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Sponsor/company:	sanofi-aventis	ClinialTrials.gov Identifier:	NCT00135096
		Study Code:	HMR1964A_3503
Generic drug name:	Insulin Glulisine	Date:	21/Jan/2009

GCP non-compliance

One investigator site in this trial was terminated for serious GCP non-compliance and a serious scientific misconduct issue. Data from 8 subjects enrolled at this site were excluded from the main efficacy analysis. The datasets were regenerated with the data included and excluded; and the outputs examined to ensure the results of the study were not compromised.

All 8 randomized subjects enrolled at this site were included in the Safety analyses.

Title of the study: APIDRA® (insulin glulisine) administered premeal vs postmeal in adult subjects with type 2 diabetes mellitus receiving LANTUS® (insulin glargine) as basal insulin: a multicenter, randomized, parallel, open label clinical study

Investigator(s): multicenter

Study center(s): 47 centers in the United States were planned; 45 centers screened subjects; 42 centers randomized subjects

Publications (reference): none

Study period:

Date first subject enrolled: 23-Aug-2004

Date last subject completed: 30-Jul-2007

Phase of development: IIIb

Objectives:

Primary:

The primary objective of the study was to compare the change in weight from baseline to study Week 52 in the Per Protocol (PP) population of premeal insulin glulisine versus postmeal insulin glulisine, in subjects receiving insulin glargine as basal insulin.

Secondary:

Efficacy: The secondary efficacy objectives of the study were to assess whether there were differences in any of the following measures between subjects who administered insulin glulisine before meals versus after meals, in subjects receiving insulin glargine as basal insulin:

- Change from baseline to study time points in weight
- Change from baseline to study time points in hemoglobin HbA_{1c} (A_{1c}),
- Percentage of subjects achieving $A_{1c} < 7.0\%$ and percentage of subjects with $HbA_{1c} < 6.5\%$
- Change from baseline to study time points in fasting blood (plasma) glucose (FPG)
- Change from baseline to study time points in 7-point blood glucose (BG) profile
- Change from baseline to study time points in basal, bolus, and total insulin doses
- Change from baseline to study time points in lipids (total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides)
- Change from baseline to study time points in meal pattern and food intake.

Safety: The safety objectives of this study were to investigate the relative differences between subjects who administered insulin glulisine before meals versus after meals (in subjects receiving insulin glargine as basal insulin) from baseline to end of study in the following: incidence and rate of hypoglycemia (BG < 70 mg/dL, < 50 mg/dL, < 36 mg/dL, severe and serious); adverse events, laboratory values (chemistry, hematology, adinopectin, ghrelin, urinalysis, and 24-hour urine glucose), and clinical values (physical examination and vital signs).

Subject-Reported Outcomes: The objective of this analysis was to assess subject treatment satisfaction among subjects treated with premeal insulin glulisine versus postmeal insulin glulisine administration. In addition, the effect of weight change on the subject's quality of life was evaluated. Self-reported measures of overall quality of life were also evaluated to ascertain possible reasons for the observed differences in treatment satisfaction between the two groups.

Methodology:
This was a multicenter, controlled, open, 1:1 randomized parallel group study in adult subjects with type 2 diabetes mellitus. The study consisted of a screening phase of up to 2 weeks and a treatment period of 52 weeks. Diabetic subjects on insulin therapy (on at least 2 injections) and with HbA_{1c} ≥7.5% and ≤10% were screened for the study. During the 2-week screening period, subjects continued to receive their current insulin therapy and metformin, if applicable. Qualified subjects were randomized via central randomization with a dynamic allocation method that balanced the treatment assignments according to study center, metformin (generic metformin, Glucophage® or Glucophage® XR) use at the time of randomization, number of injections at baseline (2 or > 2), and injection methodology (pen vs vial). All subjects were instructed to follow a healthy diet and exercise program and to document their food intake using a diary. All subjects who qualified during the screening period were randomized to one of two treatment arms:

PREMEAL ARM: Subjects received insulin glulisine administered subcutaneously (sc) three times per day 0-15 minutes before the three main meals, and insulin glargine once daily (qd), and metformin (if applicable) for 52 weeks.

