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:	NCT00271284
		Study Code:	HMR1964A_3516
Generic drug name:	INSULIN GLULISINE	Date:	19-Nov-2009

Title of the study:	A crossover, multicenter, randomized study comparing the effect on glycemic control of insulin glargine and insulin detemir, combined with insulin glulisine, used as a bolus, in patients with type 1 diabetes. STUDY CODE: HMR1964A/3516	
Investigator(s):	Pr. Eric RENARD (Centre hospitalier Lapeyronie – Service des Maladies Endocriniennes – 34090 Montpellier - France)	
Study center(s):	33 French centres of diabetology (25 active centres)	
Publications (reference):		
Study period: Date first patient enrolled: 24 October 2005 Date last patient completed: 16 September 2008		Phase of development: IIIb
Objectives:	Primary objective: to compare, with a hypothesis of non-inferiority, the variability of fasting capillary glycaemia observed with insulin glargine combined with insulin glulisine versus insulin detemir combined with insulin glulisine in patients with type 1 diabetics. Secondary objectives: ▪ To compare the variability of capillary glycaemia before dinner observed under glargine insulin associated with glulisine insulin and under detemir insulin associated with glulisine insulin in type 1 diabetics. ▪ To describe the intra-daily and inter-daily glycaemia variations using the MAGE and MODD indexes. ▪ To compare the glycemic profiles (7 points) ▪ To assess HbA1C level at the end of each treatment period, body weight evolution, insulin doses used and number of daily injections. ▪ Safety objectives: ▪ To describe adverse events ▪ To describe hypoglycaemia (symptomatic, diurnal, nocturnal, severe)	
Methodology:	Comparative, randomised (1:1), open, crossover without wash-out between the two periods study. Each treatment period lasted 16 weeks. Each patient received successively the study insulins (glargine or detemir associated with glulisine as bolus insulin used before meals) according to the order pre-established by randomisation. The crossover treatment period was proceeded by a 1 or 2-week selection period, during which patients continued their previous treatment, then by a 4-week "initial" period, during which patients were treated with one injection of glargine in the evening associated with 3 injections of glulisine (administrated before meals).	

Number of patients:	Planned: 86 randomised	Randomized: 88	Treated: 88
Evaluated:	Efficacy : 80	Safety: 88	Pharmacokinetics: NA
Diagnosis and criteria for inclusion:	Adult type 1 diabetics, diagnosed for at least 3 years, treated for at least 6 months with intensive basal-bolus insulin therapy including Lantus® administered in the evening as basal insulin, having HbA1C ≤ 8,5% at inclusion visit and more than 50% of glycaemia before diner ≤ 1,50 g/l during the last 3 weeks of the "initial" period.		
Investigational product: Dose: Administration:	Insulin glargine (Lantus ® 100 U/ml) 1 injection / day Subcutaneous way in the evening between 6:30 pm and 12:00 pm by means of Optipen Pro 1		
Duration of treatment: 16 weeks	Duration of observation: 39 weeks		
Reference therapy: Dose: Administration:	detemir (Levemir® 100 U/ml) 1 to 2 injections / day subcutaneous way in the evening between 6:30 pm and 12:00 pm (2nd injection in the morning if needed) by means of Novopen 3		
Criteria for evaluation:			
Efficacy:	Primary criterion: Fasting capillary glycaemia (measured daily for the last 2 months of each treatment period) Secondary criteria: – Capillary glycaemia before diner (measured daily for the last 2 months of each treatment period) – Intra-daily and inter-daily glycaemia variations using the MAGE and MODD indexes – 7-point glycemic profiles (before each meal, 1 or 2 hours after each meal and at bedtime I.e. at least 2h30 after diner) performed during 2 consecutive days at the end of the selection period and at the end of the last 2 months of each treatment period. – HbA1C at the end of each treatment period – Number of daily injections – Insulin doses used		
Safety:	– Adverse events reported by the patient or observed by the investigator – Number and type of hypoglycaemia (diurnal, nocturnal, severe) – Body weight and arterial blood pressure		
Statistical methods:	Determination of sample size: based on the data of a previous study (HOE901/3001), the calculation of the number of necessary subjects was performed with the following hypotheses: alpha=0.025, power (1-beta)=0.95, non-inferiority limit=1.25 (ln : 0.223), true difference=1.05 (ln : 0.049), standard deviation=0.2. Considering a percentage of about 15% of patients non assessable in Per protocol for the two periods, the total number of patients to randomise was 86. Primary efficacy criterion: Fasting capillary glycaemia variability was estimated by the coefficient of variation, calculated on the data of the patient diary for the last 2 months of each treatment period (week 8 to week 16 and week 24 to week 32). Hypothesis of non-inferiority of glargine comparatively to detemir was tested by a crossover ANOVA model in which the fixed effects were treatment group, period and sequence. 95% confidence interval was calculated and non-inferiority was established if its upper limit did not exceed 125%. The objective was to demonstrate that the coefficient of variation under glargine was ≤ 1,25 x coefficient of variation under detemir. The main analysis was performed in the Per protocol population and the robustness analysis in the mITT population. Secondary efficacy criteria: The variability of glycaemia before diner was analysed as the variability of fasting glycaemia. Analysis of other secondary criteria was only descriptive with no statistical tests		

