U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number: 21-629 /SE5-015

Drug Name: Apidra (Insulin Glulisine) Subcutaneous Injection 100U/ml

Indication(s): Treatment of (b) (4) with diabetes mellitus (b) (4)

Applicant: Sanofi Aventis

Date(s): June 27, 2007

Review Priority: Standard

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Keywords: pediatrics, active-control/non-inferiority

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1. EXECUTIVE SUMMARY

Apidra (insulin glulisine) was approved on April 16, 2004 for subcutaneous administration in the treatment of adult patients with type 2 diabetes. This supplemental New Drug Application included one pediatric study for the pediatric postmarketing study commitment which was due on December 21, 2007.

Study 3001 was a 26-week open-label, randomized, parallel group study to compare efficacy and safety of insulin glulisine compared with insulin lispro in children and adolescents with type 1 diabetes mellitus. The study was conducted at 65 study centers, in 16 countries, including 11 European countries, USA, Argentina, Australia, Russian, and South Africa.

The primary objective was to demonstrate non-inferiority of insulin glulisine compared to insulin lispro in glycated hemoglobin (GHb) change from baseline to Week 26 using the last observation on treatment. The prespecified non-inferiority margin was 0.4%.

1.1 Conclusions and Recommendations

The primary analysis of GHb change from baseline to endpoint showed non-inferiority of insulin glulisine to insulin lispro. The mean baseline GHb values were 8.20% and 8.17% and the least squares mean GHb changes were +0.10% and +0.16% for insulin glulisine and insulin lispro, respectively. The treatment difference [95% confidence interval] was -0.06% [-0.24%, +0.12%]. The upper limit of the CI was less than the 0.4% non-inferiority margin. Therefore, it is concluded that insulin glulisine is similar to insulin lispro in the treatment of children and adolescents with type 1 diabetes mellitus.

2. INTRODUCTION

2.1 Overview

Insulin glulisine (3BLys-29BGlu-human insulin, product code: HMR1964) is a recombinant rapid-acting insulin analog. The proposed indication is for children and adolescents with type 1 diabetes.

Study HMR1964D/3001 was a multicenter, randomized, open-label, parallel group, active-controlled study in children and adolescents 4 to 17 years in age with type 1 diabetes. Patients were stratified within each center according to whether they were taking NPH or insulin glargine at the time of randomization. This study consisted of a 4-week run-in phase and a 26-week treatment phase. The primary efficacy objective was to show non-inferiority of insulin glulisine compared to insulin lispro in GHb change from baseline.

A total of 646 patients were screened and 572 randomized, 277 to Glulisine and 295 to Lispro. A total of 65 centers in 16 countries (Belgium, Denmark, Finland, France, Germany, Hungary, Netherlands, Norway, Romania, Sweden, and Switzerland, Argentina, Australis, Russian, South

Africa and USA) participated in the trial. The percentage of patients was approximately 17% in the US centers. Table 1 displays the number and percent of patients by country.

Table 1 Number & % of patients by country

	Country	n	%
1	South Africa	136	23.8
2	USA	98	17.1
3	Argentina	63	11.0
4	Russia	61	10.7
5	Hungary	45	7.9
6	Romania	43	7.5
7	Germany	33	5.8
8	Belgium	21	3.7
9	France	17	3.0
10	Finland	14	2.5
11	Australia	11	1.9
12	Denmark	8	1.4
13	Switzerland	7	1.2
14	Sweden	7	1.2
15	Netherlands	5	0.9
16	Norway	3	0.5
Total		572	100%

2.2 Data Sources

The study report and electronic datasets for Study 3001 are located in the following links:

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3. STATISTICAL EVALUATION

The secondary analyses compared efficacy between treatment groups using changes in GHb at week 12 and week 26, self-monitored blood glucose (SMBG) parameters, symptomatic hypoglycemic episodes and insulin doses, and safety based on adverse events, serious symptomatic hypoglycemia, clinical chemistry, hematology and insulin antibodies.

3.1 Evaluation of Efficacy

Study Design and Endpoints

This 26-week, randomized, multicenter, multinational, open-label study evaluated the efficacy and safety of insulin glulisine noninferior to insulin lispro in children and adolescent 4 to 17 years of age with type 1 diabetes mellitus. The main inclusion criteria were onset of diabetes at

least 1 year prior to screening, uninterrupted insulin therapy for at least 1 year prior to screening and screening glycated hemoglobin (HbA_{1c}) in the range of ≥6.0 and ≤11.0%.

The 560 patients (280/group) sample size was based on a 1.3% standard deviation of the mean difference between groups of the GHb change from baseline, a one-sided significant level of 0.025, a non-inferiority margin of 0.4% with 90% power and a drop out rate of 20%.

During the 4-week run-in phase, all patients were treated with insulin lispro as meal insulin in combination with either NPH or insulin glargine as basal insulin.