POSTMEAL ARM: Subjects received insulin glulisine administered sc 3 times per day immediately after a meal (20 minutes after the start of a meal), and insulin glargine qd and metformin (if applicable) for 52 weeks.

The premeal arm administered insulin glulisine prior to plan meals. The postmeal arm adjusted the insulin glulisine dose based on actual food intake, administering only insulin that was actually needed.

Insulin glulisine was administered sc three times a day premeal or postmeal depending on the assigned treatment arm. All subjects received a single daily sc injection of insulin glargine. The timing of insulin glargine administration was according to the individual's needs, as determined by the investigator and in accordance with the product label. The dosing time could have been switched if the investigator deemed appropriate; however, this change could be made only once for each subject, and only during the first 6 months after randomization.

The initial doses of insulin glargine and insulin glulisine were calculated based on the total insulin dose from the previous treatment: 50% of the total daily insulin dose was basal insulin and 50% was bolus insulin. The total daily bolus insulin dose was divided to provide appropriate mealtime coverage during the day. The dose of insulin glargine was titrated weekly, following a phone call with the study center, according to the protocol algorithm, to meet the morning FBG (the first fasting test of the day) target value of < 110 mg/dL. Both treatment arms titrated/adjusted insulin glulisine weekly based on identified blood glucose patterns to meet the preprandial (before every meal except for breakfast) blood glucose target value of < 110 mg/dL, and bedtime target of < 130 mg/dL. The premeal arm administered insulin glulisine prior to the planned meals, while the postmeal arm adjusted the insulin glulisine dose based on the actual food intake, administering only insulin that was actually needed.

Subjects were instructed to perform self-monitored blood glucose (SMBG) measurements four times daily [preprandial: before breakfast (morning fasting); before lunch and dinner; and at bedtime], and anytime they experienced symptoms of hypoglycemia. Subjects were to perform the 7-point BG profiles on the two days prior to regularly schedule clinical visits: before randomization and during the treatment phase starting after Week 12 (visit 5). Subjects were instructed to document all insulin doses and injection times weekly or any time there was a change, along with maintaining food and intake records.
The Diabetes Treatment Satisfaction Questionnaire (DTSQ) was used to assess current and perceived changes in subject satisfaction with the regimen. In addition, in order to explain possible reasons for differences between the two groups in satisfaction, a diabetes specific quality of life questionnaire, the Audit of Diabetes Dependent Quality of Life (ADDQoL) was also administered. Since it was expected that the insulin regimen may have a negative effect on subject's weight, the impact of weight on subject health-related quality of life was evaluated using the short form of the Impact of Weight on Quality of Life questionnaire (IWQOL-Lite). These subject-reported outcomes were supplemented with the Health Behavior Questionnaire (HBQ). Questionnaires were completed at Weeks 0, 12, 28 and 52 or upon early termination.

One investigator site with 12 screened and 8 randomized subjects in this trial was terminated for serious GCP non-compliance and serious scientific misconduct issue.

Data from 8 subjects enrolled at this site were excluded from the main efficacy analysis. The datasets were regenerated with the site included and excluded; and the outputs examined to ensure the results of the study were not compromised. All 8 randomized subjects enrolled at this site were included in the Safety analysis.

Number of subjects: Planned: 345

Randomized: 173 premeal, 172 postmeal

Treated: 173 premeal, 171 postmeal

Evaluated:

Efficacy: Per protocol: 107 premeal, 106 postmeal; mITT population: 168 premeal, 162 postmeal; mITT with Site 62 excluded*: 163 premeal, 159 postmeal.

*Site 62 was excluded due to serious GCP non-compliance.

