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Sponsor/company:	sanofi-aventis	**ClinialTrials.gov Identifier:**	NCT00135083
		Study Code:	HMR1964A_3511
Generic drug name:	Insulin Glulisine	**Date:**	23/Dec/2008

GCP Noncompliance

Efficacy data from 19 randomized patients at three (3) investigator sites were excluded due to GCP noncompliance/scientific misconduct in this or other clinical trials; 2 sites from the current clinical trial and 1 site from another clinical trial. Datasets with these 3 sites included and excluded were generated and the outputs examined to ensure that the results of the study were non-compromised. Results excluding data from these 19 patients are provided in the main efficacy analysis sections, and results including data from these 19 patients are provided in the additional efficacy analysis section. All randomized patients were included in the safety analysis in the CSR.

Title of the study: One versus two versus three daily rapid-acting insulin injections of Apidra® (insulin glulisine) as add-on to Lantus®(insulin glargine) and oral sensitizer basal therapy in type 2 diabetes: a multicenter, randomized, parallel, open-label clinical study

Investigator(s): multicenter

Study center(s): 99 centers in the United States were planned; 89 centers enrolled patients

Publications (reference): none

Study period:

Date first patient enrolled: 02-August-2004

Date last patient completed: 20-November-2007

Phase of development: IIIb

Objectives:

Primary: To show noninferiority between treatment groups (insulin glargine plus insulin glulisine administered once a day, twice a day, or three times a day) in the change in glycemic control from baseline to study Week 24 as measured by A_{1c}.

Secondary:

Efficacy: To assess whether there were differences between treatment groups in any of the following measures:

- Percentage of patients achieving an A_{1c} of less than 7% at Week 24,
- Percentage of patients achieving an A_{1c} of less than 6.5% at Week 24,
- Change from baseline to individual study time points in A_{1c}
- Change from baseline to individual study time points in fasting blood (plasma) glucose (FBG) and preprandial blood glucose
- Changes in weight from baseline to individual study time points
- Change from baseline to individual study time points in basal, bolus, and total insulin doses
- Change from baseline to individual study time points in lipids (total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides)

To assess whether there were differences between treatment groups in any of the following safety measures:

- Occurrence of hypoglycemia
- Adverse events
- Laboratory values: chemistry and hematology
- Clinical assessment: physical examination, vital signs, and weight.

To assess whether there were any differences in patient treatment satisfaction between treatment groups using the following patient-

reported outcome:

- Diabetes Treatment Satisfaction Questionnaire status and change versions (DTSQs and DTSQc)

To ascertain possible reasons for the observed differences in treatment satisfaction between treatment groups using:

- A diabetes symptom checklist, the DSC-R
- A well-being questionnaire, the W-BQ12
- Health behavior questionnaire (HBQ)

Methodology:

This was a multicenter, controlled, open-label, 1:1:1 randomized, parallel-group study in adult patients with type 2 diabetes mellitus. The study consisted of a 1-week screening phase, a 14-week run-in phase with insulin glargine, and a 24-week treatment phase with insulin glulisine and insulin glargine. Approximately 99 centers in the United States were each to enroll 18 to 20 patients for the insulin glargine run-in period, for a total of about 776 patients planned. Among these patients, 6 to 9 per site were expected to be randomized into one of the three insulin glulisine treatment arms.

Patients were adults who were inadequately controlled on their current oral treatment(s) ($A_{1c} \geq 8.0\%$). Patients must have been on two or three oral agents in different therapeutic classes for at least 3 months. The three therapeutic classes were sulfonylureas (SU), biguanide (metformin), and thiazolidinediones (TZD). With sulfonylureas, the dose must have been one-half maximal or greater; with metformin (metformin, Glucophage®, Glucophage® XR) the dose must have been ≥1000 mg daily; and with a thiazolidinedione, the dose of pioglitazone or rosiglitazone must have been one-half maximal or greater. Patients were evaluated for entry criteria at the screening visit, and qualified patients entered the 1-week screening period on their pre-existing oral regimen.

All patients who met the screening criteria entered a 14-week run in- phase and started insulin glargine at 10 units (U) administered subcutaneously (sc) daily. Enrolled patients received dietary and lifestyle recommendations from a healthcare professional at each site. All sites received and used standardized training material.

Patients on rosiglitazone 8 mg daily were to reduce the dose to 4 mg daily, in accordance with the product's labeling information for patients on insulin. Other oral agents remained constant during the run-in phase. All patients received a single daily sc injection of insulin glargine. Insulin glargine was to be administered at the same time each day, and it was recommended that it be administered at bedtime. The dosing time could have been changed if the investigator deemed appropriate; however, this change could be made only once for each patient.

The patient adjusted the dose of insulin glargine every 2 days according to the mean of the morning FBG levels for 2 days. Patients reported changes to the site at weekly contacts. Patients were to contact the investigator prior to insulin glargine adjustment if the mean FBG was either >250 mg/dL or <70 mg/dL. Patients were also to contact the site for low self-monitored blood glucose (SMBG) readings (<50 mg/dL) or in the event of severe hypoglycemia.

The site staff contacted patients weekly to review titrations and to inform them if they needed to up-titrate between the two office visits (based on the A_{1c} value from the last visit). Sites could have instructed patients to make discretionary titration changes according to an algorithm that was provided. The FBG target value was <110 mg/dL (range 70-109 mg/dL) with A_{1c} <7.0%. Protocol Amendment No. 3, which was issued January 2006, changed the preprandial blood glucose (BG) target from the initial 100 mg/dL to <110 mg/dL.