After run-in, patients were randomized to insulin glulisine or insulin lispro stratified within each center by baseline NPH insulin or insulin glargine. The number of daily meal insulin injections was determined during the run-in period and was not altered from the time of randomization until the end of the study.

Insulin glulisine and insulin lispro were taken at least twice daily by subcutaneous (SC) injection 0 to 15 minutes prior to a meal. Basal insulin NPH was dosed twice daily in the morning and in the evening and insulin glargine once daily in the evening. Insulin glargine was recommended in adolescents and children of 6 years or above in the European Summary of Product Characteristics. In this study, children 4 and 5 years of age, therefore, received NPH as basal insulin.

The doses of meal insulin and basal insulin were titrated to glycemic targets below:

Table 2 Titration target

	Plasma-reference blood glucose meters	Whole blood-referenced blood glucose meters
FBG or pre-meal BG value		
<8 years old	106 to 150 mg/dL (5.9 to 8.3 mmol/L)	100 to 140 mg/dL (5.6 to 7.8 mmol/L)
≥8 years old	95 to 150 mg/dL (5.3 to 8.3 mmol/L)	90 to 140 mg/dL (5.0 to 7.8 mmol/L)
2-hour post-prandial BG value		
<8 years old	128 to 194 mg/dL (7.1 to 10.8 mmol/L)	120 to 180 mg/dL (6.7 to 10.0 mmol/L)
≥8 years old	106 to 172 mg/dL (5.9 to 9.6 mmol/L)	100 to 160 mg/dL (5.6 to 8.9 mmol/L)

The primary efficacy variable was GHb change from baseline at endpoint using the last available observation post baseline. The secondary variables compared efficacy between treatment groups using GHb change from baseline at week 12 (visit 9) and week 26 (visit 11), the number of patients reaching GHb values of 8.5% or less at weeks 12, 26 and endpoint, number of patients with a decrease in GHb from baseline of 0.7% or higher at weeks 12, 26 and endpoint, and self-monitored blood glucose (SMBG) parameters, symptomatic hypoglycemic episodes and insulin

doses, and safety based on adverse events, serious symptomatic hypoglycemia, clinical chemistry, hematology and insulin antibodies.

The intent-to-treat (ITT) population for the primary efficacy variable was defined as randomized patients who had a baseline and at least one post baseline efficacy measurement.

A total of 656 patients were screened and 572 patients (89%) were randomized. One patient randomized in the insulin lispro group was treated with insulin glulisine by mistake. This patient was included in insulin glulisine group for ITT analyses but was excluded from the PP analyses.

Patient Disposition, Demographic and Baseline Characteristics

Approximately 97% of the patients completed the study (Table 3).

Table 3 Patient Disposition

	Glulisine		Lispro	
	n	%	n	%
Randomized	276		296	
Randomized and treated	277		295	
Completed	265	95.7	287	97.3
Withdrawn	12	4.5	8	2.8
Reason for withdrawal				
Adverse event	1	0.4	0	0.0
Lack of efficacy	1	0.4	0	0.0
Protocol violation	1	0.4	1	0.3
Subject did not wish to continue	3	1.1	4	1.4
Parent legal guardian withdrew subj part	3	1.1	0	0.0
Other	3	1.1	3	1.0

Table 4 displays (sponsor's Table 9) the demographic characteristics by treatment group. The two treatment groups were similar with respect to gender, age, race, BMI, and puberty stage (Tanner stage) at baseline. Overall, the mean age of patients was 12.5 years. Approximately 7 % of patients were <8 years (1.6% <6 years), 26% were between 8 and 12 years old, and 67% were above 12 years. Overall, the mean BMI was 20.6 kg/m².

Table 4 Demographic characteristics at baseline

		Glulisine	**Lispro**
		(N=277)	**(N=295)**
Gender	Female: n (%)	131 (47.3)	156 (52.9)
	Male: n (%)	146 (52.7)	139 (47.1)
Age (years)	Mean (SD)	12.5 (3.05)	12.6 (2.92)
	Median [min ; max]	13.0 [4 ; 17]	13.0 [4 ; 17]
	<8 years: n (%)	22 (7.9)	19 (6.4)
	≥8 years and <12 years: n (%)	78 (28.2)	71 (24.1)

		Glulisine (N=277)	Lispro (N=295)
	≥12 years: n (%)	177 (63.9)	205 (69.5)
Race	White: n (%)	246 (88.8)	275 (93.2)
	Black: n (%)	3 (1.1)	3 (1.0)
	Asian/Oriental: n (%)	8 (2.9)	7 (2.4)
	Multiracial: n (%)	17 (6.1)	10 (3.4)
	Other: n (%)	3 (1.1)	0 (0.0)
BMI (kg/m2)	Mean (SD)	20.8 (3.4)	20.5 (3.3)
	Median [min ; max]	20.5 [14.1 ; 30.4]	20.1 [14.8 ; 30.8]
Tanner stage	Stage 1: n (%)	74 (26.7)	72 (24.4)
	Stage 2: n (%)	33 (11.9)	50 (16.9)
	Stage 3: n (%)	37 (13.4)	35 (11.9)
	Stage 4: n (%)	64 (23.1)	64 (21.7)
	Stage 5: n (%)	69 (24.9)	71 (24.1)