Safety: 173 premeal, 171 postmeal

Diagnosis and criteria for inclusion: Subjects 18 to 70 years of age with type 2 diabetes mellitus for at least 6 months; HbA_{1c} ≥7.5% and ≤10% at screening; at least 2 injections per day of insulin therapy for at least 3 continuous months, with or without metformin; negative glutamic acid decarboxylase autoantibodies; ability and willingness to perform SMBG testing at least 4 times a day, and at least 7 times a day during the 7-point BG profile measurement days.

Investigational product: HMR1964/Apidra® (insulin glulisine)

Dose (initial for both treatment arms): 50% of the total daily insulin from the previous treatment was divided to cover each meal; remaining 50% was insulin glargine (basal insulin). After the initial regimen, the insulin glulisine dose was titrated weekly after review with the study personnel, with adjustments based on identified BG patterns to meet the preprandial (before every meal except for breakfast) BG target of < 110 mg/dL and bedtime target of < 130 mg/dL. After the initial regimen, the insulin glargine dose was titrated weekly according to the SMBG value based on the mean of the last three existing morning FBG values (the first fasting test of the day) according to the following algorithm: FBG target < 110 mg/dL (range 70 – 109 mg/dL) with HbA_{1c} < 7.0%

Administration: by sc injection 3 times a day 0-15 minutes before each meal for the premeal arm, or immediately after a meal (20 minutes after the start of a meal) for the postmeal arm. The postmeal bolus insulin dose was adjusted based on the actual food intake for a specific meal.

Duration of treatment: 52 weeks (12 months)

Duration of observation: 52 weeks + 1 day (12 months plus 1 day)

Reference therapy: not applicable

Criteria for evaluation:

Efficacy: Primary efficacy criterion: weight measurements at baseline and study Week 52; secondary criteria: weight at baseline and Weeks 3, 6, 12, 20, 28, 36, and 44; peripheral venous blood: HbA_{1c} at baseline and Weeks 12, 28, 36 and 52; fasting BG at baseline and Weeks 12, 28, 36 and 52; preprandial BG and postprandial BG values using diary collections; 7-point blood glucose profiles using diary collections; insulin doses using diary collections; lipids: total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and triglycerides at baseline and Weeks 12, 28, 36 and 52.

Safety: Safety was assessed on the basis of an analysis of hypoglycemia events, adverse events, clinical chemistry, clinical hematology, adinopectin level, urinalysis and 24-hour urine glucose; and clinical values: physical examination and vital signs.

Statistical methods: The primary efficacy variable was the change in weight from baseline to Week 52. The non-inferiority of the postmeal arm compared with the premeal arm was analyzed in the Per Protocol (PP) population as the primary analysis and in the modified Intent-to-treat (mITT) population as a supportive analysis. The change from baseline to Week 52 in weight was investigated using analysis of covariance (ANCOVA). The non-inferiority of the postmeal arm compared with the premeal arm was established if the upper bound from the 2-tailed 95% confidence intervals (CI) on the difference of mean weight change postmeal arm minus mean weight change premeal arm was less than or equal to 1.5 kg. If the conclusion of non-inferiority of the postmeal arm was made, and the estimated change from baseline to Week 52 in weight from the postmeal arm was smaller than the corresponding change from the premeal arm then the test for superiority (of the postmeal arm over the premeal arm) was to be made using the same 2-tailed 95% CIs in the mITT population as a primary analysis and in PP population as a supportive analysis. If the upper 95% confidence bound was less than 0 kg, then the conclusion of superiority of the postmeal arm compared to the premeal arm was made.

Secondary efficacy variables were analyzed using the mITT and PP populations where the mITT population was considered as the primary population. The change from baseline to study time points in weight, HbA_{1c}, FPG, cholesterol, triglycerides, LDL levels, HDL levels, dose of insulin glargine, insulin glulisine, and total insulin was analyzed using repeated measurement analysis of covariance.

Change from baseline of each of the 7-point SMBG was analyzed individually using the same repeated measurement analysis of covariance.

The change from baseline to endpoint of these variables was summarized by descriptive statistics.