Daily fasting glucose monitoring was required during the run-in phase. Beginning at Week –1 all patients performed SMBG four times daily, before each meal and at bedtime.

After 14 weeks of insulin glargine therapy, patients with an A_{1c} level >7.0%, who were compliant with the study protocol and diary recording, were randomized to one of three treatment arms via central randomization using the ClinPhone (vendor) system. Treatment group assignment tended to be balanced according to study site and oral agent combination.

- Once-Daily Insulin: Patients received insulin glulisine, administered once daily 0-15 minutes before the *greatest glycemic impact* meal of the day, starting at one-tenth the total dose of insulin glargine with a maximum starting dose of 10 U.
- Twice-Daily Insulin: Patients received insulin glulisine, administered twice daily 0-15 minutes before the 2 *greatest glycemic impact* meals of the day, starting at one-tenth the total dose of insulin glargine with a maximum starting dose of 10 U.
- Three-Times-Daily Insulin: Patients received insulin glulisine administered three times daily 0-15 minutes before each meal of the day starting at one-tenth the total dose of insulin glargine with a maximum starting dose of 10 U.

On-site study personnel reviewed the patient diary from Week –1 to the randomization visit and averaged the bedtime, predinner, and prelunch glucose readings. The meal prior to the highest average (e.g., dinner if bedtime mean was highest) was the *greatest glycemic impact meal.* The meals prior to the two highest averages (e.g., dinner and lunch if bedtime and predinner mean was highest) were the two *greatest impact meals.* The meals selected initially were not changed during the study. Sulfonylurea agents were discontinued after randomization in all patients using them. Patients on combination products with sulfonylurea switched to the single-agent product at the same dose; metformin, and/or TZD were continued. Insulin glargine administration and weekly dosing adjustments continued in all three arms after randomization. In addition to continuing monitoring of morning FBG, additional monitoring of premeal or bedtime values was done after randomization, according to a prespecified schedule for each study arm. Titration of insulin glulisine took place weekly. The site made prandial insulin glulisine dose adjustments with guidance based on preprandial and bedtime values.

At randomization, all patients were required to decide if they would be administering insulin glulisine using either syringes and vials or

pens (OptiPen Pro1). This assignment was kept throughout the study.

SMBG values were recorded in a patient diary as well as stored in a glucose memory meter and reviewed by a health professional between and during all visits. Patients were asked to communicate with the investigator by phone, e-mail, or fax between the mandatory visits and mandatory phone calls.

Patients were instructed to complete a patient-reported outcomes questionnaire at Weeks 0, 8, and 24. Patients' treatment satisfaction, symptom burden, health behavior, and well-being were assessed using questionnaires at the corresponding study visits.

Number of patients: Planned: 776 in run-in phase; 315 (105 per arm) in treatment period

Randomized: 343

Treated: 343

Evaluated:

Efficacy: Per Protocol Population: 200 total (64, 68, 68 insulin glulisine 1x, 2x, 3x, respectively); modified intent-to-treat (mITT) population with GCP noncompliant sites excluded*: 303 total (101, 102, 100 insulin glulisine 1x, 2x, 3x, respectively); mITT Population with all sites included: 322 total (107, 109, 106 insulin glulisine 1x, 2x, 3x, respectively)

*Three sites were excluded from the main efficacy analysis due to serious GCP noncompliance issues and were included in the additional analysis.

Safety: 343 total (115, 113, 115 insulin glulisine 1x, 2x, 3x, respectively)

Diagnosis and criteria for inclusion: Men and women 18 to 79 years of age with type 2 diabetes mellitus for at least 6 months; A_{1c} ≥8%; current treatment with stable doses of two or three oral agents from three different therapeutic classes: sulfonylurea, biguanide, thiazolidinedione; and fasting C-peptide concentration >0.27 nmol/L.

Investigational product: HMR1964/Apidra® (insulin glulisine)

Dose: insulin glargine once daily plus one of the following dosage regimens:

- Insulin glulisine administered once daily 0-15 minutes before the greatest glycemic impact meal
- Insulin glulisine administered twice daily 0-15 minutes before the two greatest glycemic impact meals
- Insulin glulisine administered three times daily 0-15 minutes before each meal

The initial insulin glargine dose was 10 U, with dose adjustments every 2 days according to the mean of the morning FBG levels for 2 days.

The initial dose of insulin glulisine was one-tenth of the total daily dose of insulin glargine at randomization, up to a maximum of 10 U. This starting dose was for each meal according to treatment arm.

Administration: insulin glargine and insulin glulisine were both administered subcutaneously

Duration of treatment: 24 weeks

Reference therapy: none

Criteria for evaluation:

Efficacy: The primary efficacy variable was the change in A_{1c} from baseline to Week 24 in the Per Protocol Population.

Secondary efficacy variables: Percentage of patients achieving A_{1c} <7.0% at study Week 24, percentage of patients achieving A_{1c} <6.5% at study Week 24; change from baseline to individual study time points in A_{1c}; change from baseline to individual study time points in FBG and preprandial BG; changes in weight from baseline to individual study time points; change from baseline to individual study time points in basal, bolus and total insulin doses; change from baseline to individual study time points in lipids (total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides).

