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Sponsor/company:	Sanofi-aventis	**ClinialTrials.gov Identifier:**	NCT00135057
		Study Code:	HMR1964A_3502
Generic drug name:	Insulin glulisine	**Date:**	16 April 2007

STUDY SYNOPSIS

Study number

HMR1964A/3502

Title

Apidra® (insulin glulisine) administered in a fixed-bolus regimen vs. variable-bolus regimen based on carbohydrate counting in adult subjects with type 2 diabetes receiving Lantus® (insulin glargine) as basal insulin: a multicenter, randomized, parallel, open-label clinical study.

Investigators, study sites

Multicenter, 35 US sites. Coordinating Investigator: Richard Bergenstal, MD

Study duration and dates	Approximately 15 months (16 April 2004-29 August 2005)	**Phase**	IIIb

Objectives

Primary: To compare the change in hemoglobin A1c (HbA1c) between treatment regimens from baseline to Week 24.

Secondary: To assess differences between the treatment regimens in the change from baseline to individual study time points for HbA1c; and the change from baseline in other study parameters including blood glucose (fasting plasma glucose (FPG), preprandial and postprandial blood glucose, 7-point blood glucose profiles, percentage of subjects achieving a HbA1c <7.0%); average basal, bolus, and total insulin doses; lipids [total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides]; average weight and body mass index (BMI); hypoglycemic episodes; adverse events (AEs); chemistry and hematology laboratory values; physical examination results, vitals signs, and weight; and patient treatment satisfaction (health behavior, diabetes-specific quality of life, and general well-being).

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Generic drug name:	Insulin glulisine	**Date:**	16 April 2007

Study design

This was a multicenter, controlled, open-label, 1:1 randomized, parallel-group study in adult subjects with type 2 diabetes mellitus in which approximately 35 centers within the US with a total of approximately 270 subjects. Subjects were randomized to the Fixed or Variable regimen for Apidra® using a dynamic stratification to tend to balance the 2 treatment groups with respect to use of metformin at the time of randomization (yes or no), number of daily injections at baseline prior to the study (2 or >2), injection method (pen or vial), and study center. The study consisted of a screening phase of up to 2 weeks and a 24-week treatment phase. The planned duration of the study was 15 months.

Number of subjects planned

Approximately 270 randomized subjects (approximately 135 per treatment regimen).

Inclusion criteria

Subjects were eligible if they had a diagnosis of type 2 diabetes mellitus for at least 6 months, had a HbA1c 7% to 10% at screening, had received at least 3 months of continuous insulin with at least 2 injections/day with/without Metformin, were between 18 and 70 years of age, and had a negative test for glutamic acid decarboxylase (GAD) autoantibodies. Subjects were excluded if they were treated with sulfonylureas, thiazolidinediones, or other oral antidiabetic medications.

Treatments

Apidra® (HMR1964), 10-mL vials of 100 IU/mL or 3-mL cartridges of 100 IU/mL, administered subcutaneously (sc) 3 times daily 0-15 minutes before each meal (10-mL vial) and (3-mL vial) in a fixed-dose (Fixed regimen) or variable-dose regimen (Variable regimen), each with Lantus® (HOE 901), 10-mL vials of 100 IU/mL , co-administered sc once-daily.

Efficacy data

Primary efficacy data: HbA1c change from baseline to endpoint

Secondary efficacy data: FPG; preprandial and postprandial blood glucose; 7-point blood glucose profiles; insulin doses; blood lipids; and weight and BMI.

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Safety data

Safety data included AEs reported by the subject or noted by the investigators, standard hematology and blood chemistry laboratory tests; hypoglycemia as defined in the protocol; and physical examinations, vital signs, and weight.

Quality-of-life data

Patient treatment satisfaction was assessed at Weeks 0, 12, 24 or on early termination using the Diabetes Treatment Satisfaction Questionnaire (status and change versions), the Audit of Diabetes Dependent Quality of Life (ADDQoL), a well-being scale (W-BQ12), and health behavior questions.

Statistical procedures

Efficacy

Primary analysis: The primary analysis of change in HbA1c from baseline to Week 24 was conducted on the per-protocol (PP) population using an Analysis of Covariance (ANCOVA) model to test for non-inferiority of the Fixed Regimen to the Variable Regimen (standard) for Apidra® dosing. Covariates included HbA1c at baseline, treatment regimen, the 3 randomization factors, and study site

Secondary analyses: A repeated measures ANCOVA model was used to analyze continuous efficacy variables (e.g. change from baseline in HbA1c, FBG, pre- and postprandial blood glucose, basal and bolus insulin dose, HDL cholesterol, LDL cholesterol, triglycerides, weight, and BMI) over the post-baseline visits for all post-treatment assessments between Weeks 2 and 24, and adjusting for baseline assessments as well as the 3 randomization factors and study site.

