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Sponsor/company:	sanofi-aventis	**ClinialTrials.gov Identifier:**	NCT00609895
		Study Code:	HOE901_4038
Generic drug name:	insulin glargine	**Date:**	19 March 2008

Title of the study:	The Incidence of Hypoglycemia in Insulin Glargine-treated Subjects with Diabetes Mellitus upon Switching between Bedtime and Morning Dosing HOE901_4038
Investigator(s):	Sergio Zúñiga-Guajardo Henry Dunant 100, Monterrey, NL, CP 64410 Mexico Phone: (52) 81.8368.7832 Fax: (52) 81.8368.7835 Email: sergiozungua@hotmail.com
Study center(s):	Country: Mexico Active centers: 1
Publications (reference):	No publications were done

Study period: Date first **patient/subject** enrolled: 23-Feb-2004 Date last **patient/subject** completed: 09-Aug-2004	**Phase of development:** Phase IV

Objectives:	Primary: • To compare the percentage of subjects with a glucose measurement ≤56 mg/dL at any point of the 8-point glucose profiles during 3 consecutive days before vs. 3 consecutive days after switching insulin glargine dosing time from bedtime to morning and vs. 3 consecutive days after switching back to bedtime dosing of insulin glargine. Secondary: • To compare the percentage of subjects with glucose measurements ≤72 mg/dL and ≤36 mg/dL at any point of the 8-point glucose profile during 3 consecutive days before vs. 3 consecutive days after switching insulin glargine dosing time from bedtime to morning and vs. 3 consecutive days after switching back to bedtime dosing of insulin glargine. • To compare the mean daily rate of hypoglycemia (i.e., the number of home glucose monitored values ≤72 mg/dL, ≤56 mg/dL, and ≤36 mg/dL at any point of the 8-point glucose profile) during 3 consecutive days before vs. 3 consecutive days after switching insulin glargine dosing time from bedtime to morning and vs. 3 consecutive days after switching back to bedtime dosing of insulin glargine. • To compare the changes from baseline in glucose values at each specific measurement time of the 8-point glucose profile during 3 consecutive days before vs. 3 consecutive days after switching insulin glargine dosing time from bedtime to morning and vs. 3 consecutive days after switching back to bedtime dosing of insulin glargine. • To compare the incidence of symptomatic hypoglycemia [unconfirmed and confirmed by SMPG (self-monitored plasma glucose) values] at **any time** during 3 consecutive days before vs. 3 consecutive days after switching insulin glargine dosing time from bedtime to morning and vs. 3 consecutive days after switching back to bedtime dosing of insulin glargine. • To evaluate overall safety and tolerability based on adverse event reporting, laboratory tests, and clinical examinations.		
Methodology:	This study is an uncontrolled, open-label single center cross-over study with a ≤14-day screening period, an 11-day treatment period, and 48-hour follow-up period.		
Number of patients/subjects:	Planned: 20	Randomized: 22	Treated: 22
Evaluated:	Efficacy: 22	Safety: 22	
Diagnosis and criteria for inclusion:	Patients with Diabetes Mellitus diagnosis, males or non-pregnant females between the ages of 6 and 75 years.		

Investigational product: Dose: Administration:	Insulin glargine Subjects should continue to receive their usual dose of insulin glargine at bedtime on days 1, 2, and 3. Subjects will take one-half of their usual insulin glargine dose at bedtime on day 4, and one-half of their usual insulin glargine dose pre-breakfast on day 5. Subjects will continue to take their usual dose of insulin glargine before breakfast on days 6 and 7. On day 8, subjects will take one-half their usual insulin glargine dose before breakfast and one-half their usual glargine dose at bedtime. Subjects will then continue to take their usual insulin glargine dose at bedtime again on days 9 and 10 Subcutaneous injection
Duration of treatment: 11 days	**Duration of observation:** 48 hours
Reference therapy: Dose: Administration:	*NA*
Criteria for evaluation:	
Efficacy:	The primary efficacy variable will be the proportion of subjects with a glucose measurement ≤56 mg/dL at any point of the 8-point glucose profiles during 3 consecutive days before vs. 3 consecutive days after switching insulin glargine dosing time from bedtime to morning and vs. 3 consecutive days after switching back to bedtime dosing of insulin glargine The secondary efficacy variables will be: • Proportion of subjects with at least one home glucose value ≤ 72 mg/dL at any time during each treatment regimen. • Proportion of subjects with at least one home glucose value ≤ 36 mg/dL at any time during each treatment regimen. • The daily rate of home glucose value ≤ 72 mg/dL (and for ≤ 56 mg/dL and ≤ 36mg/dL as well) at any time during each treatment regimen. • The changes in glucose values from the previous regimen at each specific measurement time during an 8-point glucose profile. • The incidence of symptomatic hypoglycemia, both unconfirmed and confirmed by SMPG values of ≤72 mg/dL, ≤56 mg/dL and ≤36 mg/dL.