The primary efficacy analysis was GHb change from baseline to endpoint using the ITT population. The endpoint was defined as the patient's last available measurement during the treatment phase. GHb changes from baseline to endpoint in the ITT population is summarized in Table 5. Patients in both treatment groups had similar GHb levels at baseline. The adjusted mean change (SE) from baseline to endpoint in the ITT population was +0.10% (0.08) in the insulin glulisine group and +0.16% (0.07) in the insulin lispro group. The difference in the adjusted means between the two treatment groups was -0.06% with a 95% CI of (-0.24, 0.12). The 0.12% upper bound of the 95% CI was less than the 0.4% non-inferiority margin; therefore, the non-inferiority of insulin glulisine compared to insulin lispro in the GHb change from baseline to endpoint was achieved (Table 5). The completers analysis was similar to the ITT analysis. The descriptive statistics of completers population were presented in Table 6. Figures 1 and 2 display the GHb change from baseline over time and GHb from baseline over time, respectively using the completers population. The ANCOVA analyses on glycemic variables are presented in the Appendix (Table 11).

Table 5 GHb (%) Change from baseline at endpoint - ITT

	Glulisine		Lispro		Glulisine-Lispro
	n	Mean	n	Mean	LSM Difference
Baseline	271	8.20 (1.05)	291	8.17 (1.02)	
Endpoint	271	8.31 (1.37)	291	8.37 (1.32)	
LSM change from baseline (SE) [95% CI]	271	0.10 (0.08) [-0.04, 0.03]	291	0.16 (0.07) [0.03, 0.29]	- 0.06 (0.09) (-0.24, 0.12)

Table 6 Descriptive statistics of GHb (%) - Completers

	Glulisine n=261				Lispro n=276			
	Mean	**StdDev**	**Min**	**Max**	**Mean**	**StdDev**	**Min**	**Max**
Baseline	8.21	1.05	5.90	12.40	8.15	1.03	5.50	11.60
Week 26	8.32	1.39	5.60	14.30	8.38	1.33	5.60	14.20
Change Week 26 -baseline	0.11	1.20	-5.00	5.40	0.23	1.05	-2.80	5.10

Figure 1 GHb (%) Mean change from baseline over time - completers

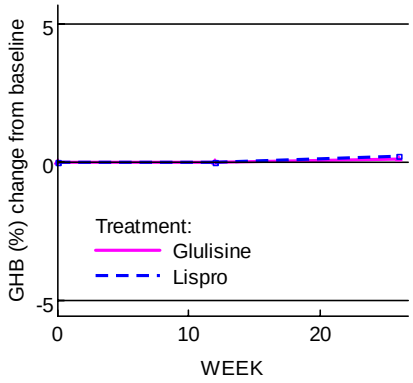
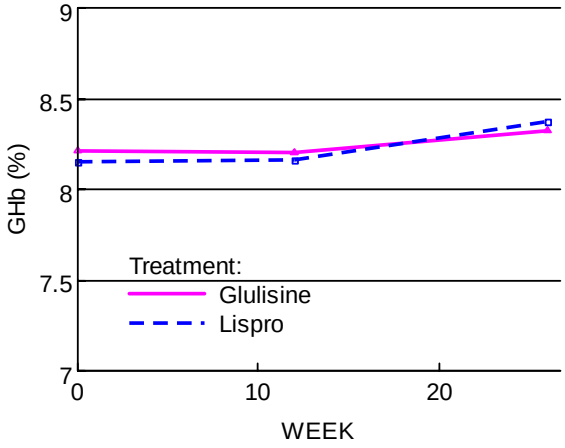


Figure 2 Mean GHb (%) over time - completers



Insulin:

Descriptive statistics were presented for daily doses of basal insulin, rapid-acting insulin and total insulin (Tables 7 to 10) using the ITT population. Figure 3 displays the mean daily insulin doses per body weight (kg) over time. Figure 4 displays the mean body weight by time that corresponds to the insulin dose/kg/day by time using the completers population.