The percentage of subjects with HbA1c <7% was analyzed using a logistic regression model with treatment regimen, baseline HbA1c, and the 3 randomization factors included.

Safety

AEs were tabulated. Laboratory tests results, physical examination results, vital signs, and weight were summarized using descriptive statistics. Hypoglycemia incidence was analyzed using a logistic regression, adjusting for the stratification factors and study site. Hypoglycemia rates were analyzed using a Poisson regression model patterned after that used above for responders (ie, subjects with HbA1c <7%).

Quality of life

Statistical methods used to analyze quality of life as measured using patient-reported outcome (PRO) variables are described in the PRO report that is provided in Appendix.

Interim analysis

No interim analysis was performed.

Results - Study subjects and conduct

Of the 281 subjects diagnosed with type 2 diabetes who were randomized to treatment, 277 received at least one dose of study medication, 233 completed the study, and 44 discontinued. The subjects were predominantly Caucasian, with a adjusted mean age of 56 years, a adjusted mean weight of 102 kg to 107 kg, and had been diagnosed with diabetes mellitus for a adjusted mean of 13 years prior to study. The adjusted mean HbA1c at baseline was 8.15% in the Fixed regimen and 8.30% in the Variable regimen.

The treatment groups were comparable in terms of study duration. There were no differences between the treatment groups in the baseline demography and disease states. The following is the summary table of subject accounting.

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Study Phase	Fixed Regimen	Variable Regimen	Total
Screened:	NA	NA	541
Randomized:	139	142	281
Treated:	138	139	277
Completed:	124 (89.9)	109 (78.4)	233 (84.1)
Discontinued:	14 (10.1)	30 (21.6)	44 (15.9)
Reason for discontinuing:			
Adverse event	3 (2.2)	6 (4.3)	9 (3.8)
Protocol violation	3 (2.2)	4 (2.9)	7 (2.9)
Lost to follow-up	1 (0.7)	6 (4.3)	7 (2.9)
Death[a]	0 (0.0)	1 (0.7)	1 (0.4)
Subject did not wish to continue	6 (4.3)	10 (7.2)	16 (6.7)
Other	1 (0.7)	3 (2.2)	4 (1.7)

[a] subject died of a myocardial infarction

Results - Efficacy

Results of the study are briefly summarized below for the PP population:

- The Fixed regimen (simple algorithmic regimen), at the end of study, showed non-inferiority to the Variable regimen (carbohydrate-counting regimen) in terms of reducing HbA1c values.
- Overall, there was no treatment difference in the responder rates in lowering HbA1c values ≤7% or 6.5%.
- Overall, there was no treatment difference between the 2 regimens in controlling self-monitored blood glucose (SMBG).

- There was no treatment difference between the 2 regimens in the change from baseline in HbA1c at Weeks 2, 6, 12, and 18.

- There was no treatment difference between the 2 regimens in the change from baseline in FBG at Weeks 2, 6, 12, 18, and 24.

- There was no treatment difference between the 2 regimens in the change from baseline to Weeks 12, 18, and 24 in preprandial and postprandial blood glucose as assessed using the 7-point blood glucose profile.

- The adjusted mean dose of insulin at Week 24 (Lantus®, Apidra®, total insulin and total insulin per kg) was significantly different between the 2 regimens, being higher for subjects treated with the Fixed regimen than the Variable regimen, beginning at Week 6 for Lantus® and total insulin and at Week 18 for Apidra®.

- Overall, there was no treatment difference between the 2 regimens in the change from baseline to Weeks 12 and 24 in lipids (total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides).

- Overall, the adjusted mean changes from baseline in weight and BMI were significantly different between the 2 regimens at Weeks 12 and 24, with subjects receiving the Fixed regimen gaining about 1.6 kg more than those treated with the Variable regimen by Week 24.

The following table provides a change from baseline to endpoint for the clinically relevant efficacy variables in the PP population.