Safety: Hypoglycemia as defined in the protocol; adverse events; laboratory values: blood chemistry and hematology; clinical assessments: physical examination, vital signs (sitting systolic and diastolic blood pressure, heart rate), weight, and body mass index.

Statistical methods: This was a noninferiority trial with insulin glulisine three times daily as the standard to which twice daily insulin glulisine and once daily insulin glulisine were compared. The primary analysis was an analysis of covariance (ANCOVA) of the change from baseline in A_{1c} at study Week 24, which was the primary response variable.

The primary comparisons of once daily versus three times daily and twice daily versus three times daily were based on the least squares mean changes from baseline. A conclusion of noninferiority of the once-a-day treatment was made if the upper 97.5% (two-tailed) confidence bound on the difference in the least squares means, three times daily minus once daily, was less than 0.5% for the change in A_{1c}.

The primary analysis population for the noninferiority hypothesis was the Per Protocol Population. The equivalence limit for the change in A_{1c} was 0.5 %. A superiority hypothesis was to be tested in the intent-to-treat population if the results of the noninferiority hypothesis testing warranted.

Summary

Efficacy Results:

A total of 1232 patients were screened, 447 were screen failures, and 785 (64%) participated in the 14-week insulin glargine run-in period. The most common reason for failing Screening was not meeting one or more inclusion criteria (79.6%). Among the 785 patients who were treated during the insulin glargine run-in period, 441 patients (56.2%) discontinued early, 343 patients (43.7%) completed the run-in phase and were randomized, and 1 patient (0.1%) completed run-in but was not randomized. Patients were withdrawn or not randomized primarily because their A_{1c} value was ≤7% (288 patients, 36.7%). The percentage of patients who were randomized and completed the study was comparable in the insulin glulisine 1x, 2x, and 3x groups (80.0%, 81.4%, and 79.1%, respectively). The most common reason for withdrawing besides "other" in the Safety Population was because the patient did not want to continue in the study. Other reasons for discontinuing included withdrawal of consent, vacation, patient moved away, noncompliance, facility closure, and pre-existing condition. The insulin glulisine 3x group in the Safety Population had the greatest number of discontinuations because of an adverse event (4 patients), and even in that group, the number represented only 3.5% of patients. In the mITT Population with GCP noncompliant sites excluded, 16 patients (5.3%), 14 patients (4.6%), and 15 patients (5.0%) discontinued from the insulin glulisine 1x, 2x, and 3x arms, respectively. The distribution of reasons for discontinuing for the mITT Population with the three GCP noncompliant sites excluded and the mITT Population with the three GCP noncompliant sites included paralleled that of the Safety Population.

Demographics

The majority of patients in the study were white and there was a comparable number of men and women overall (173 men, 170 women). Numerically there were more women in the insulin glulisine 3x arm (63) compared with the other two arms (56 and 51), but the difference was not statistically significant (p=0.3370). The treatment arms were balanced with regard to the other demographic and background characteristics. Demographic and background characteristics in the mITT Population with patients from the three GCP noncompliant sites excluded paralleled those in the Safety Population.

Primary Efficacy Analysis

A_{1c} at Week 24 in the Per Protocol Population

Insulin glargine treatment during the 14-week run-in phase reduced the mean A_{1c} value to approximately 8% from over 10% in each treatment group. The mean A_{1c} value was further reduced in all three treatment arms during the randomization phase. The reduction in A_{1c} was about 0.5% to 0.6% in the Per Protocol Population.

Change from Baseline in A_{1c} (%) at Week 24 (Per Protocol Population)

	Insulin Glulisine 1x		Insulin Glulisine 2x		Insulin Glulisine 3x		Insulin Glulisine 1x - 3x			Insulin Glulisine 2x - 3x		
	N	Adj. Mean (SE)	N	Adj. Mean (SE)	N	Adj. Mean (SE)	Adj. Mean (SE)	97.5% CI[a]	P-Value	Adj. Mean (SE)	97.5% CI[a]	P-Value
Run-in Baseline	64	10.17 (0.202)	68	10.13 (0.197)	68	10.15 (0.201)						
Randomization Baseline	64	8.05 (0.126)	68	7.86 (0.123)	68	7.94 (0.125)						
Change from Baseline at Week 24	64	-0.46 (0.140)	68	-0.48 (0.136)	68	-0.58 (0.139)	0.12 (0.174)	(-0.27, 0.51)	0.4897	0.10 (0.169)	(-0.28, 0.48)	0.5486

In the Per Protocol Population, the noninferiority of insulin glulisine 1x to insulin glulisine 3x was not demonstrated; however, the noninferiority of insulin glulisine 2x to insulin glulisine 3x was demonstrated since the upper 97.5% CI was less than 0.5%.

Overall, there was no strong evidence of superiority between any of the study arms based on A_{1c} mean changes from the randomization baseline.

The primary analysis was also conducted for the mITT Population excluding patients from three GCP noncompliant sites and in the mITT Population with patients from these sites included. In both populations, the noninferiority of insulin glulisine 1x to insulin glulisine 3x and the noninferiority of insulin glulisine 2x to insulin glulisine 3x was demonstrated since the upper 97.5% CI was less than 0.5%.