Safety:	Adverse events, including severe hypoglycemia and serious adverse events; clinical laboratory assessments (hematology and clinical chemistry); vital signs (including body weight); and physical examination will be assessed.
Statistical methods:	The primary population of interest for this study is defined as all treated subjects who successfully complete the study. In addition, the intent to treat population, consisting of all patients treated with at least one dose of study medication, will be analyzed as well. The primary efficacy analysis is defined as the proportion of subjects with a home glucose monitor value $\leq$ 56 mg/dL at any time during each treatment regimen will be summarized. For each regimen, all data from any 8-point glucose profile performed during that regimen will be used. For each proportion, 95% confidence intervals will be constructed. Secondary efficacy variables that use glucose levels of $\leq$ 56 mg/dL and $\leq$ 36mg/dL will be analyzed in a similar manner to the primary efficacy variable. Descriptive statistics of results from the 8-point glucose profiles at each specific measurement time will be calculated for baseline, endpoint, and the change from baseline to endpoint. The proportion of subjects with treatment emergent adverse events, overall and by body system, will be tabulated for each study period. In addition, subjects with possibly related TEAE, serious adverse events, and adverse events leading to withdrawal will be listed overall and, if appropriate, frequency distributions by body system will be provided. Descriptive statistics of results from laboratory variables, clinical variables, body weight, and vital signs will be calculated for baseline, endpoint, and the change from baseline to endpoint

Summary:	There were no statistical differences among periods regarding hypoglycemia for all patients.
Efficacy results:	There were no statistical differences among periods regarding hypoglycemia for all patients. Neither for diabetes type 1 nor type 2 patients, at any point of the 8-point glucose profiles. There were no patients with glucose measurements ≤72 mg/dL and ≤36 mg/dL at any point of the 8-point glucose profile during 11 day study for any of the defined populations. There were no patients with glucose measurements ≤72 mg/dL, ≤56 mg/dL, and ≤36 mg/dL at any point of the 8-point glucose profile during 11 day study for any of the defined populations, so any statistical test is applicable for this objective. A repeated measured analysis was done for every point of the 8-point glucose profile for the 3 periods and diabetes type as intersubject factor. • At point 1 (pre-breakast) there are significant differences among periods.

Descriptive Statistics	DIABETES MELLITUS	Mean	Std. Deviation	N
GLUCOSE POINT 1 PERIOD 1	TYPE 1	118.9394	48.98408	11
	TYPE 2	129.5455	34.00172	11
	Total	124.2424	41.50402	22
GLUCOSE POINT 1 PERIOD 2	TYPE 1	165.6667	56.09298	11
	TYPE 2	138.0909	31.97815	11
	Total	151.8788	46.73765	22
GLUCOSE POINT 1 PERIOD 3	TYPE 1	130.1818	62.97043	11
	TYPE 2	127.7879	39.71433	11
	Total	128.9848	51.3886	22

Effect	Multivariate Tests	Value	F	Hypothesis df	Error df	Sig.
GLUCOSE	Pillai's Trace	0.304	4.155	2	19	**0.032**
	Wilks' Lambda	0.696	4.155	2	19	**0.032**
	Hotelling's Trace	0.437	4.155	2	19	**0.032**
	Roy's Largest Root	0.437	4.155	2	19	**0.032**
GLUCOSE * DIABETES	Pillai's Trace	0.142	1.575	2	19	0.233
	Wilks' Lambda	0.858	1.575	2	19	0.233
	Hotelling's Trace	0.166	1.575	2	19	0.233
	Roy's Largest Root	0.166	1.575	2	19	0.233

Source	Tests of Within-Subjects Contrasts	Type III Sum of Squares	df	Mean Square	F	Sig.
GLUCOSE	Period 2 - Period 1	16802.91	1	16803	5.417	**0.031***
	Period 3 - Period 1	494.793	1	494.79	0.171	0.684
GLUCOSE * DIABETES	Period 2 - Period 1	8018.182	1	8018.2	2.585	0.124
	Period 3 - Period 1	929.5	1	929.5	0.321	0.577
Error(GLUCOSE)	Period 2 - Period 1	62042.91	20	3102.1		
	Period 3 - Period 1	57857.37	20	2892.9		

• At point 2 – 8 the analysis does not show any statistical difference among periods or between diabetes type.