Summary	
Efficacy results:	– Subjects disposition Planned randomized : 86 Screened : 135 Entred in initial period : 116 Randomized : 88 Treated : 88

Analysed population	Randomized and treated (n = 88)
Safety population	88 (100.0 %)
Treatment period with glargine completed	85 (96.6 %)
Treatment period with detemir completed	86 (97.7 %)
Patients that completed both treatment periods	83 (94.3 %)
Population Per-protocol	78 (88.6 %)
Patients excluded from Per-protocol population	10 (11.4 %)
Population mITT	80 (90.9 %)
Patients excluded from mITT population (Study withdrawal)	8 (9.1 %)

– Description of the population

The treated population (88 patients), in male ascendancy (61.4%) was 46.8 ± 13.7 years old at inclusion (range: 18 to 81 years). Diabetes was known since 18 ± 9 years in mean (range: 3 to 45 years) and the duration of the treatment by glargine insulin was 35 ± 14 months, at the median dose of 20 U/day. The rapid-insulin associated with glargine was administered in at least 3 injections a day at the average dose of 24 ± 10 U/day. The most frequent complications of the diabetes were the diabetic retinopathy (24%) and neuropathy (18%). The body mass index was 25.0 ± 3.5 kg/m² and 40 % of the population was overweight or obese. At baseline, all patients had HbA1c ≤ 8.5%, median of this parameter being 7.1%, and fasting glycaemia was 1.50 ± 0.73 g/l.

There was no difference in the baseline characteristics of the 2 groups randomised in the 1st period.

– Primary efficacy criterion

Coefficient of variation (CV) of fasting glycaemia in Per protocol population

	Glargine N=78	Detemir N=78
Mean ± Std deviation	41.08 ± 12.01	39.88 ± 10.89
Median (Min ; Max)	40.72 (7.32 ; 66.94)	41.90 (9.31 ; 66.76)
ln [CV(glargine)] - ln[CV(detemir)]	0.016	$IC_{95\%}$ [-0.031 ; 0.063]
CV(glargine) / CV(detemir)	1.016	$IC_{95\%}$ [0.970 ; 1.065]

The between treatment difference, estimated by the difference of the natural logarithm of the coefficient of variation of the fasting glycaemia was 0.016 with a 95% confidence interval [-0.031 ; 0.063], the upper limit of which did not exceed the non-inferiority limit fixed to 0.223 (Ln 1.25). The glargine/detemir ratio (1.016) had a 95% confidence interval, [0.970; 1.065], the upper limit of which did not exceed the non-inferiority limit fixed to 1.25. These results allowed to conclude in the non-inferiority of glargine with regard to detemir for the variability of fasting glycaemia. Their interpretation was made valid by the absence of significant fixed effect (effect insulin: p=0.4940, effect period of treatment: p=0.1116, effect sequence of treatments: p=0.9617). The mITT analysis confirmed the robustness of the main analysis. The glargine/detemir ratio was 1.014 with a 95% confidence interval, [0.969; 1.062], the upper limit of which did not exceed the non-inferiority limit fixed to 1.25.