Secondary Efficacy Analyses

A_{1c} Values <7%

Comparison of the percentage of patients achieving glycemic control (A_{1c} <7%) at Week 24 provided evidence that the treatment received by patients in the insulin glulisine 3x group was statistically significantly better in comparison with that of the other two groups.

The following table provides estimates of the cumulative percentage of patients who achieved glycemic control at some time during the 24-week randomization period. The methodology accounts for patients lost to follow-up before having a Week 24 A_{1c} assessment completed so that all patients in the mITT Population were included (excluding patients enrolled in GCP noncompliant sites).

In addition, the pattern of cumulative glycemic control shown in the table suggests that response increased with the number of insulin glulisine injections. The comparison of insulin glulisine 1x to insulin glulisine 3x was statistically significant for the time to first observation of A_{1c} <7% ($p < 0.005$, log-rank test), confirming this pattern of insulin glulisine efficacy beyond insulin glargine therapy. None of the other comparisons was statistically significant ($p > 0.1$, log-rank test). The statistically significantly higher cumulative glycemic control rate in the insulin glulisine 3x arm compared with the insulin glulisine 1x arm also suggested evidence against the noninferiority of insulin glulisine 1x to insulin glulisine 3x in this population. Achievement of glycemic control at some time during the 24-week randomization period did not differ in the mITT Population when patients from GCP noncompliant sites were included in the analysis.

Time to First Observation of A_{1c} <7% (mITT Population Excluding Patients from Sites 13, 74, 199)

				A_{1c}<7%	
			Pts. Who dropped out within Visit Interval		
Treatment	Visit Intervals	Number Entering Interval	**Pts. Who Never Achieved A_{1c}<7% before drop-out**	**Pts. Who Achieved A_{1c}<7% before drop-out**	Cumulative % (SE) of Patients Achieving A_{1c} <7% at Any Time[a]
Insulin glulisine 1x	Week 0 – 8	101	9	21	20.79 (4.040)
	Week 9 – 16	71	10	14	36.41 (4.950)
	Week 17 – 24	47	41	6	44.53 (5.310)
Insulin glulisine 2x	Week 0 – 8	102	9	23	22.55 (4.140)
	Week 9 – 16	70	5	25	50.21 (5.170)
	Week 17 – 24	40	34	6	57.68 (5.220)
Insulin glulisine 3x	Week 0 – 8	100	4	36	36.00 (4.800)
	Week 9 – 16	60	6	19	56.27 (5.050)
	Week 17 – 24	35	28	7	65.01 (5.010)

a Cumulative percent estimates are based on the lifetable methodology with last visit follow-up assumed to the end of the interval.

P-value comparing the study arms was based on the log-rank test: insulin glulisine 1x vs. insulin glulisine 2x = 0.1018; insulin glulisine 1x vs. insulin glulisine 3x = 0.0041; insulin glulisine 2x vs. insulin glulisine 3x = 0.1931.

Note: Subjects who did not have a week 24 HbA_{1c} done were considered to have not reached 7%

At Week 24, 30/101 (29.7%), 34/102 (33.3%), and 46/100 (46%) patients in the insulin glulisine 1x, 2x, and 3x arms (mITT Population excluding GCP noncompliant sites) had A_{1c} values <7%. The insulin glulisine 3x arm had a statistically significantly higher glycemic control success rate compared with the insulin glulisine 1x and insulin glulisine 2x arms ($p < 0.02$ for insulin glulisine 1x vs. insulin glulisine 3x, and $p < 0.05$ for insulin glulisine 2x vs. insulin glulisine 3x). This result is potentially supportive of the superiority of the insulin glulisine 3x treatment regimen over the insulin glulisine 1x and 2x treatment regimens for patients who failed to achieve glycemic control following 14 weeks of intensive insulin glargine therapy.

In the mITT Population with GCP noncompliant sites included, the percentage of patients in each study arm achieving an A_{1c} value <7% was comparable to that in the mITT Population excluding patients from the GCP noncompliant sites. The insulin glulisine 3x arm had a statistically significantly higher glycemic control success rate compared with the insulin glulisine 1x arm but not compared with the 2x arm ($p <0.02$ for insulin glulisine 1x vs. insulin glulisine 3x, and $p = 0.06$ for insulin glulisine 2x vs. insulin glulisine 3x).

A_{1c} Values <6.5%

The pattern of time to first observation of A_{1c} <6.5% values seen in the study suggests a response that increased with the number of insulin glulisine injections; however, the differences between treatment arms did not achieve statistical significance for A_{1c} <6.5% ($p \geq 0.18$, log rank test).

At Week 24, 14/101 (13.9%), 11/102 (10.8%), and 17/100 (16.7%) patients in the insulin glulisine 1x, 2x, and 3x arms (mITT Population excluding GCP noncompliant sites) had A_{1c} values <6.5%. The insulin glulisine 3x arm, while numerically superior, was not statistically significantly different from the insulin glulisine 1x or 2x arms in the percentage of patients achieving A_{1c} <6.5% at Week 24.

These results did not differ when patients from GCP noncompliant sites were included in the analysis.

A_{1c} at Weeks 8,16, and 24

The changes from baseline to posttreatment time points (Weeks 8, 16, and 24) in mean A_{1c} values were analyzed for the mITT Population with GCP noncompliant sites excluded. There was no statistically significant difference between treatment groups at any week for the change from baseline in A_{1c} ($p>0.05$, repeated-measures mixed model). However, the difference in change from baseline in A_{1c} approached statistical significance for the insulin glulisine 1x and insulin glulisine 3x arms at Week 8 ($p=0.0532$). These results did not differ when patients from GCP noncompliant sites were included in the analysis.