A multivariate analysis of covariance was done for every point of the 8-point glucose profile (as change percent) for the 3 periods and diabetes type as intersubject factor regarding glucose baseline and glucose baseline as covariate. The analysis does not show any statistical difference among periods or between diabetes type.

• The analysis does not show any statistical difference among periods or between diabetes type at point 1 (pre-breakfast):

• The analysis shows that statistical difference among periods at point 2 (post-breakfast), but there are no difference between diabetes type.

Descriptive Statistics	DIABETES MELLITUS	Mean	Std. Deviation	N
CHANGE PERCENT POINT 2 PERIOD 1	TYPE 1	28.8929	49.12475	11
	TYPE 2	22.1084	45.86993	11
	Total	25.5006	46.50964	22
CHANGE PERCENT POINT 2 PERIOD 2	TYPE 1	37.2087	67.12424	11
	TYPE 2	30.8678	55.77069	11
	Total	34.0382	60.30931	22
CHANGE PERCENT POINT 2 PERIOD 3	TYPE 1	31.5032	57.55705	11
	TYPE 2	25.2291	50.11275	11
	Total	28.3661	52.7607	22

Effect	Multivariate Tests	Value	F	Hypothesis df	Error df	Sig.
CHANGE PERCENT	Pillai's Trace	0.318	4.198	2	18	**0.032**
	Wilks' Lambda	0.682	4.198	2	18	**0.032**
	Hotelling's Trace	0.466	4.198	2	18	**0.032**
	Roy's Largest Root	0.466	4.198	2	18	**0.032**
CHANGE PERCENT * BASE LINE	Pillai's Trace	0.274	3.403	2	18	0.056
	Wilks' Lambda	0.726	3.403	2	18	0.056
	Hotelling's Trace	0.378	3.403	2	18	0.056
	Roy's Largest Root	0.378	3.403	2	18	0.056
CHANGE PERCENT * DIABETES	Pillai's Trace	0.015	0.137	2	18	0.873
	Wilks' Lambda	0.985	0.137	2	18	0.873
	Hotelling's Trace	0.015	0.137	2	18	0.873
	Roy's Largest Root	0.015	0.137	2	18	0.873

In this point Period 2 and 1 is the pair which shows statistical difference as it is showed in the following table:

Source	Tests of Within-Subjects Contrasts	Type III Sum of Squares	df	Mean Square	F	Sig.
CHANGE PERCENT	Period 2 - Period 1	8882.123	1	8882.123	8.452	**0.009**
	Period 3 - Period 1	2640.669	1	2640.669	3.301	0.085
CHANGE PERCENT * BASE LINE	Period 2 - Period 1	7363.391	1	7363.391	7.007	0.016
	Period 3 - Period 1	2475.072	1	2475.072	3.094	0.095
CHANGE PERCENT * DIABETES	Period 2 - Period 1	301.734	1	301.734	0.287	0.598
	Period 3 - Period 1	113.507	1	113.507	0.142	0.711
ERROR (CHANGE PERCENT)	Period 2 - Period 1	19965.749	19	1050.829		
	Period 3 - Period 1	15199.215	19	799.959		

- The analysis does not show any statistical difference among periods or between diabetes type at point 3 (pre-lunch)
- The analysis shows that statistical difference among periods, but there are no differences between diabetes type at point 4 (post-lunch).

Descriptive Statistics	DIABETES MELLITUS	Mean	Std. Deviation	N
CHANGE PERCENT POINT 4 PERIOD 1	TYPE 1	36.2188	62.16247	11
	TYPE 2	3.6785	24.06496	11
	Total	19.9487	48.92011	22
CHANGE PERCENT POINT 4 PERIOD 2	TYPE 1	56.2683	114.45862	11
	TYPE 2	2.4493	21.44751	11
	Total	29.3588	84.94771	22
CHANGE PERCENT POINT 4 PERIOD 3	TYPE 1	59.0178	102.10101	11
	TYPE 2	8.683	29.94253	11
	Total	33.8504	77.81127	22

