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:**	NA
		Study Code:	HOE901_4023
Generic drug name:	insulin glargine	**Date:**	28 August 2007

Title of the study:	32-week, open, randomized, cross-over, local, multicenter clinical trial comparing insulin glargine in combination with insulin analogue (insulin lispro) to NPH insulin in combination with regular insulin in type 1 diabetes mellitus patients in an intensified insulin regimen. Study number: HOE901/4023	
Investigator(s):	Coordinating investigator: Dr. Ramón Gomis. Hospital Clinic I Provincial. C/ Villarroel 170. 08036 Barcelona.	
Study center(s):	The study was performed in the following Spanish hospitals: Hospital Clinic I Provincial (Barcelona), Hospital Puerta del Mar (Cadiz), Hospital Dr Negrín (Las Palmas), Hospital la Princesa (Madrid), Fundación Sardá-Farriol (Barcelona), Hospital Ramón y Cajal (Madrid), Hospital La Paz (Madrid), Hospital Clínico (Valencia), Hospital Clínico (Madrid).	
Publications (reference):	Not applicable	
Study period: Date first patient enrolled: 26-Nov-2001 Date last patient completed: 04-Feb-2004		**Phase of development:** III b
Objectives:	Primary objective: To compare the efficacy (in terms of metabolic control evaluated through HbA1c levels) of treatment with insulin glargine as basal insulin and insulin analogue (insulin lispro) as mealtime insulin with a regimen of insulin NPH as basal insulin with regular insulin, as mealtime insulin, after a 16 week treatment phase with each regimen and to compare the safety of both treatments, evaluated through hypoglycemic rates.	

Objectives:	Secondary objectives: To compare the following variables between both treatment regimens: a) ***HbA1c values*** during treatment phases; b) ***Fasting glycaemia*** *(FG)*: mean value derived from 5 determinations (5 determinations documented in the diary or from 2 consecutive complete 7 point glycaemic profiles in 24 hours + 3 determinations documented in the diary) documented within the 5 days prior to the visit; FG variability: coefficient of variation (CV) of these 5 FG values for each patient; c) ***Nocturnal Glycaemia***: mean of nocturnal glycaemia values (3:00 a.m.) calculated from 2 consecutive complete 7 point glycaemic profiles in 24 hours; Nocturnal glycaemia variability: CV of the 2 nocturnal glycaemia values (3:00 a.m.) derived from 2 consecutive complete 7 point glycaemic profiles in 24 hours; d) ***Mean daily glycaemia***: mean of all daily glycaemia values calculated from 2 consecutive complete 7 point glycaemic profiles in 24 hours; Variability of mean daily glycaemia: CV of daily glycaemia obtained from 2 consecutive complete 7 point glycaemic profiles in 24 hours; e) ***Rates of response***: HbA1c response after each phase of treatment was evaluated in three categories: ≤ 7.5%, 7.5-8%, > 8%. Frequency of nocturnal hypoglycemia and severe hypoglycemia in every subgroup. Response of FG after each phase of treatment considering three categories: ≤ 100 mg/dl; 100-120 mg/dl, > 120 mg/dl. Frequency of nocturnal hypoglycemia and severe hypoglycemia in every subgroup. f) ***Hypoglycemia***: frequency of all hypoglycemic events, frequency of symptomatic hypoglycemic events, severe hypoglycemias and nocturnal hypoglycemias in each patient during the first month of each treatment phase, during the rest of each treatment phase and during each complete phase of treatment. g) ***Requirements of mean daily insulin*** in each visit: daily dose of basal insulin, daily dose of mealtime insulin, total daily insulin dose (sum of basal insulin doses and mealtime insulin doses) and ratios of basal insulin : mealtime insulin. h) ***Body weight, size and body mass index***; I) ***Lipid profile*** (total cholesterol, HDL-cholesterol, LDL-cholesterol and triglycerides); j) ***Quality of life:*** The Diabetes Treatment Satisfaction Questionnaire (DTSQ) was used and performed before start of treatment (week 0), during each phase of treatment (weeks 8 and 24) and at the end of each phase of treatment (weeks 16 and 32) analyzing the differences between patients that receive insulin glargine/insulin lispro compared with patients that receive insulin NPH/regular insulin. k) ***Resources utilization***: a pharmacoeconomic questionnaire was performed before start of treatment (week 0) during each treatment phase (weeks 8 and 24) and at the end of each treatment phase (weeks 16 and 32), analyzing the differences between patients that received insulin/glargine and lispro compared with patients that received insulin NPH/regular insulin. The following should be analyzed: a) Health resources utilization: hospitalization (number of days, type of complication, reason of hospital admission and responsible department); not planed medical consultations (ambulatory, at hospital or house calls) (number and reason); not planed nurse consultations (ambulatory, at hospital or house calls) (number and reason); use of reactive strips (number) for self measurement of blood or urine glucose; use of reactive strips for self measurement of cetonuria (number); Not planed analytical blood glucose determinations (number); b) Labour resources utilization: days (number) of sick leave because of diabetes
Methodology:	It was a multicentre, open-label, randomized (allocation ratio 1:1), cross-over study with two treatment phases of 16 weeks each in two treatment groups: a) Study arm with insulin glargine + insulin analogue (phase 1) and insulin NPH + regular insulin (phase 2) and b) Insulin NPH + regular insulin (phase 1) and insulin glargine + insulin analogue (Phase 2). Insulin glargine was administered once a day in the evening while insulin NPH was administered twice (in the morning and in the evening). Insulin Lispro and regular insulin were used as mealtime insulins with glargine and NPH respectively