Table 7 Descriptive statistics, mean (SD) of Basal insulin – ITT

Daily insulin dose (U)	Timepoint	Glulisine n=275		Lispro n=294	
		Mean	(SD)	Mean	(SD)
Basal	Baseline	27.2	(13.96)	26.55	(14.14)
Basal	Change	1.23	(4.80)	2.31	(5.25)
Basal/kg	Baseline	0.53	(0.23)	0.52	(0.24)
Basal/kg	Change	0.00	(0.09)	0.03	(0.10)

Table 8 Descriptive statistics, mean (SD) of Rapid-acting insulin – ITT

Daily insulin dose (U) or # of injections	Timepoint	Glulisine n=274		Lispro n=294	
		Mean	(SD)	Mean	(SD)
Rapid-acting	Baseline	24.26	(14.64)	24.34	(14.72)
Rapid-acting	Change	1.21	(7.91)	2.63	(8.30)
Rapid-acting/kg	Baseline	0.46	(0.21)	0.47	(0.23)
Rapid-acting/kg	Change	0	(0.13)	0.03	(0.14)

Table 9 Descriptive statistics, mean (SD) of Total insulin – ITT

Daily insulin dose (U)	Timepoint	Glulisine n=275		Lispro n=294	
		Mean	(SD)	Mean	(SD)
Total	Baseline	51.3	(23.75)	50.86	(22.07)
Total	Change	2.55	(10.48)	4.94	(10.66)
Total/kg	Baseline	0.99	(0.32)	0.99	(0.29)
Total/kg	Change	0.01	(0.18)	0.05	(0.18)

Table 10 Mean number of daily insulin injection – ITT

Daily insulin Dose (U)	Timepoint	Glulisine n=275*		Lispro n=294	
		Mean	(SD)	Mean	(SD)
Basal	Baseline	1.3	(0.47)	1.27	(0.44)
Basal	Change	0	(0.11)	0	(0.04)
Rapid-acting	Baseline	3	(0.71)	3.05	(0.70)
Rapid-acting	Change	0.03	(0.51)	0.06	(0.51)
Total	Baseline	4.28	(0.73)	4.32	(0.70)
Total	Change	0.05	(0.57)	0.05	(0.53)

* n=274 for rapid-acting insulin

Figure 3 Insulin daily dose (U) per body weight (kg) by week - Completers

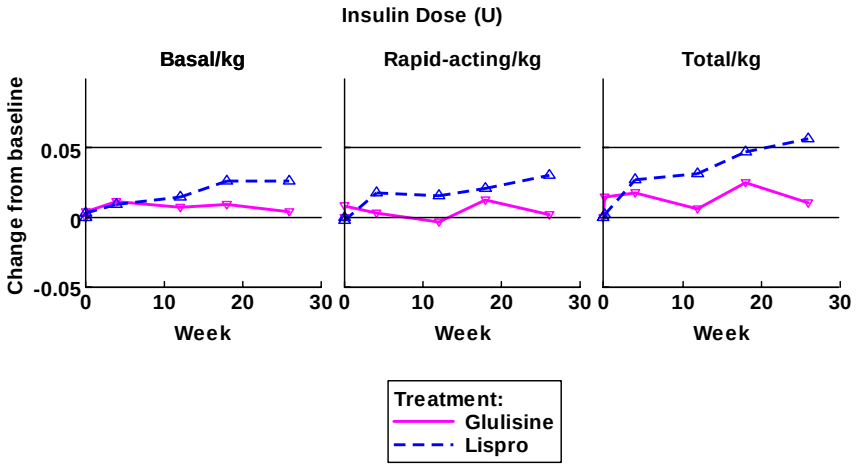
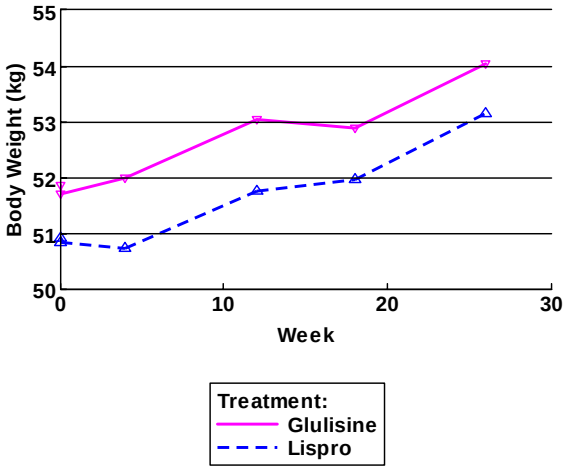


Figure 4 Body weight (kg) by week - Completers



3.2 Evaluation of Safety

The percent of patients with severe symptomatic episodes of hypoglycemia was 16.2% (45/277) for insulin glulisine group and 19.3% (57/295) for insulin lispro group. The incidence rates were not statistically different.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

The treatment-by-subgroup interactions on GHb change from baseline in gender, race, age, duration of diabetes, basal insulin at randomization and baseline GHb were not significant.

5. Labeling Recommendations

1. (b) (4) [redacted]

2. To be consistent with Table 4, please move up the row with number of patients to the columns under each Treatment.

3. The tables in the clinical studies section presented endstudy means for basal insulin dose and short-acting insulin dose (IU/day). The baseline means for basal and short-acting insulin dose should be presented instead of the endstudy means.