Logistic regression was used to analyze binary HbA_{1c} < 7.0% and HbA_{1c} < 6.5% at Week 52 in mITT and PP populations. As a supportive analysis, the visit where HbA_{1c} < 7.0% was first observed and HbA_{1c} < 6.5% was first observed, was analyzed using survival analysis life table methodology. The comparison of the study arm cumulative distribution functions was made using the log rank test statistic.

Among the safety variables, change from baseline to study time points in adinopectin, ghrelin, 24-hour urine glucose, and body mass index (BMI) were analyzed using the same repeated measurement analysis of covariance. The number of events and percentage of subjects on each treatment who experienced any hypoglycemia (BG < 70 mg/dL, < 50 mg/dL and < 36 mg/dL), symptomatic hypoglycemia (BG < 70 mg/dL, < 50 mg/dL), severe hypoglycemia, nocturnal hypoglycemia, and serious hypoglycemia were summarized. For each type of hypoglycemia, a logistic regression model including treatment, BMI, and randomization strata was used to test the hypothesis of no difference between any pair of treatment groups in incidence. Adjusted odds ratios, 95% CIs of odds ratios and p-values were provided. The annual rate (number of episodes per subject year) will also be estimated for each type of hypoglycemia using a general linear model, negative binomial distribution with log link or Poisson distribution with log link using the empirical estimate of standard error. For analyses of serious hypoglycemic events, if an insufficient number of events were observed, alternative analyses may have been performed. In addition, severe and serious hypoglycemic events were also combined for inferential analyses of incidence and annual rate. In the absence of clinical noteworthy patterns of events, the remaining safety variables were to be summarized but not analyzed.

Summary:

Efficacy results:

One investigator site in this trial was terminated for serious GCP non-compliance and a serious, scientific misconduct issue (8 randomized subjects). As a result of the observations and findings identified, the data from the subjects enrolled at this site were excluded from the primary efficacy analysis (PP population) and the secondary efficacy analysis (mITT population). However, all randomized subjects from this site were included in the safety analyses.

A total of 716 subjects were screened for this study and 371 (52%) were screen failures. Among the 345 subjects randomized to premeal or postmeal treatment, 229 (66%) completed the study. The percentage of subjects who completed the study was comparable in the two arms (68% premeal and 64% postmeal). The most common reason for withdrawing was because the subject did not want to continue in the study. A small percentage of subjects in each treatment group withdrew because of an adverse event (3% premeal, 4% postmeal). Excluding data from the GCP non-compliant site, a total of 322 subjects were randomized, 163 subjects to the premeal arm and 159 to the postmeal arm. One randomized subject in the postmeal arm withdrew from the study before receiving the first dose of study medication and, therefore, was not included in the Safety population, which included 173 subjects in the premeal arm and 171 in the postmeal arm.

Demographics

The majority of subjects in the study were white and there were slightly more females than males (approximately 56% versus 44%, respectively). There was a predominance of smokers in the premeal arm, with 52.6% of subjects being previous or current smokers, compared with only 40.4% previous or current smokers in the postmeal arm. Other demographic and background characteristics in the Safety population were similar between the treatment arms. There were no statistically significant differences between the treatment groups with respect to age, sex, race, weight, BMI, or smoking history. Demographic and background characteristics in the mITT population (excluding the GCP non-compliant site) paralleled those in the Safety population. There were no statistically significant differences between the study arms with respect to age, sex, race, weight, or BMI. However, in the mITT population with Site 62 excluded the difference between treatment arms with regard to smoking history achieved statistical significance (p=0.0453).

The most common insulin products used by the subjects before the study, in order of use, were Lantus®, Premix, and NPH in both premeal and postmeal arms. This was also true for metformin users and pen users overall, and for metformin and pen users in the postmeal arm and pen users in the premeal arm. Metformin users in the premeal arm used NPH more often than Premix. Previous insulin usage in the mITT and PP populations generally paralleled that of the Safety population.