Number of patients:	Planned: 80	Randomized: 80	ITT population: 80
Evaluated:	PP population: 62	Safety: 80	
	***ITT (intention to treat)* population** was composed by all those randomized patients that received at least one dose of the study medication and had at least one measurement of the primary efficacy variable after the basal visit. ***PP (per protocol)* population** was defined as all those ITT population subjects who had a measurement of the primary efficacy variable after each phase of treatment, excluding those subjects who had significant protocol deviations.		
Diagnosis and criteria for inclusion:	Subjects with type 1 diabetes mellitus, 18≤age≤65 years, C-Peptide negative, treated at least for 6 months with multiple daily doses of insulin and with HbA1c ≥7.0% and ≤9.5% and a BMI ≤ 35 kg/m². Women of childbearing potential must have a negative pregnancy test in visit 1 and must use an effective contraceptive method during the study.		
Investigational product: Dose: Administration:	Insulin glargine 3 mL cartridge (100 IU/mL). The dose was individualized to get preset glycaemic targets (fasting glycaemia close to 100 mg/dl) Subcutaneously once a day (in the evening).		
Duration of treatment: 32 weeks		**Duration of observation**: adverse events, hypoglycemic episodes and possible local reactions on injection's site that occurred until 48 hours after the last injection of the study drug were recorded by the investigator.	
Reference therapy: Dose: Administration:	Insulin NPH 3 mL cartridge (100 IU/mL). The dose was individualized to get preset glycaemic targets (fasting glycaemia close to 100 mg/dl) Subcutaneously twice a day (in the morning and in the evening).		
Criteria for evaluation:			
Efficacy:	Main efficacy variable was HbA1c determined after each phase of 16 weeks of treatment (visits 10/18) in a central laboratory. Secondary efficacy variables were: a)Rates of response: HbA1c values during each phase of treatment (considering 3 categories: ≤ 7.5%, 7.5% - 8%, > 8%.); b)Hypoglycemic events: incidence of global hypoglycemic episodes, severe hypoglycemic episodes and nocturnal episodes in each phase of treatment. Nocturnal episodes were those that occurred from 22:00 to 08:00 hours or between last insulin injection in the evening and first insulin injection in the morning; c)Fasting glycaemia: mean value taken from 5 results recorded in the diary of the patient within the 5 days prior to the visit ; d)Mean daily glycaemia: mean of all daily glucose values taken from two 7-point plasma glucose profiles performed in 2 different days; e)Nocturnal glycaemia: mean of glucose values at 03:00 AM, taken from two 7-point plasma glucose profiles performed in 2 different days; f) Mean total daily insulin dose: sum of basal and mealtime insulin daily doses.		
Safety:	Adverse events reported by the patient or noted by the investigator were registered. Hypoglycemic episodes were considered adverse events only if they were classified as severe (symptoms compatible with hypoglycemia with a glucose level < 50 mg/dL and help of other person for recovery was needed)		

<table>
<tr><td>Statistical methods:</td><td>Baseline characteristics and demographics were summarized using descriptive statistics. Primary objective was analyzed based on a non inferiority hypothesis: H0: difference between insulin glargine regimen and NPH regimen is ≤ 0.5%; H1: difference between insulin glargine regimen and insulin NPH regimen is > 0.5%. An ANCOVA model that included the period, patient and treatment was used with an unilateral confidence interval of 97.5%. If the obtained confidence interval was over the non-inferiority margin [-0.5%], the inferiority hypothesis could be rejected with an α error of 2.5%. Missing values were extrapolated by last observation carried forward approach from the closer data after visit 2. Carry-over effect was firstly analyzed for all the variables due to the cross-over design of the study. Analysis of efficacy results was performed for the ITT and PP populations. Secondary objectives were analyzed by means of a symmetry test (for rates of response) and the t Student test for other secondary objectives. Adverse events were coded using MedDRA and presented by system organ class, intensity, severity, relation with the study drug, evolution and action taken by the investigators. SAS software (v. 8.02) was used for the analysis.</td></tr>
<tr><td>Summary:</td><td>80 patients were included (62 for PP population), mean age 32.5±9.3 years, 52.5% males. Basal BMI 24.3 ± 2.8 Kg/m^2. Mean time of diabetes evolution and insulin treatment were 12.8±7 and 12.7±7 years respectively. Mean HbA1c (%) was 8.1±0.7 and mean fasting plasma glucose 180.3±46.2 mg/dl. Mean total daily insulin dose was 50.2±16.7 IU whereas mean total daily glucose was 177.5 ± 42.3 mg/dl.</td></tr>
<tr><td>Efficacy results:</td><td>Primary objective: Confidence interval of the difference of HbA1c means between glargine and NPH regimen was above non-inferiority margin (-0.05). Thus, treatment with glargine + lispro was non-inferior to treatment with NPH + regular insulin in terms of HbA1c control. Results are presented for ITT population. Similar results were obtained for PP population.
<table>
<tr><th>Treatment</th><th>HbA1c (mean)</th><th colspan="2">Confidence interval (95%)</th></tr>
<tr><td>NPH</td><td>7.69</td><td>7.56</td><td>7.81</td></tr>
<tr><td>Glargine</td><td>7.54</td><td>7.42</td><td>7.66</td></tr>
<tr><td>Difference</td><td>0.14</td><td>-0.03</td><td>0.31</td></tr>
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Efficacy results:

Secondary objectives: the following objectives were finally analyzed:

a) Rates of response: Null hypothesis of symmetry was rejected (p=0.0069). 39 patients (53.4%) had a similar HbA1c control with both treatment regimens; 23 patients (31.5%) had a better metabolic control with insulin glargine and 11(15.1%) with NPH. Data given for ITT population. Similar results for PP population.

	NPH group			Total
Glargine group	≤ 7.5%	7.5 – 8%	> 8%	
≤ 7.5%	24	12	2	38 (52%)
7.5– 8%	2	3	9	14 (19.2%)
> 8%	6	3	12	21 (28.8%)
Total	32 (43.8%)	18 (24.7%)	23 (31.5%)	73 (100%)

b) Hypoglycemic events: no significant differences were found between both treatment regimens in mean total number of hypoglycemic episodes per patient (12.4 [10.6;14.2] in NPH regimen vs. 11.2 [9.4;12.9] in glargine) or in nocturnal episodes (3.9 [2.7;5.2] vs. 5.1 [3.8;6.4] respectively). There were only 17 serious hypoglycemic episodes (11 patients) according to protocol definition, 6 during treatment with NPH + regular insulin and 10 with glargine + lispro. 1 episode occurred before treatment assignation. Results, given for ITT population, were similar in PP population.

c) Fasting glycaemia: lower values were obtained with glargine + lispro (ITT and PP population; p < 0.0001 in both cases) as shown in this table:

	ITT population			PP population		
Treatment	Mean	IC (95%)		Mean	IC (95%)	
NPH	165.5	157.7	173.3	164.2	155.5	172.9
Glargine	129.9	122.3	137.5	130.2	121.7	138.8
Difference	35.7	24.7	46.6	34	21.8	46.2

d) Mean daily glycaemia: No differences were found for ITT population but a lower value was found for the glargine + lispro regimen in the PP population (p = 0.042)

	ITT population			PP population		
Treatment	Mean	IC (95%)		Mean	IC (95%)	
NPH	157.9	152.6	163.1	158.8	153.1	164.6
Glargine	151.5	146.4	156.6	150.5	144.8	156.1
Difference	6.4	-0.96	13.7	8.4	0.3	16.4

e) *Nocturnal Glycaemia*: values of this parameter were higher during treatment with the glargine regimen compared with the NPH regimen (166.6 mg/dl C.I. 95% [154.7;178.5] vs. 147.5 mg /dl CI 95% [134.8;160.2], p= 0.032) in the ITT population. In the PP population no significant differences were found though there was a trend (p=0.055) to higher values with the glargine regimen (167. 2 mg/dl [153;181.3] vs. 147.1 mg/dl [132.2;162]) during NPH phase of treatment.

f) *Total daily insulin dose*: No significant differences were found between both insulin regimens in this variable in the ITT nor in PP population: mean dose 53.9 UI [48.5;59.2] for NPH regimen vs. 52.6 [47.8;57.5] for glargine and lispro (ITT population).

Safety results:	*Adverse events*: *ITT population*: There were a total of 335 adverse events (AE) in 68 patients. Most frequent adverse events were coded as nervous system disorders (21.5%), respiratory thoracic and mediastinic disorders (15.5%), gastrointestinal disorders (11%) and infections and infestations (10.1%) according to MedDRA system organ class codification. 5.4% (18 AE) were considered as SAE (serious adverse events) according to protocol definition. For all the AE, the relation with the trial drug was considered suspicious by the investigator in 10.4% of the cases (35 AE). Regarding the outcome of the AEs in 92.8% the event was recovered/resolved at the end of the study. Only in one case the AE (pregnancy) caused the study drug discontinuation. *PP population*: a total of 52 patients presented 248 AE. Most frequent were nervous system disorders (19.8%), respiratory, thoracic and mediastinic disorders (14.1%), gastrointestinal disorders (10.1%), infections and infestations (9.3%) and musculoskeletal and connective tissue disorders (9.3%) according to MedDRA system organ class codification. 4.4 % (11 AE) were considered SAEs. Relationship with study drug was considered suspicious by the investigator in 9.7% of the cases. Outcome at the end of the study was resolved for 93.5% of the cases. None of the AEs motivated the study drug discontinuation. *Premature discontinuation*: There were 5 patients withdrawn from the study. The reasons were: lost of follow-up (1), protocol deviation (1), lack of treatment efficacy (1) and other issues (2).
Date of report:	18-June-2007