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	Fixed Regimen		Variable Regimen			
Variable	**Adjusted mean baseline**	**Adjusted mean change from baseline to Week 24**	**Adjusted mean baseline**	**Adjusted mean change from baseline to Week 24**	**Adjusted mean difference (Fixed-Variable)**	**p-value**
HbA_{1C} (%) [a]	8.13 (N=119)	-1.47	8.23 (N=106)	-1.59	-0.12	0.3011
Responder* (HbA_{1C} <7%), %	N/A (N=88)	73.95	N/A (N=73)	68.87	N/A	0.511
Responder* (HbA_{1C} <6.5%), %	N/A (N=53)	44.54	N/A (52)	49.06	N/A	0.371
FPG (mg/dL)	152.7 (N= 113)	-40.0	152.7 (N=99)	-51.1	-10.1	0.0652
Lantus diary dose (U)	53.3[c] (N=118)	102.2[b]	49.6[c] (N=106)	86.3[b]	-15.9	<0.0001
Apidra diary dose (U)	53.3[c] (N=118)	109.3[b]	49.6[c] (N=106)	91.0[b]	-18.3	0.0039
Total insulin diary dose (U)	106.5[c] (N=118)	207.4[b]	99.2[c] (N=106)	177.7[b]	-29.7	0.0011
Total insulin diary dose per kg(U)	0.99[c] (N=118)	1.88[b]	0.95[c] (N=106)	1.64[b]	-0.23	0.0032
TC (mg/dL)	174.22 (N=111)	-5.09	173.74 (N=100)	-5.81	-0.72	0.8486
HDL cholesterol (mg/dL)	42.83 [c] (N=111)	0.04	44.62 [c] (N=100)	0.66	0.61	0.4497
LDL cholesterol (mg/dL)	90.68 [c] (N=101)	-3.37	94.38 [c] (N=95)	-2.85	0.52	0.8461
TG (mg/dL)	162.19 [c] (N=111)	-8.15	140.87 [c] (N=100)	-13.81	-5.67	0.2741
BMI (kg/m^2)	37.9 [c] (N=119)	1.40	36.04 [c] (N=106)	0.84	-0.56	0.0133
Weight (kg)	107.6 [c] (N=119)	3.98	103.9 [c] (N=106)	2.44	-1.55	0.02127

BMI = body mass index; FBG = fasting blood glucose; HDL = high-density lipoprotein; LDL = low-density lipoprotein; TC = Total cholesterol; TG = triglycerides

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[a] p-value and adjusted means from ANCOVA

[b] Week-24 value

[c] sample mean

* Percentage of subjects responded to each category

Results – Safety

- The 2 regimens had an acceptable safety profile and the study medication was well tolerated in both regimens. There were no treatment-related deaths. There was no difference between treatments in the overall incidences of individual AEs. There were no clinically significant changes from baseline in clinical laboratory variables in either treatment regimen. ECG abnormalities and vital signs changes were infrequent.

- Hypoglycemia episodes were common but generally mild. Severe hypoglycemia was observed in 11%-13% of subjects but resolved promptly with countermeasures and did not results in any discontinuations from the study. Annualized event rates of several categories of hypoglycemia were higher in the Variable regimen than the Fixed regimen.

- Subjects in the Fixed regimen required significantly more insulin (Lantus®, Apidra®, and total insulin) than subjects in the Variable regimen.

- One subject died during the study. The death resulted from myocardial infarction and not study drug related. Subject 005009, was a 70-year-old white man with type 2 diabetes mellitus since 63 years of age, who was randomized to the variable-dose regimen of Apidra® and received the initial dose of Apidra® in combination with Lantus® (insulin glargine) on 23 August 2004. On 22 October 2004 (Study Day 61) a scheduled stent insertion was attempted because of increased angina, but failed due to stricture in the left anterior descending coronary artery and the subject was sent home instead. The next day (23 October 2004/Study Day 62) he collapsed due to a syncopal episode and was transported by emergency services to the hospital emergency room and diagnosed with a suspected myocardial infarction, a serious adverse event. No information regarding treatment for this event is available and the subject expired on 24 October 2004 (Study

Day 63). An autopsy was not performed. The subject had received 62 days of treatment with study drug prior to expiring.

Relevant medical history included coronary artery bypass graft, hypercholesterolemia, syncope, acid reflux, hypertension, cardiac arrhythmia, angina, Dupuytren's contractures, asthma, and paresthesias of his hands and feet. Concomitant medications included metformin, esomeprazole magnesium, clopidogrel sulfate, fluvastatin sodium, metoprolol succinate, valsartan, and isosorbide.

The following table summarizes on-treatment AEs during the study in the safety population.

	On-Treatment AE		Possibly related Apidra		Possibly related Lantus	
Category	**Fixed Regimen (N=138)**	**Variable Regimen (N=139)**	**Fixed Regimen (N=138)**	**Variable Regimen (N=139)**	**Fixed Regimen (N=138)**	**Variable Regimen (N=139)**
Reported at Least One On-Treatment AE [n (%)]	102 (73.9)	98 (70.5)	9 (6.5)	12 (8.6)	5 (3.6)	8 (5.8)
Reported at Least One Serious On-Treatment AE [n (%)]	22 (15.9)	19 (13.7)	4 (2.9)	7 (5.0)	1 (0.7)	5 (3.6)
Subjects Discontinued Due to a On-Treatment AE [n (%)]	6 (4.3)	6 (4.3)	2 (1.4)	1 (0.7)	1 (0.7)	1 (0.7)
Subjects Who Died During the Study [n (%)]	0 (0.0%)	1 (0.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

On-Treatment AE = On-Treatment Adverse Event

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Annualized hypoglycemia adjusted event rates[a] in the Safety population