4. The name short-acting or rapid-acting should be consistently used in the label.

5. (b) (4)

6. Similar to table 4, HbA_{1c} means with 2 decimal points should be changed to 1 decimal point.

6. Appendix

Table 11 presents the ANCOVA results for change from baseline to endpoint in glycemic efficacy variables using LOCF data for ITT population.

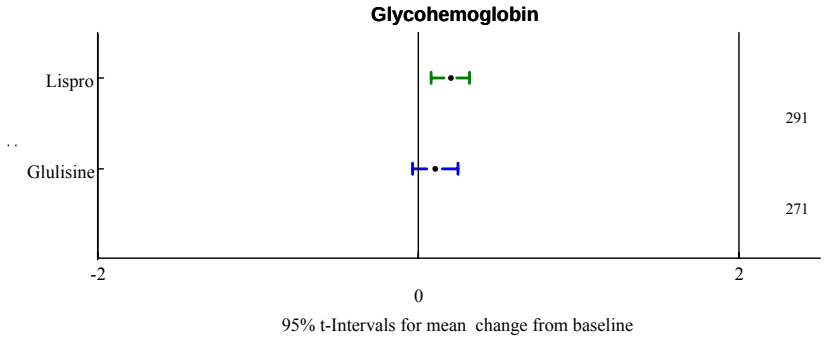
Table 11 ANCOVA results of glycemic efficacy variables - ITT

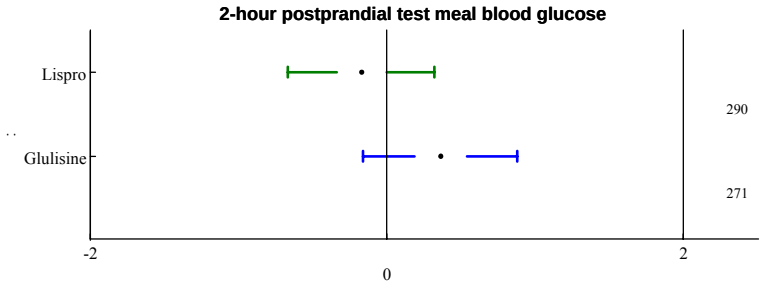
	Glulisine			Lispro			Difference				
	n	**LSM**	**(SE)**	**n**	**LSM**	**(SE)**	**LSM**	**(SE)**	**Prob**	**95% CL**	
GHB	271	0.10	(0.08)	291	0.16	(0.07)	-0.06	(0.09)	0.50	-0.24	0.12
test meal BG											
2-hr excursion	271	0.62	(0.28)	290	0.37	(0.28)	0.25	(0.34)	0.46	-0.42	0.92
2-hr excursion E*	259	0.48	(0.30)	284	0.39	(0.29)	0.09	(0.36)	0.80	-0.61	0.80
2-hr Postprandial	271	0.28	(0.23)	290	0.07	(0.23)	0.21	(0.28)	0.47	-0.35	0.76
2-hr Postprandial E*	259	0.35	(0.24)	285	0.19	(0.24)	0.16	(0.29)	0.58	-0.41	0.73
Before test meal	272	-0.36	(0.26)	292	-0.28	(0.26)	-0.08	(0.32)	0.79	-0.71	0.54
pre-breakfast test meal	272	-0.78	(0.23)	292	-0.09	(0.23)	-0.69	(0.28)	0.01	-1.24	-0.15
Variability in BG											
variability post test meal	254	-0.16	(0.17)	272	-0.11	(0.17)	-0.05	(0.21)	0.81	-0.46	0.35
variability post test meal E*	215	-0.28	(0.19)	247	-0.19	(0.19)	-0.09	(0.22)	0.68	-0.53	0.35
Variability all	272	-0.32	(0.11)	292	-0.21	(0.11)	-0.11	(0.13)	0.42	-0.37	0.15

E* selected values if BG profile time is >1 hr and < 2 hr 30 min after the start time of the main meal
ANCOVA model with treatment, type of basal insulin at randomization and (pooled) center as fixed effects and baseline as covariate.

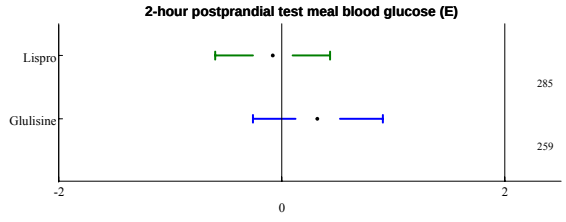
Figure 6 presents the mean change from baseline to endpoint for glycemic efficacy variables using LOCF data for ITT population.