Fasting Blood Glucose and Preprandial Glucose

The geometric mean baseline FBG value for all randomized patients at the beginning of the run-in period was approximately 230 mg/dL. Insulin glargine therapy reduced this geometric mean to about 120 mg/dL by the beginning of the randomization phase. The geometric mean baseline FBG values were comparable in the three study arms (117 mg/dL insulin glulisine 1x arm, 118 mg/dL insulin glulisine 2x, 122 mg/dL insulin glulisine 3x) as were Week 24 FBG values (116 mg/dL insulin glulisine 1x, 117 mg/dL insulin glulisine 2x, and 121 mg/dL insulin glulisine 3x). FBG levels remained essentially unchanged during the 24 weeks of combination therapy with insulin glargine and insulin glulisine. None of the between treatment group comparisons in the mean change from baseline were statistically significant ($p \geq 0.05$). The results of this analysis were not different when patients at the GCP noncompliant sites were included.

Preprandial blood glucose levels tended to decrease over the course of the study in all groups and generally the levels were similar among the three arms at each time point.

For the mITT Population excluding patients from GCP noncompliant sites, baseline mean preprandial blood glucose values in the insulin glulisine 1x group were 160.9 mg/dL prelunch, 166.9 mg/dL predinner, and 193.0 mg/dL at bedtime. During the study, mean prelunch blood glucose levels ranged between 114.0 mg/dL and 171.7 mg/dL, predinner between 130.4 mg/dL and 184.6 mg/dL, and bedtime between 132.0 mg/dL and 196.4 mg/dL.

For the mITT Population excluding patients from GCP noncompliant sites, baseline mean preprandial blood glucose values in the insulin glulisine 2x group were 152.1 mg/dL prelunch, 162.6 mg/dL predinner, and 185.7 mg/dL at bedtime. During the study, mean prelunch blood glucose levels ranged between 126.6 mg/dL and 171.1 mg/dL, predinner between 128.9 mg/dL and 174.0 mg/dL, and bedtime between 141.2 mg/dL and 202.0 mg/dL.

For the mITT Population excluding patients from GCP noncompliant sites, baseline mean preprandial blood glucose values in the insulin glulisine 3x group were 145.6 mg/dL prelunch, 166.0 mg/dL predinner, and 185.2 mg/dL at bedtime. During the study, mean prelunch blood glucose levels ranged between 113.9 mg/dL and 156.4 mg/dL, predinner between 113.0 mg/dL and 168.4 mg/dL, and bedtime between 132.8 mg/dL and 190.4 mg/dL.

Preprandial blood glucose levels did not differ substantially between the mITT Population excluding patients from GCP noncompliant sites and the mITT Population including GCP noncompliant sites.

Body Weight

During the randomization phase, mean weight progressively increased at each visit for all three insulin glulisine-treated groups. The adjusted mean change from baseline at Week 24 in the mITT Population excluding patients from GCP noncompliant sites was 3.78 kg in the insulin glulisine 1x group, 4.09 kg in the insulin glulisine 2x group, and 3.90 kg in the insulin glulisine 3x group. There were no statistically significant differences ($p > 0.05$) among the treatment groups in change from baseline to posttreatment mean weight at any time point for the mITT Population excluding patients from GCP noncompliant sites. These increases in weight were not different from those seen in the mITT Population when GCP noncompliant sites were included.

Body Mass Index

During the randomization phase, mean BMI increased gradually in each of the three insulin glulisine treatment groups, mirroring the increases seen in body weight. There were no statistically significant differences among the treatment groups ($p > 0.05$) in change from baseline to posttreatment mean BMI at any time point. These results did not differ when patients from GCP noncompliant sites were included in the analysis.

Insulin Dose

The absolute mean insulin glargine titration doses at Week 24 were 88.3 U (range: 16.0 to 256.0 U), 88.1 U (range: 8.0 to 260.0 U), and 84.6 U (range: 14.0 to 226.0 U) in the insulin glulisine 1x, 2x, and 3x arms, respectively. The adjusted mean insulin glargine titrated dose increased in all arms over the course of the study (baseline dose, end of treatment dose per arm). Numerically, the adjusted mean dose increases from baseline were slightly greater in the insulin glulisine 1x arm compared with the insulin glargine 2x and 3x arms, although the difference between any pair of dose groups was not statistically significant ($p \geq 0.05$) at any time point for the mean change from baseline. Therefore, there was no difference among the arms in basal insulin glargine requirement.

The adjust (least square) mean insulin glulisine titration doses at Week 24 were 28.42 U, 51.15 U, and 69.87 U in the insulin glulisine 1x, 2x, and 3x arms, respectively. Given the definitions of the study arms, the mean change from baseline of total insulin glulisine titration doses increased with the number of meals at which insulin glulisine was administered: one, two, or three meals, and the p values for each pairwise comparison at each visit were generally less than 0.01 for the mITT Population excluding patients from GCP noncompliant sites.