Primary Efficacy Analysis

Change in Weight

The adjusted mean change from baseline in subject weight was 5.5 kg in the premeal arm and 4.7 kg in the postmeal arm at Week 52. The non-inferiority analysis showed that the upper bound of the 95% CI on the difference in mean weight gain between the two arms was less than 1.5 kg; therefore, it could be concluded that the postmeal arm is not inferior to the premeal arm with regard to change in subject weight. The non-inferiority of the postmeal arm versus the premeal arm was also confirmed in the mITT population (95% CI -2.17, 0.71).

Change in Weight (kg) from Baseline to Week 52 (PP Population)

	Premeal		Postmeal		Premeal - Postmeal		
	N	Adj. Mean (SE)	N	Adj. Mean (SE)	Adj. Mean (SE)	95% CI	p-value[a]
Baseline	107	106.51 (2.30)	106	108.16 (2.32)	1.65 (2.83)	--	--
Change from baseline at Week 52	107	5.53 (0.61)	106	4.66 (0.61)	-0.87 (0.75)	-2.35, 0.60	0.2430

a p-value from Overall Model of Change from Baseline to Week 52

The SAP provided for a test for superiority if, as in this case, the non-inferiority of the postmeal arm was demonstrated and the change from baseline to Week 52 in weight was smaller in the postmeal arm versus the premeal arm. The test of superiority was made using the same analysis, with the mITT population (excluding Site 62) as primary. Superiority of the postmeal arm over the premeal arm could not be concluded, since the upper 95% CI boundary on the difference between the two groups was not less than zero. The difference between the premeal and postmeal arms in adjusted mean weight at Week 52 was not statistically significant (p=0.3165).

The non-inferiority of the postmeal arm versus the premeal arm was confirmed in the mITT population including the GCP non-compliant site (95% CI -2.14, 0.73, p=0.3356).

Secondary Efficacy Analysis

Similar results were observed in the primary and secondary efficacy analyses when data from the GCP non-compliant site were both included and excluded from the analysis.

Change from Baseline in Weight at Weeks 3, 6 ,12, 20, 28, 36, 44, and 52

The changes from baseline in weights were consistently slightly greater in the premeal arm compared with the postmeal arm, but the differences between dosing arms were never statistically significant (p≥ 0.05, repeated measures mixed model) at any time point. Weight changes from baseline seen before Week 52 in the mITT population including the GCP non-compliant site paralleled those seen in the mITT population excluding this site. The changes from baseline in weights were consistently slightly greater in the premeal arm compared with the postmeal, but the difference between dosing arms was not statistically significant (p> 0.05) at any time point.

Change from Baseline in HbA_{1c}

The premeal and postmeal dosing of insulin glulisine provided subjects with similar glycemic control because the between-group differences in change from baseline for A_{1c} were not statistically significantly different (p> 0.05) at any time point.

Change in HbA_{1c} (%) from Baseline to Weeks 12, 28, 36, and 52 (mITT Population, Excluding Site 62)

	Premeal			Postmeal			Premeal – Postmeal		
	N	Adj.Mean	Adj Mean Change (SE)	N	Adj Mean	Adj Mean Change (SE)	Adj Mean (SE)	95% CI	Prob
Week 12	155	7.049	-1.27 (0.07)	149	7.211	-1.10 (0.07)	0.16 (0.09)	-0.01, 0.34	0.0726
Week 28	140	6.863	-1.45 (0.08)	127	6.957	-1.36 (0.08)	0.09 (0.10)	-0.10, 0.29	0.3459
Week 36	128	6.981	-1.33 (0.08)	117	6.966	-1.35 (0.08)	-0.02 (0.10)	-0.22, 0.19	0.8842
Week 52	114	7.035	-1.28 (0.09)	112	7.164	-1.15 (0.09)	0.13 (0.12)	-0.10, 0.36	0.2762

Change = change from baseline

Note: Adjusted means and p-values are from a repeated measures mixed model.

