to insulin glargine regimen treatment (**table 2**).

Table 6

	Hypoglycemia*	Excluding hypoglycemia*
Any TEAE	103(32.9%)	88(28.1%)
Any severe TEAE	2(0.6%)	4(1.3%)
Any treatment emergent SAE	0(0.0%)	7(2.2%)
Any TEAE leading to discontinuation	0(0.0%)	6(1.9%)

* Results are shown by patients number and percentage of patients with at least one TEAE

Exploratory Analysis:

We further stratified baseline HbA_{1c} to four groups which were $7.5\% \leq HbA_{1c} < 8.0\%$, $8.0\% \leq HbA_{1c} < 8.5\%$, $8.5\% \leq HbA_{1c} < 9.0\%$ and $9.0\% \leq HbA_{1c} \leq 9.5\%$, it showed that the higher HbA_{1c} level at baseline, the more decrease, the decrease were 0.24%, 0.47%, 0.70% and 0.72% respectively (P=0.0087).

We also stratified endpoint $HbA_{1c}$to three groups which were HbA_{1c} <7%, $7\% \leq HbA_{1c} < 8\%$ and $HbA_{1c} > 8\%$ (**table 7**), it showed that the patients who achieved the HbA_{1c} target were characterized by shorter diabetes duration, higher baseline 2hCP level and lower endpoint FBG.

Table 7

	<7.0% N=54	**[7.0,8.0) N=126**	**>=8.0% N=117**	**P-value**
Age (years)	54.67(7.99)	56.91(8.56)	57.97(7.92)	0.0521
Diabetes duration (years)	6.06(2.85)	7.58(2.49)	7.96(2.26)	<0.0001
2hCP at baseline (nmol/L)	1.47(0.69)	1.43(0.68)	1.12(0.51)	<0.0001
Prior pre-mix insulin dose (IU/day)	32.52(10.32)	33(9.56)	34.75(9.48)	0.2457
Mean insulin glargine dose (IU/day)	25.36(8.38)	26.33(8.24)	27.7(9.7)	0.2456
FBG at week 16 (mmol/L)	5.42(0.76)	5.68(0.8)	6.47(1.31)	<0.0001

Also logistic regression analysis showed that disease duration, HbA_{1c} at baseline and endpoint FBG level have statistical significance, i.e. the higher level of their values, the lower rate to achieve the HbA_{1c} target (**table 8**).

Table 8

	OR	OR 95%CI	P-value
Diabetes duration (years)	0.785	0.692, 0.890	0.0002
FBG at week 16 (mmol/L)	0.464	0.303, 0.710	0.0004
HbA1c at baseline (%)	0.482	0.255, 0.914	0.0255

Date of report: September 8, 2010