The absolute mean total insulin titration doses at Week 24 were 114.4 U (range: 28.0 to 303.0 U), 137.1 U (range: 20.0 to 372.0 U), and 152.0 U (range: 24.0 to 395.0 U) in the insulin glulisine 1x, 2x, and 3x arms, respectively. As would be expected, the mean total titration dose was consistently greatest in the insulin glulisine 3x group. The estimated mean change from baseline of total insulin titration doses increased numerically in all groups over the course of the study with the greatest increases from baseline in the insulin glulisine 3x dose group. The comparisons of insulin glulisine 1x versus insulin glulisine 3x at Weeks 8, 16, and 24 were the only comparisons that achieved statistical significance (generally $p < 0.025$, repeated-measures mixed model).

The total insulin titrated dose per kilogram increased in all three study arms over the course of the study, with the greatest increases in the insulin glulisine 3x group. The differences between the insulin glulisine 1x and insulin glulisine 3x arms in adjusted mean total insulin titration dose per kilogram was statistically significant at Weeks 8, 16, and 24 ($p \leq 0.01$, repeated-measures mixed model) as were the differences between the insulin glulisine 3x and insulin glulisine 2x arms at Weeks 8, 16, and 24 ($p < 0.05$, repeated-measures mixed model).

Dosing results in the mITT Population with GCP noncompliant sites included did not differ from those of the mITT Population excluding patients from these sites.

Lipids

Lipid parameters including total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides were analyzed to identify possible treatment effects.

Total Cholesterol: Overall, mean total cholesterol levels did not change substantially from baseline as a result of treatment in any study arm in the mITT Population excluding patients from GCP noncompliant sites. The difference in adjusted mean change from baseline between treatment arms was not statistically significant at Weeks 8 or 24.

HDL Cholesterol: Mean HDL cholesterol levels did not change substantially from baseline as a result of treatment in any study arm in the mITT Population excluding patients from GCP noncompliant sites. The difference in adjusted mean change from baseline between treatment arms was not statistically significant at Weeks 8 or 24.

LDL Cholesterol: Mean LDL cholesterol levels did not change substantially from baseline as a result of treatment in any study arm in the mITT Population excluding patients from GCP noncompliant sites. The exception was at Week 24 when mean LDL cholesterol in the 2x arm decreased 0.12 mg/dL from baseline and in the 3x arm it increased 0.12 mg/dL from baseline. The difference between the two arms in the change from baseline was statistically significant ($p=0.0257$, repeated-measures mixed model).

Triglycerides: Mean triglyceride levels did not change substantially from baseline as a result of treatment in any study arm in the mITT Population excluding patients from GCP noncompliant sites. The difference in adjusted mean change from baseline between treatment arms was not statistically significant at Weeks 8 or 24.

For all lipids, results in the mITT Population with all patients included were not different from those in the mITT Population with the GCP noncompliant sites excluded.

Safety Results:

Adverse Events

Overall, during the run-in phase, treatment-emergent adverse events (TEAEs) were reported for 418 (53.2%) of the 785 patients, and the majority was mild or moderate in severity. The most frequently reported TEAEs during the run-in phase were upper respiratory tract infection (6.2%), peripheral edema (3.3%), headache (3.1%), sinusitis (2.7%), and bronchitis (2.5%). A total of 45 events were considered possibly related to insulin glargine during this phase, many more than during the randomization phase. Six (0.8%) of the 33 SAEs that occurred during run-in were considered possibly related to insulin glargine treatment. Two deaths occurred during the run-in phase due to pneumonia and acute renal failure. Overall, 15 (1.9%) patients withdrew from the study due to TEAEs during the run-in phase.

During the randomization phase, TEAEs were reported for 209 of 343 (60.9%) patients. The percentage of patients with TEAEs in each treatment group was similar, i.e., 66 (57.4%) patients in the once-daily group, 72 (63.7%) patients in the twice-daily group, and 71 (61.7%) patients in the three-times-daily group. Overall the most frequently occurring TEAEs in the randomization phase were: upper respiratory tract infection (5.2%), peripheral edema (4.1%), pain in extremity (3.8%), nasopharyngitis (3.5%), and sinusitis and back pain (each 3.2%). The majority of TEAEs in each study arm was mild or moderate in severity. Thirty-two patients (9.3%) experienced severe TEAEs. Eight patients (4, 2, and 2 patients in 1x, 2x, and 3x, respectively) had AEs that were considered possibly related to insulin glargine only, 24 patients (13, 4, and 7 patients in 1x, , 2x, and 3x, respectively) had AEs possibly related to insulin glulisine only, and 9 patients (3, 2, and 4 patients in 1x, 2x, and 3x, respectively) had AEs possibly related to insulin glargine and insulin glulisine. The incidence of all SAEs was equivalent among the treatment groups (7.0%, 7.1%, and 7.0%, respectively). No patient died during the randomization phase. Six patients withdrew from the study due to AEs during the randomization phase: 1/115 (0.9%) received insulin glulisine once daily, 1/113 (0.9%) received insulin glulisine twice daily and 4/115 (3.5%) received insulin glulisine three times daily.

One patient became pregnant and discontinued from the study. The pregnancy was carried full term and resulted in delivery of a healthy baby (see Section 13.3.3 for patient narrative). Five patients (1.5%) reported overdoses, all of whom recovered without sequelae.

Hypoglycemia

Overall, 65% of patients had a hypoglycemic event during run-in, and there was no difference between Randomized and Run-in Only patients (both 65%). During run-in, 9 patients experienced hypoglycemia that was considered a SAE by the investigator. Hypoglycemic coma occurred in 4 patients and 1 patient experienced hypoglycemic seizure and unconsciousness.