Efficacy results:

– Secondary efficacy criteria

Coefficient of variation of the glycaemia before diner in Per protocol population

	Glargine N=72	Detemir N=72
Mean ± Std deviation	40.07 ± 11.66	38.92 ± 11.34
Median (Min ; Max)	39.47 (6.60 ; 72.01)	38.11 (10.03 ; 72.08)
ln [CV(glargine)] - ln[CV(détémir)]	0.024	$IC_{95\%}$ [-0.022 ; 0.070]
CV(glargine) / CV(détémir)	1.025	$IC_{95\%}$ [0.979 ; 1.073]

The glargine/detemir ratio (1.025) had a 95% confidence interval, [0.979 ; 1.073], the upper limit of which did not exceed the non-inferiority limit fixed to 1.25. These results allowed to conclude in the non-inferiority of glargine with regard to detemir for the variability of glycaemia before dinner. Their interpretation was made valid by the absence of significant fixed effect (effect insulin: p=0.2947, effect period of treatment: p=0.6947, effect sequence of treatments: p=0.6193).

Other secondary criteria in Per protocol population

	Glargine	Detemir
MAGE (g/l) intra-daily variations		
N	72	71
Mean ± Std deviation	1.01 ± 0.67	0.97 ± 0.47
Median (Min ; Max)	0.86 (0.12 ; 3.89)	0.91 (0.11 ; 2.23)
MODD (g/l) inter-daily variations		
N	69	64
Mean ± Std deviation	0.55 ± 0.27	0.55 ± 0.27
Median (Min ; Max)	0.55 (0.06 ; 1.37)	0.54 (0.08 ; 1.24)
HbA1C (%)		
N	77	76
Mean ± Std deviation	6.94 ± 0.72	6.98 ± 0.65
Median (Min ; Max)	6.9 (5.0 ; 8.9)	7.0 (4.8 ; 8.5)

The above table shows similar results between the two groups.

Safety results:

The frequency of adverse events (32.9% of patients under glargine and 36.0% under detemir) was expected considering the target population and the 4-month duration of each treatment period. It was essentially concomitant diseases, associated or facilitated by diabetes, among which infections were predominant (17.6% under glargine and 23.3% under detemir) and which occurred so often under glargine as under detemir). Only 3 adverse events were related by investigator to the basal insulin: 1 weight increase during the glargine period (1.2%) and 2 cases of poor local tolerability under detemir (2.3%). Serious adverse events, none of which was related to basal insulin, were reported in 4 patients (4.7%) during each of the two treatment periods (under glargine: 1 angle closure glaucoma, 1 foot fracture, 1 prostatectomy, 1 severe hypoglycaemia related to glulisine; under detemir: 1 hysterectomy for uterine leiomyoma, 1 hospitalisation for coronary artery stenosis, inguinal hernia repair and accidental overdose of glulisine insulin in one patient). No death was reported during the study.

The number of symptomatic hypoglycaemia under glargine and detemir was respectively 19.0 ± 23.7 and 15.2 ± 20.3 per patient. The number of nocturnal symptomatic hypoglycaemia was similar for both insulins (glargine: 3.7 ± 5.7; detemir: 3.5 ± 5.2 per patient). The total of severe symptomatic hypoglycaemia under glargine and detemir was respectively 13 and 5. Most of these episodes occurred during the phase of titration (weeks 1 to 8) of the period, only 2 patients under glargine and 1 patient under detemir having presented a severe hypoglycaemia during the phase of maintenance (weeks 9 to 16) of period.

Date of report:

06 october 2009