Fasting Blood Glucose

Mean baseline FBG values were comparable in the two study arms (174 mg/dL premeal arm, 168 mg/dL postmeal arm) as were endpoint FBG values (133 mg/dL premeal arm, 138 mg/dL postmeal arm). The adjusted mean changes from baseline were generally similar numerically between study arms, with the exception of Week 28. At Week 28 the adjusted mean change from baseline was greater in the postmeal than in the premeal arm (-41.0 mg/dL versus -33.8 mg/dL), but the difference between dosing arms was not statistically significant (p=0.1875). This difference between study arms at Week 28 was not evidenced in the PP population (adjusted mean change: -38.0 mg/dL versus -41.5 mg/dL; p=0.6660). At all visits the difference between arms in FBG was not statistically significant.

Insulin Doses, Lipids

The adjusted mean insulin glargine and insulin glulisine titrated doses (U/day) increased in both arms over the course of the study. Numerically, the adjusted mean dose increases were slightly greater in the premeal arm compared with the postmeal arm, although the difference in adjusted mean change from baseline between arms was not statistically significant ($p \geq 0.05$) at any time point. Therefore, there was no difference between the premeal and postmeal arms in basal insulin glargine requirement or insulin glulisine requirement. At Week 52, adjusted mean doses were 116.4 U/day (premeal) and 109.1 U/day (postmeal) for insulin glargine, and 148.9 U/day (premeal) and 141.7 U/day (postmeal) for insulin glulisine. Lipid parameters including total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides were not changed as a result of treatment.

Meal Pattern and Food Intake

The secondary efficacy objective - Change from baseline to study time points in meal pattern and food intake - specified in the protocol and in the SAP, was not evaluated because of the inability to analyze the food diary data due to the amount and quality of the collected data and a flaw in the study design/conduct, specifically, the protocol and the SAP did not clearly delineate how these data would be used. In effort to remedy this situation in retrospect, the Sponsor evaluated the collected food diary data after the database lock and concluded that the data could not be interpreted or analyzed.

Additional Efficacy Analyses

To ensure that the results of the study were not compromised, the Sponsor performed additional analyses of the efficacy data based on the primary and secondary efficacy variables. These analyses were conducted in the mITT population that included the subjects randomized in the GCP non-compliant site. These results were compared to the efficacy analysis data generated excluding the non-GCP compliant site and were similar.

Safety results:

The percentage of subjects with TEAEs was similar in the premeal and postmeal arms (74.6% and 70.8%, respectively). The most common TEAEs were: upper respiratory tract infection (16.2% premeal, 14.0% postmeal), peripheral edema (11.0% premeal, 9.9% postmeal), arthralgia (7.5% premeal, 5.8% postmeal), bronchitis (6.4% premeal, 5.8% postmeal), nasopharyngitis (3.5% premeal, 8.8% postmeal), urinary tract infection (5.2% premeal, 5.3% postmeal), sinusitis (5.2% premeal, 5.8% postmeal), viral gastroenteritis (4.6% premeal, 7.0% postmeal), headache (6.9 premeal, 4.7% postmeal), back pain (8.1% premeal, 2.9% postmeal), and diarrhea (6.4% premeal, 3.5% postmeal).

The incidence of treatment-related AEs (possibly related to insulin glargine and insulin glulisine) was greater in the premeal arm (6.4%) compared with the postmeal arm (4.7%), but the overall percentage of treatment-related TEAEs was small. Weight increase was the most frequently noted possibly related TEAE in both arms, 2.9% and 1.8%, respectively.

The majority of TEAEs in both arms were mild or moderate in severity, but the percentage of severe TEAEs was greater in the premeal arm (24.9%) than in the postmeal arm (13.5%). Hyperglycemic coma, reported in 5 subjects (2.9%), was the most frequently reported severe TEAE in the premeal group. Severe hypoglycemia, which occurred in 4 subjects (2.3%) in the postmeal arm, was the most frequently reported severe event in that group, as well as the most frequently reported severe TEAE overall [3 subjects (1.7%) in the premeal arm and 4 subjects (2.3%) in the postmeal arm].