Description of Event	Fixed Regimen N=138			Variable Regimen N=139			Rate Ratio Variable/Fixed		
	Number Events	Exposure (subject/ years)	Rate(SE)[1] (events/subject _yr)	Number Events	Exposure (subject/ years)	Rate(SE)[1] (events/subject _yr)	Ratio	95% CI	P Value
SMBG < 70 mg/dL or Severe	3438	60.10	52.84 (5.017)	4052	55.97	69.03 (5.837)	1.31	(1.04, 1.65)	0.023
Symptomatic and SMBG < 70 mg/dL or Severe	2195	60.10	32.19 (3.366)	2505	55.97	41.24 (3.928)	1.28	(0.97, 1.70)	0.084
SMBG < 70 mg/dL or Severe - Nocturnal	332	60.10	5.503 (0.737)	492	55.97	8.933 (1.208)	1.62	(1.14, 2.30)	0.007
SMBG < 50 mg/dL or Severe	514	60.10	7.096 (1.118)	727	55.97	11.24 (1.662)	1.58	(1.06, 2.37)	0.026
Symptomatic and SMBG < 50 mg/dL or Severe	375	60.10	4.908 (0.813)	536	55.97	8.009 (1.124)	1.63	(1.07, 2.48)	0.022
SMBG < 50 mg/dL or Severe - Nocturnal	82	60.10	1.280 (0.261)	151	55.97	2.643 (0.464)	2.06	(1.26, 3.39)	0.004
Severe	53	60.10	0.893 (0.368)	38	55.97	0.689 (0.250)	0.77	(0.28, 2.13)	0.616
Severe - Nocturnal	12	60.10	0.215 (0.107)	10	55.97	0.190 (0.074)	0.88	(0.26, 3.02)	0.842

[1]The standard error took into account any over-dispersion within the Poisson regression model; Estimates were adjusted for metformin usage, # of injections of insulin and injection method.

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Results - Quality-of-life

Diabetes treatment satisfaction measured by DTSQ at the end of the study improved ($p<0.0001$) from baseline but did not differ between treatment groups (possible score range: 0-36; change=4.97 for Variable (carbohydrate counting) group and 3.16 for Fixed (simple algorithm) group, p=0.1597). Perceived frequency of hyperglycemia decreased ($p<0.0001$) from baseline but did not differ between treatment groups (possible score range: 0-6; change=-1.79 for Variable group and -2.08 for Fixed group, p=0.7961). Perceived frequency of hypoglycemia increased ($p<0.0001$) from baseline but did not between treatment groups (possible score range: 0-6; change=0.84 for Variable group and 0.91 for Fixed group, p=0.4823). No group difference was found in treatment satisfaction at the end of study.

No change occurred over study in diabetes dependent quality of life measured by ADDQoL.

Positive wellbeing decreased (possible score range: 0-12; change=-0.5, p=0.02) at the end of study from baseline for the Variable group. The magnitude of change, however, was less than 5% of the maximum score. No statistically significant change in general wellbeing from baseline to end of study in either treatment group.

Additional analysis of exploratory nature was performed to evaluate unique contributions of patient reported outcomes to clinical endpoints. Two statistical models were tested: (a) estimating relationships of baseline and Week-12 patient reported outcomes and repeated measures of A1c, and (b) estimating relationships of baseline and Week-12 patient reported outcomes and early study termination.

a. Frequent events of hyperglycemia reported in response to item 2 of the DTSQ by subjects at Week 12 (p=0.0073) was associated with an elevated average levels of A1c ($\Delta_{A1c} = 0.26$ between the extreme item scores of 0 and 6, p=0.0073) across follow up visits. This association between subjects reported hypoglycemia at study midpoint and average follow-up A1c was statistically significant and robust even after controlling for age, sex, baseline A1c, history of subject diet and practice of carbohydrate counting and treatment effects on A1c across visits.
b. On early study termination:

- Low impact of diabetes on patients' quality of life reported at baseline was associated (p=0.002) with a higher risk of early study termination.
- Low impact of diabetes on patients' quality of life reported at Week 12 was associated (p=0.0015) with a lower risk of early study termination.
- Risk for early study termination increased moderately but significantly (p=0.0001) associated with subjects' report on hyperglycemia reported at baseline in both treatment groups.
- Risk of early study termination increased (interaction with p=0.0027) with reports of hypoglycemia at Week 12 for subjects in the Variable treatment group but not for the subjects in the fixed dosing group.
- Subject level of exercise reported at baseline was a contributing factor to early study termination (see appendix for details).
- Subjects who kept healthy diet by avoiding carbohydrates reported at baseline showed (p<0.0001) a lower risk of early study termination, compared with those who did not report such diet practice, regardless of treatment group.

Report Date : 27 Feb 2007