Effect	Multivariate Tests	Value	F	Hypothesis df	Error df	Sig.
CHANGE PERCENT	Pillai's Trace	0.284	3.573	2	18	**0.049**
	Wilks' Lambda	0.716	3.573	2	18	**0.049**
	Hotelling's Trace	0.397	3.573	2	18	**0.049**
	Roy's Largest Root	0.397	3.573	2	18	**0.049**
CHANGE PERCENT * BASE LINE	Pillai's Trace	0.223	2.579	2	18	0.104
	Wilks' Lambda	0.777	2.579	2	18	0.104
	Hotelling's Trace	0.287	2.579	2	18	0.104
	Roy's Largest Root	0.287	2.579	2	18	0.104
CHANGE PERCENT * DIABETES	Pillai's Trace	0.002	0.02	2	18	0.981
	Wilks' Lambda	0.998	0.02	2	18	0.981
	Hotelling's Trace	0.002	0.02	2	18	0.981
	Roy's Largest Root	0.002	0.02	2	18	0.981

There are two pairs which present differences at point 4, Period 2 and Period 1, and Period 3 and Period 1 are the pairs which show statistical difference as it is showed in the following table:

Source	Tests of Within-Subjects Contrasts	Type III Sum of Squares	df	Mean Square	F	Sig.
CHANGE PERCENT	Period 2 - Period 1	8853.069	1	8853.069	4.697	**0.043**
	Period 3 - Period 1	9565.446	1	9565.446	7.209	**0.015**
CHANGE PERCENT * BASE LINE	Period 2 - Period 1	7141.604	1	7141.604	3.789	0.067
	Period 3 - Period 1	6634.736	1	6634.736	5	0.038
CHANGE PERCENT * DIABETES	Period 2 - Period 1	65.744	1	65.744	0.035	0.854
	Period 3 - Period 1	4.34	1	4.34	0.003	0.955
ERROR (CHANGE PERCENT)	Period 2 - Period 1	35813.547	19	1884.924		
	Period 3 - Period 1	25211.756	19	1326.935		

At point 5 (pre-dinner) the analysis does not show any statistical difference among periods or between diabetes type.

The analysis shows at point 6, that are statistical difference among periods, but there are no differences between diabetes type.

Descriptive Statistics	DIABETES MELLITUS	Mean	Std. Deviation	N
CHANGE PERCENT POINT 6 PERIOD 1	TYPE 1	20.9265	96.57594	11
	TYPE 2	10.3834	33.35719	11
	Total	15.655	70.71321	22
CHANGE PERCENT POINT 6 PERIOD 2	TYPE 1	31.9435	116.71378	11
	TYPE 2	11.8842	42.66361	11
	Total	21.9139	86.36466	22
CHANGE PERCENT POINT 6 PERIOD 3	TYPE 1	14.1415	68.1049	11
	TYPE 2	2.0486	33.15861	11
	Total	8.095	52.63623	22

Effect	Multivariate Tests	Value	F	Hypothesis df	Error df	Sig.
CHANGE PERCENT	Pillai's Trace	0.285	3.591	2	18	**0.049**
	Wilks' Lambda	0.715	3.591	2	18	**0.049**
	Hotelling's Trace	0.399	3.591	2	18	**0.049**
	Roy's Largest Root	0.399	3.591	2	18	**0.049**
CHANGE PERCENT * BASE LINE	Pillai's Trace	0.242	2.871	2	18	0.083
	Wilks' Lambda	0.758	2.871	2	18	0.083
	Hotelling's Trace	0.319	2.871	2	18	0.083
	Roy's Largest Root	0.319	2.871	2	18	0.083
CHANGE PERCENT * DIABETES	Pillai's Trace	0.034	0.32	2	18	0.73
	Wilks' Lambda	0.966	0.32	2	18	0.73
	Hotelling's Trace	0.036	0.32	2	18	0.73
	Roy's Largest Root	0.036	0.32	2	18	0.73

Period 2 and Period 1 is the pair which shows statistical difference.

Source	Tests of Within-Subjects Contrasts	Type III Sum of Squares	df	Mean Square	F	Sig.
CHANGE PERCENT	Period 2 - Period 1	744.169	1	744.169	0.901	0.354
	Period 3 - Period 1	6934.034	1	6934.034	7.257	**0.014**
CHANGE PERCENT * BASE LINE	Period 2 - Period 1	325.081	1	325.081	0.394	0.538
	Period 3 - Period 1	5716.379	1	5716.379	5.983	0.024
CHANGE PERCENT * DIABETES	Period 2 - Period 1	458.627	1	458.627	0.555	0.465
	Period 3 - Period 1	53.305	1	53.305	0.056	0.816
ERROR (CHANGE PERCENT)	Period 2 - Period 1	15690.765	19	825.83		
	Period 3 - Period 1	18153.271	19	955.435		

- At point 7 (bed time) the analysis shows that statistical difference among periods, but there are no difference between diabetes type.