During the study, 67 subjects [40 (23.1%) premeal, 27 (15.8%) postmeal] had treatment emergent serious adverse events (TESAEs), some of which were life threatening. There were 15 cardiac TESAEs (7 premeal, 8 postmeal) and 11 infection and infestation TESAEs (8 premeal, 3 postmeal). Other body systems with more than just a few TESAEs included injury, poisoning and procedural complications (9 TESAEs, 5 premeal and 4 postmeal), nervous system disorders (8 TESAEs, 6 premeal and 2 postmeal), gastrointestinal disorders (7 TESAEs, 5 premeal and 2 postmeal), general disorders and administration site conditions (3 premeal, 2 postmeal), and musculoskeletal and connective tissue disorders (5 premeal, 1 postmeal). Hypoglycemia (3 premeal, 4 postmeal) and hypoglycemic coma (5 premeal, 0 postmeal) were the most frequently reported TESAEs.

The majority of TESAEs were not considered treatment related by the investigator and the majority of subjects recovered from the event without sequelae. For the most part, possibly related TESAEs were associated with hypoglycemia, and more serious hypoglycemic events occurred in the premeal arm compared with the postmeal arm.

Treatment was well tolerated because only a small number of subjects (12, 5 premeal arm, 7 postmeal arm) in each arm discontinued from the study due to an AE. Two subjects in the premeal arm and 4 in the postmeal arm received accidental overdoses of study medication (insulin glulisine) and overdose was considered a SAE.

During the study one subject, in the premeal group died of pneumonia that was considered to be unrelated to treatment. A second subject, in the premeal group, died of bleeding esophageal varices after treatment ended. This death was also considered unrelated to the study treatments.

In the study two subjects in the premeal arm, and four subjects in the postmeal arm had experienced accidental overdose of study medication. All subjects fully recovered from the overdose.

There was one pregnancy reported for one subject. The subject discontinued from the study due to pregnancy after 226 days on the study treatment The subject was lost to follow-up and no further details regarding the pregnancy or its outcome were reported. The outcome of the pregnancy is unknown.

The overall incidence of subjects experiencing hypoglycemia was 92.5% in the premeal group and 89.5% in the postmeal group. The number of episodes of hypoglycemia was greater in the postmeal arm (7442 episodes) compared with the premeal arm (6206). Also, a similar percentage of subjects in both arms experienced nocturnal hypoglycemia (65% premeal, 70% postmeal), but again more episodes occurred in the postmeal arm than in the premeal arm (1108 versus 696, respectively). Generally the incidence of all types of hypoglycemia was similar in both study arms, with no study arm comparison achieving statistical significance; however, the number of episodes of SMBG < 70 mg/dL and nocturnal hypoglycemia episodes with SMBG < 70 mg/dL were significantly

higher in the postmeal arm (p=0.0270 and p=0.0017, respectively).

The estimated rates of severe (events requiring assistance and either SMBG < 36 mg/dL or countermeasure indicated of oral carbohydrate, intravenous glucose, or glucagon with prompt response to therapy) and serious hypoglycemic events (hypoglycemia with coma/loss of consciousness or seizure/convulsion) were numerically (but not significantly) higher in the premeal arm. Overall, 66 subjects from both arms reported severe hypoglycemia, with a slightly higher percentage of subjects (20.8%) in the premeal group compared with the postmeal group (17.5%). Serious hypoglycemia occurred in more subjects in the premeal group (8 subjects, 4.6%) than in the postmeal group (3 subjects, 1.8%). The number of episodes of serious hypoglycemia was greater in the premeal arm (12 episodes) compared with the postmeal arm (5 episodes) as was the number of episodes of hypoglycemia with coma/loss of consciousness (11 episodes versus 4 episodes, respectively). One subject in each group experienced seizure/convulsion.