Figure 5 Change from baseline mean and 95% CI by treatment group for glycemic efficacy variables





95% t-Intervals for mean change from baseline



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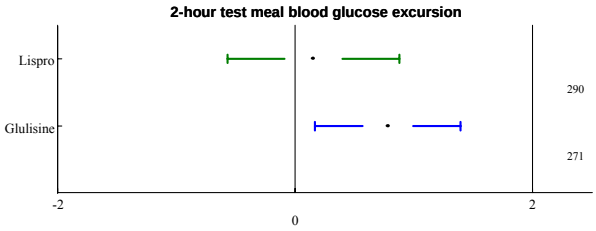

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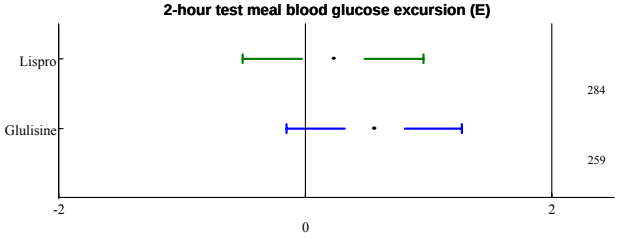
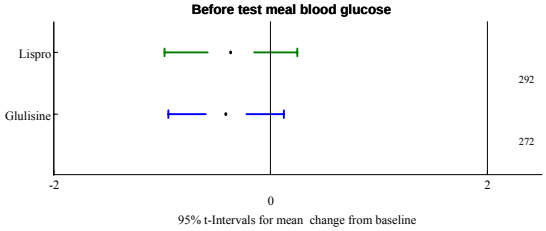


95% t-Intervals for mean change from baseline



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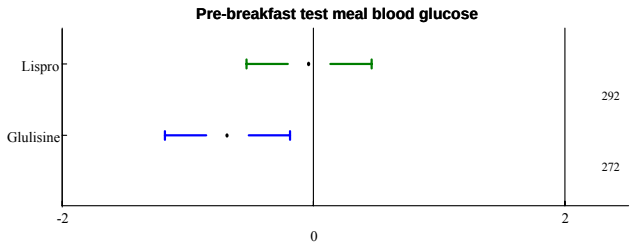
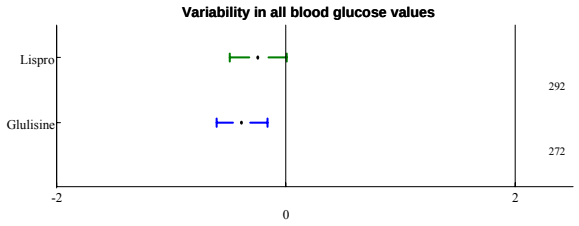
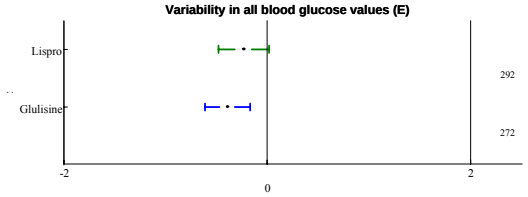


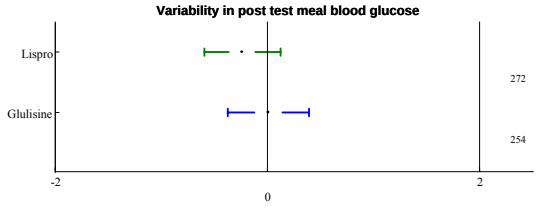
95% t-Intervals for mean change from baseline



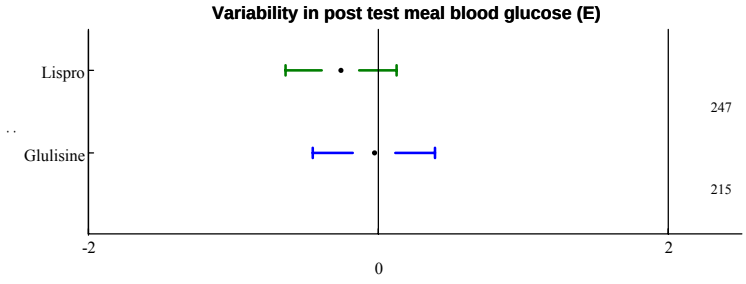
95% t-Intervals for mean change from baseline



95% t-Intervals for mean change from baseline



95% t-Intervals for mean change from baseline



95% t-Intervals for mean change from baseline

Figure 6 displays the least squares mean difference between glulisine and lispro in GHb change from baseline to endpoint by center (from the least variability on left to the most on right) using LOCF data of the ITT population. Figure 7 displays the same as Figure 6 by country. The LSM difference less than zero indicates glulisine reduced GHb more than Lispro and vice versa for LSM difference greater than zero. The 0.4% gridline is the noninferiority margin.