Descriptive Statistics	DIABETES MELLITUS	Mean	Std. Deviation	N
CHANGE PERCENT POINT 7 PERIOD 1	TYPE 1	29.3474	98.5216	11
	TYPE 2	5.26	26.69358	11
	Total	17.3037	71.50812	22
CHANGE PERCENT POINT 7 PERIOD 2	TYPE 1	40.1405	117.8918	11
	TYPE 2	5.7139	39.83441	11
	Total	22.9272	87.66037	22
CHANGE PERCENT POINT 7 PERIOD 3	TYPE 1	2.6636	46.86562	11
	TYPE 2	-7.9718	24.05962	11
	Total	-2.6541	36.75831	22

Effect	Multivariate Tests	Value	F	Hypothesis df	Error df	Sig.
CHANGE PERCENT	Pillai's Trace	0.408	6.203	2	18	**0.009**
	Wilks' Lambda	0.592	6.203	2	18	**0.009**
	Hotelling's Trace	0.689	6.203	2	18	**0.009**
	Roy's Largest Root	0.689	6.203	2	18	**0.009**
CHANGE PERCENT * BASE LINE	Pillai's Trace	0.315	4.134	2	18	0.033
	Wilks' Lambda	0.685	4.134	2	18	0.033
	Hotelling's Trace	0.459	4.134	2	18	0.033
	Roy's Largest Root	0.459	4.134	2	18	0.033
CHANGE PERCENT * DIABETES	Pillai's Trace	0.053	0.5	2	18	0.615
	Wilks' Lambda	0.947	0.5	2	18	0.615
	Hotelling's Trace	0.056	0.5	2	18	0.615
	Roy's Largest Root	0.056	0.5	2	18	0.615

Period 3 and Period 1 is the pair which shows statistical difference.

Source	Tests of Within-Subjects Contrasts	Type III Sum of Squares	df	Mean Square	F	Sig.
CHANGE PERCENT	Period 2 - Period 1	754.959	1	754.959	1.002	0.329
	Period 3 - Period 1	20553.278	1	20553.278	13.091	**0.002**
CHANGE PERCENT * BASE LINE	Period 2 - Period 1	360.493	1	360.493	0.478	0.497
	Period 3 - Period 1	13648.055	1	13648.055	8.693	0.008
CHANGE PERCENT * DIABETES	Period 2 - Period 1	579.632	1	579.632	0.769	0.391
	Period 3 - Period 1	929.783	1	929.783	0.592	0.451
ERROR (CHANGE PERCENT)	Period 2 - Period 1	14315.869	19	753.467		
	Period 3 - Period 1	29831.515	19	1570.08		

- At point 8 (3:00 h) the analysis does not show any statistical difference among periods or between diabetes type.

Safety results:	There were 8 adverse events in 5 patients, and none of them was reported as related to study drug. Only one serious adverse event was reported as worsening of diabetic retinopathy with moderate intensity. However, no relationship with study medication was reported. Serious adverse event represents 12.50% regarding total number of adverse events reported (N =8), or 4.54% regarding total number of patients in study (N=22). There wasn't any report on severe hypoglycemia in 22 recruited patients during 11 treatment days and 48 hrs following. The rate of patients that reported hypoglycemia was 54.5% at any time during the study by self-monitored plasma glucose. Symptomatic hypoglycemias were evaluated as any blood glucose value that is less or equal than 72 mg/dL reported by the patient. **Population / Period 1 / Period 2 / Period 3 / Number of Hypoglycemia** Complete: 29 / 17 / 32 / 78 Diabetes Type 1: 20 / 13 / 24 / 57 Diabetes Type 2: 9 / 4 / 8 / 21 **Hypoglycemia / Number of Hypoglycemia / %of Hypoglycemia** ≤72 mg/dL: 22 / 28.2 ≤ 56mg/dL: 55 / 70.5 ≤36 mg/dL: 1 / 1.3 **TOTAL**: 78 / 100 Friedman test results for complete population is described in following table for mean ranks, which points out a statistical difference among periods, and minimum mean rank is for period 2. **Description / Mean Rank** HYPOGLYCEMIA PERIOD 1 <72: 2.23 HYPOGLYCEMIA PERIOD 2 <72: 1.7 HYPOGLYCEMIA PERIOD 3 <72: 2.07 N: 22 Chi-Square: 6.178 df: 2 p: **0.046** Friedman test results for diabetes mellitus type 1 population, which points out that there is no statistical difference among periods. For diabetes mellitus type 2 population is the same.
Date of report:	15-Oct-2007