BMI in the mITT population increased in both arms compared with baseline. In the premeal arm, the adjusted mean BMI value was 39.56 kg/m^2 at Week 52, with an adjusted mean change from baseline of 2.06 (±0.16). Corresponding values in the postmeal arm were 39.17 kg/m^2 and 1.66 (±0.16). The adjusted mean increase in BMI was not statistically significantly greater ($p \geq 0.05$) in the postmeal arm compared with the premeal arm at any time point

There were no clinically meaningful changes in mean hematology, biochemistry, or urinalysis values in either dosing group, and there was no evidence that treatment had an effect on vital signs, electrocardiograms (ECGs) or physical findings. Pre-defined abnormal changes (PCAs) were noted in some laboratory values and vital signs over the course of the study, but the percentages of subjects from both study arms with PCAs was generally small (< 10%).

Health Outcomes results:

A significant relationship was found between the number of hypoglycemic events (as previously defined) and the DTSQs Perceived Hypoglycemia actual score ($p = 0.0005$) and change score ($p = 0.0485$), providing evidence of the DTSQs Perceived Hypoglycemia score's clinical validity. No significant interaction was found between the number of hypoglycemic events between baseline and end-of-study and treatment group in predicting DTSQs Treatment Satisfaction, indicating that hypoglycemic events did not impact on treatment satisfaction measured by DTSQ differently between the two treatment groups.

Significant differences in premeal versus postmeal groups were found in the ADDQoL Present Quality of Life change score from baseline to Week 12 ($p = 0.0490$), in the DTSQ Perceived Hyperglycemia change score from baseline to Week 28 ($p = 0.0322$) and in the IWQOL-Lite Work change score from baseline to end-of-study ($p = 0.0386$) using available data. A significant relationship was found between weight change from baseline to end-of study and the ADDQoL Present Quality of Life actual score ($p=0.0238$) and change score ($p=0.0136$) the IWQOL-Lite Physical Function actual score ($p = 0.0008$) and change score ($p < 0.0001$) and the IWQOL-Lite Self Esteem actual score ($p = 0.0079$). No significant interactions between the domain scores and treatment group in predicting two treatment clinical outcomes (end-of-study change from baseline in weight and the number of hypoglycemic events between baseline and end-of study) were found, suggesting the relationships between the domain scores and weight change or hypoglycemic events were consistent between the two treatment groups.

Prior to adjustment for multiplicity, a significant difference in premeal versus postmeal groups in longitudinal analyses was found for the W-BQ12 Energy change score from baseline to end-of-study ($p=0.0360$), with subjects in the postmeal group indicating a higher increase in energy level as compared to the premeal group. After adjustment for multiplicity this difference was non-significant.

The longitudinal GEE results did not show any difference between treatment groups in treatment satisfaction or other PROs after adjustment for multiplicity. These analyses lead us to believe that the treatment regimen (premeal versus postmeal) had no direct clinically meaningful impact on the subjects' satisfaction or other aspects of HRQoL measured in this study. However, subjects' satisfaction with treatment increased from baseline to end-of-study within each group, indicating subjects' satisfaction with insulin glulisine and insulin glargine.

Interesting findings from the exploratory analyses indicated a relationship between change in weight during the study and domains of ADDQoL and IWQOL-Lite. Specifically, weight gain was associated with lower Present Quality of Life as well as with declines from baseline in Present Quality of Life; with lower levels of Physical Functioning and with declines from baseline in Physical Functioning; and with worse Self Esteem at study end. These results suggested that any regimen for treating diabetes that has a substantial impact on weight, whether a drug compound, diet and exercise, or combination, is likely also to show impact on assessing these concepts.

Results from analyses exploring correlates of withdrawal indicated that subjects who withdraw were less satisfied with treatment than were subjects who stayed in the study ($p < 0.0001$), and that experiencing more (day adjusted) hypoglycemic events was trended to be associated with an increased probability of withdrawal ($p = 0.0531$, MLEstimate = 3.7408).

Date of report: 23-Dec-2008