Figure 6 LSM difference (95% CI) of Glulisine vs. Lispro in GHb change from baseline to endpoint by pooled center

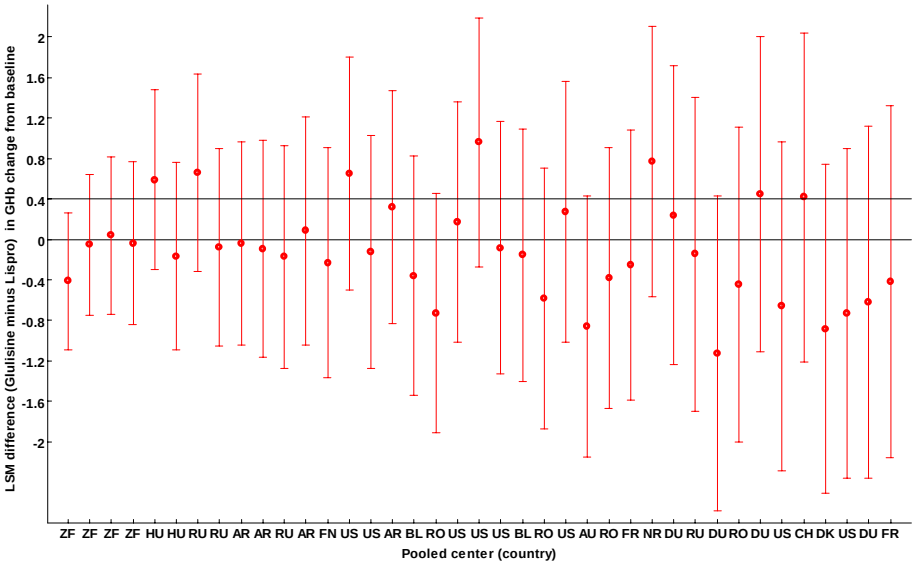
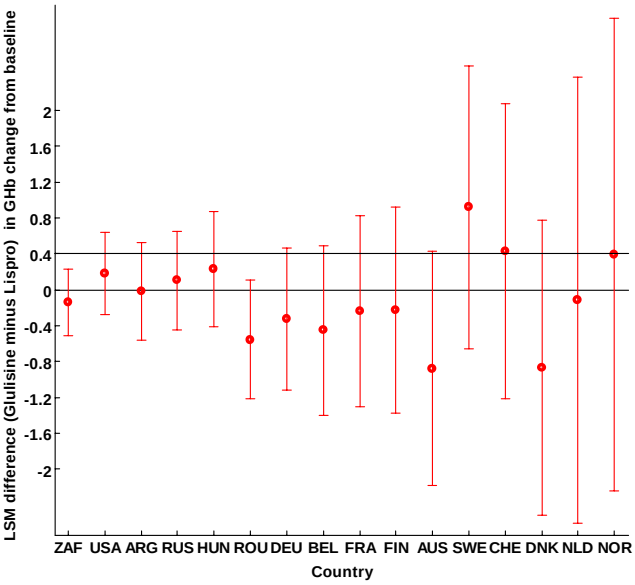


Figure 7 LSM difference (95% CI) of Glulisine vs. Lispro in GHb change from baseline to endpoint by country*



*Country code:
ARG, Argentina, AUS, Australia, BEL, Belgium, CHE, Switzerland , DEU, Germany, DNK, Denmark, FIN, Finland, FRA, France, HUN, Hungary, NLD, Netherlands, NOR, Norway, ROU, Romania, RUS, Russia, ZAF, South Africa, SWE, Sweden,

The following graphs present GHb change from baseline to endpoint by treatment and subgroup using LOCF data of the ITT population:

Figure 8 Mean GHb change from baseline (95% CI) to endpoint by race

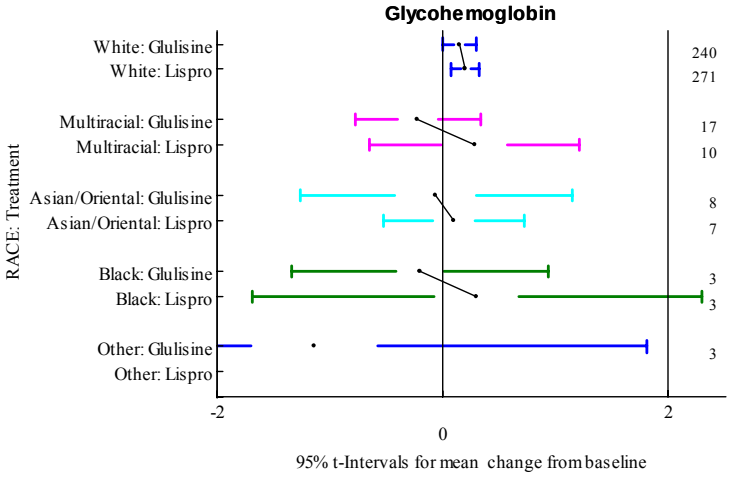


Figure 9 Mean GHb change from baseline (95% CI) to endpoint by gender

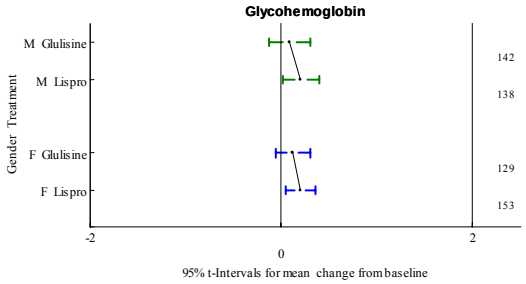


Figure 10 mean GHb change from baseline (95% CI) to endpoint by age group

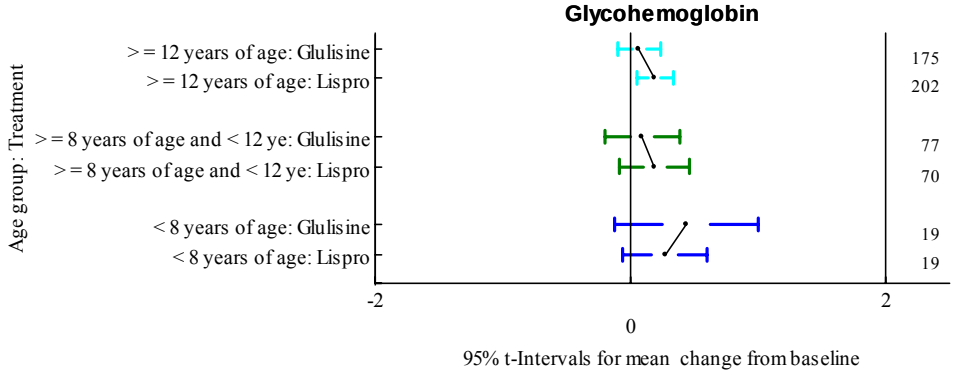


Figure 11 mean GHb change from baseline (95% CI) to endpoint by basal insulin and treatment group

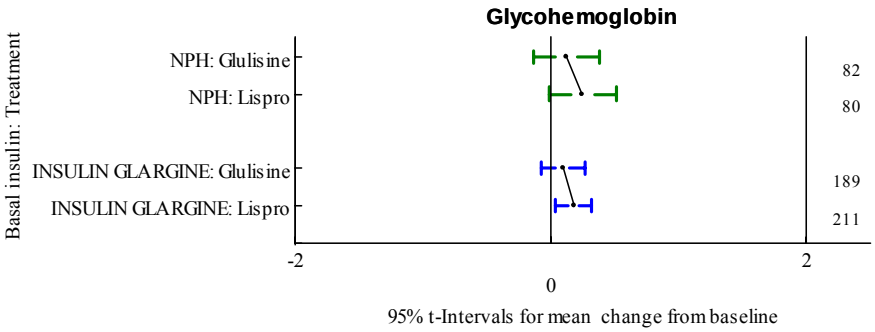


Figure 12 mean GHb change from baseline (95% CI) to endpoint by baseline GHb and treatment group

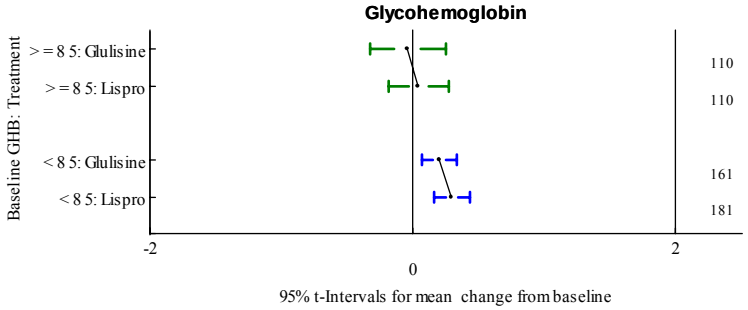
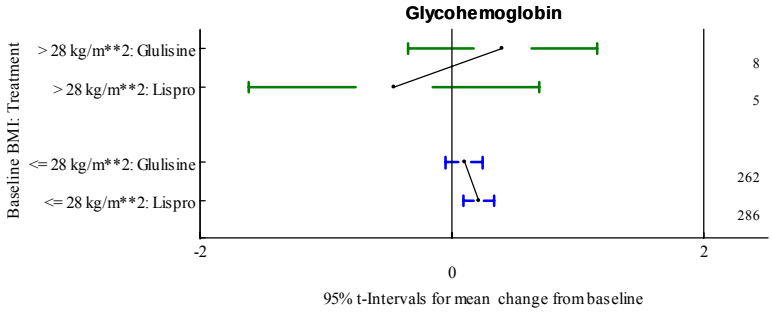


Figure 13 mean GHb change from baseline (95% CI) to endpoint by baseline BMI and treatment group



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