Analysis of hypoglycemic events showed a greater incidence in the insulin glulisine 3x group compared with the insulin glulisine 2x and 1x groups. Overall, the percentage of patients having any hypoglycemic event was slightly higher in the insulin glulisine 3x arm as compared with the 2x and 1x arms (78% vs. 73% and 73%, respectively). However, severe hypoglycemia (events requiring assistance and either SMBG <36 mg/dL or prompt response to counter measures) occurred twice as often in the insulin glulisine 3x group compared with the other two groups (16% vs. 8% and 7%). The comparison for insulin glulisine 1x vs. 3x incidence of severe or serious hypoglycemic events

approached statistical significance (p=0.058). As per the investigator's assessment, 2 patients in the insulin glulisine 1x group experienced serious hypoglycemia; 1 patient in the insulin glulisine 2x group had serious hypoglycemic coma; and 1 patient in the insulin glulisine 3x group experienced serious hypoglycemic seizure.

The number of hypoglycemic events per patient year was calculated as the event rate. The rate of severe and serious hypoglycemia was 0.10, 0.30, and 0.26 events/patient-year in the insulin glulisine 1x, 2x, and 3x groups, respectively. The insulin glulisine 1x arm had a significantly lower event rate of severe and serious hypoglycemic events compared with the insulin glulisine 2x arm (p = 0.0434). None of the other comparisons was statistically significant.

Laboratory Values (Chemistry and Hematology)

Mean changes from screening in hematology values were minimal for all analytes during the run-in phase and not clinically meaningful. Similarly, no clinically meaningful changes were noted in mean change from baseline for any of the hematology analytes during the randomization phase in any treatment arm.

Body Weight

Body weight was measured at screening, baseline, Week 8, Week 16, and Week 24. The change from baseline at Week 24 in the Safety population was 3.69 kg in the insulin glulisine 1x group, 3.79 kg in the insulin glulisine 2x group, and 3.89 kg in the insulin glulisine 3x group. These results were similar to the results seen for the mITT Population with GCP noncompliant sites excluded: 3.78 kg in the insulin glulisine 1x group, 4.09 kg in the insulin glulisine 2x group, and 3.90 kg in the insulin glulisine 3x group. There were no statistically significant differences among the treatment groups (p > 0.05) in change from baseline to posttreatment mean weight at any time point for the Safety Population.

Body Mass Index

BMI was measured at screening, baseline, Week 8, Week 16, and Week 24. During the run-in phase, small increases in mean BMI were progressive from Week -15 to Week-1 in both the Randomized and Run-in Only patients. There was, however, no statistically significant differences (p>0.08) between Randomized and Run-in Only patients at any time point.

During the randomization phase, mean BMI increased gradually in each of the three insulin glulisine treatment groups, mirroring the increases seen in body weight. The change from baseline at Week 24 in the Safety population was 1.27 kg/m^2 in the insulin glulisine 1x group, 1.32 kg/m^2 in the insulin glulisine 2x group, and 1.34 kg/m^2 in the insulin glulisine 3x group. Similar results were seen for the mITT Population with GCP noncompliant sites excluded: 1.30 kg/m^2 in the insulin glulisine 1x group, 1.42 kg/m^2 in the insulin glulisine 2x group, and 1.34 kg/m^2 in the insulin glulisine 3x group. There were no statistically significant differences among the treatment groups (p > 0.05) in change from baseline to posttreatment mean BMI at any time point for any of the patient populations.

Vital Signs, Physical Findings, and Electrocardiograms

Study drug treatment did not have a clinically meaningful effect on vital signs, physical findings, or electrocardiogram results.

Health Economics Results: Descriptive Analysis: Of the 47 descriptive variables for which baseline treatment comparisons were performed, none of the variables demonstrated statistically significant baseline differences (p > 0.05) among treatment groups. At baseline, a high ceiling effect (i.e., patients scoring at the highest score) was found on the DTSQs Treatment satisfaction score (n = 77, 27%), DTSQs Perceived Hyperglycemia (n = 31, 11%), indicating that patients were already satisfied with the treatment, or indicated more frequent hyperglycemia. In addition, a high floor effect was found on all DSC-R scales, indicating that patients were not experiencing the diabetes-related psychological fatigue (n = 51, 18%), cognitive dysfunction (Psychology cognitive, n = 61, 21%), neurological pain (n = 106, 37%), neurological sensation (Neurologic sensoric, n = 57, 20%), cardiovascular symptoms (n = 75, 26%), ophthalmologic symptoms (n = 92, 32%), hypoglycemia (n = 87, 30%), or hyperglycemia (n = 70, 24%). A third of the patients (n = 107, 37%) scored at floor on the W-BQ12 Negative Well-being indicating that patients did not feel down, upset, afraid or like crying at baseline.

Clinical Trial Patient-reported Outcomes Treatment Effect Analyses:

Longitudinal Analyses

Primary endpoint: There were no significant differences on the DTSQs Treatment Satisfaction between one daily dose versus three daily doses, or between two daily doses versus three daily doses in the longitudinal analyses.

Secondary endpoints: Prior to the Hochberg-Benjamini adjustment for multiple endpoints, a significant difference (at p < 0.025), between two daily doses versus three daily doses (p = 0.0107) groups was found for the W-BQ12 Energy change score from baseline to end-of-study, with patients in the two daily doses group indicating a higher increase in energy level as compared to the three daily doses group. After adjustment for multiplicity, this difference was nonsignificant.

No significant difference was found between the groups on the other scales.

By Time-point Analyses

Primary endpoint: No statistically significant differences in Treatment Satisfaction were found between one daily dose and three daily doses, or between two daily doses and three daily doses of insulin glulisine at any of the time points.

Secondary endpoints: At 0.025, a statistically significant difference between two daily doses and three daily doses of insulin glulisine was found only in the W-BQ12 Energy in change score from baseline to week 24/end-of-study (contrast testing discrete time-point, p-value = 0.0198). After adjusting for multiplicity, this effect was nonsignificant.

Exploratory Analyses

Mediating effects of patient-reported outcomes on clinical endpoints: No significant interactions were found between the DTSQs and DTSQc Treatment Satisfaction and treatment groups in predicting the treatment clinical outcomes (end-of-study change from baseline in A_{1c} and the number of hypoglycemic events between baseline and end-of-study), indicating that Treatment Satisfaction did not mediate treatment effect.

No significant interactions were found between treatment and HBQ items, indicating diet/exercise strategies did not mediate treatment effect. Additionally there were no significant effects for these covariates, indicating they were not related to the clinical outcomes.

A significant relationship between treatment satisfaction and change in A_{1c} was detected ($p = 0.0013$) after adjusting for all other covariates and treatment effects, with a decrease in Treatment Satisfaction related to an increase in A_{1c}, therefore providing evidence of the DTSQs Treatment Satisfaction score's clinical validity.

Mediating effects of clinical endpoints on patient reported outcomes: No significant interactions between treatment group and A_{1c} (actual and change) covariates in predicting the DTSQs and DTSQc Treatment Satisfaction, indicating no mediating effects of clinical endpoints on Treatment Satisfaction.

There was only one case of a significant interaction between treatment group and the clinical efficacy covariates in predicting patient reported outcomes (PROs); a significant interaction was found between treatment group and A_{1c} change from Baseline ($p = 0.0393$) in predicting DSC-R Neurology Pain.

A significant relationship between change from baseline to end-of-study in A_{1c} covariate and DTSQs Treatment Satisfaction (actual score at end-of-study and change from baseline to end-of-study) was found at end-of-study (last observation carried forward [LOCF]), indicating that both actual and change from baseline A_{1c} relate significantly to treatment satisfaction (type III results $p = 0.0137$ and $p = 0.0013$, respectively). A decrease in A_{1c} was related to an increase or a higher score in DTSQs Treatment Satisfaction.

A significant relationship was found between change in A_{1c} events and the DTSQs Perceived Hyperglycemia actual score and change in score from baseline to end-of-study ($p = 0.0474$ and $p = 0.0354$, respectively), with an increase in A_{1c} related to more frequent Perceived Hyperglycemia.

No significant relationship between the hypoglycemic event covariate and (DTSQs and DTSQc) treatment satisfaction was found at end-of-study (LOCF), indicating that this clinical endpoint did not relate significantly to treatment satisfaction above and beyond the other covariates in the model.

A significant relationship was found between hypoglycemic events and the DTSQs and DTSQc Perceived Hypoglycemia actual score ($p < 0.0001$ and $p = 0.0019$, respectively), with a higher number of hypoglycemic events related to more frequent Perceived Hypoglycemia, validating the DTSQs and DTSQc Perceived Hypoglycemia questions. In addition, hypoglycemic events had a significant relationship with the DSC-R Ophthalmology actual score ($p = 0.0443$), with a higher number of hypoglycemic events related to more frequent ophthalmology symptoms; and with the W-BQ12 Well-being actual scores including Positive Well-being ($p = 0.0415$), Negative Well-being ($p = 0.009$) and General Well-being ($p = 0.0144$), with a higher number of hypoglycemic events related to a decrease in Positive Well-being and in General Well-being and an increase in Negative Well-being.

Early withdrawal and patient-reported outcomes: The difference in treatment satisfaction between withdrawn patients versus those who stayed in the study (28.5 ± 6.68 versus 30.0 ± 6.91, respectively) was not statistically significant ($p = 0.2217$). Ophthalmology events (e.g., blurred vision, flashes or black spot) as evaluated through the DSC-R Ophthalmology score at the end-of-study ($p = 0.0105$, MLEstimate = -1.1941), decrease of positive well-being (e.g., feeling happy, feeling able to handle serious P-Valuelems) as evaluated through the W-BQ12 Well-being change in score ($p = 0.0225$, MLEstimate = -0.2477), HBQ Diet Strategy ($p = 0.0991$, MLEstimate = 1.4516), DTSQ Perceived Hyperglycemia ($p = 0.0699$, MLEstimate = 0.3273), and Change of DSC-R Cardiovascular ($p = 0.0674$, MLEstimate = -0.6282) were significant predictors of withdrawal when the actual and change scores of all patient reported outcome (PRO) domain scores were used in the model. When change scores only were included in the model to predict early withdrawal, then change in cardiovascular events (e.g., palpitation, shortness of breath) ($p = 0.0058$, MLEstimate = -0.8228) and change in W-BQ12 Well-being ($p = 0.0863$, MLEstimate =-0.1598) were significant predictors of withdrawal.

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