

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-629

STATISTICAL REVIEW(S)



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

STATISTICAL REVIEW AND EVALUATION
CLINICAL STUDIES

NDA/Serial Number: 21-629 / N000
Drug Name: Apidra (Insulin glulisine (rDNA human insulin analog) for injection, 100 IU/ml
Indication(s): Treatment of adult patients with diabetes mellitus for control of hyperglycemia
Applicant: Aventis
Date(s): June 18, 2003 submission
Review Priority: Standard

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Keywords: NDA review, Clinical studies

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1. EXECUTIVE SUMMARY

Insulin glulisine is a recombinant rapid-acting insulin analog. The submission included 3 completed efficacy study reports: 3001 and 3002 were for type 1 and type 2 patients with diabetes and 3004 in type 1 patients for timing of injection. Study 3005 in type 2 patients with diabetes was submitted as safety update without a study report, therefore, this reviewer will summarize the study results only with no detailed review. Basal insulin glargine was administered once daily in type 1 diabetes studies and NPH twice daily in type 2 diabetes studies with or without oral hypoglycemic agent (OHA). Tables 1 and 2 summarize the study results in the two patient populations.

Table 1 Study results in patients with type 1 diabetes

Study # duration	# of Centers country	Treatment n	GHb (%)			Daily insulin change from baseline		Severe Symptomatic Hypoglycemia	
			Baseline	Endpoint	Δ	Rapid	Basal	Total	Nocturnal
3001 26 wks	67 13 European, South Africa	glulisine: 331	7.60	7.46	-0.14	-1.07	+0.12	11%	6%
		lispro: 322	7.58	7.45	-0.14	-0.81	+1.82	9%	3%
		Total 653	0.00 (-0.09, 0.10)						
3004 12 wks	94 US, Canada, Australia	Premeal glulisine: 286	7.73	7.46	-0.26	-0.88	+0.99	8%	7%
		Postmeal glulisine: 276	7.70	7.58	-0.11	-0.47	+0.24	8%	6%
		Regular: 257	7.64	7.52	-0.13	+1.75	+0.65	10%	5%
		Total 819	Pre/reg -0.13 (-0.26, 0.01)						
			Post/reg +0.02 (-0.11, 0.16)						
		Pre/Post -0.15 (-0.29, -0.02)							

Table 2 Study results in patients with type 2 diabetes

Study	# of Centers country	Treatment n	GHb (%)			Daily insulin change from baseline		Severe Symptomatic Hypoglycemia	
			Baseline	Endpoint	Diff	Rapid	Basal	Total	Nocturnal
3002 26 wks	89 US, Canada, Australia)	glulisine: 404	7.57	7.11	-0.46	+3.5	+5.8	4%	2%(8/435)
		Regular: 403	7.50	7.22	-0.30	+5.2	+5.7	3%	1%(6/441)
			-0.16 (-0.26, -0.05)						
3005 26 wks	90 17 European, Argentina, Australia, Israel, NZ & S Africa	glulisine: 429	7.58	7.25	-0.32	+2.9	+4.5	1%	0.7%(3/448)
		Regular: 431	7.50	7.19	-0.35	+4.4	+4.7	3%	1% (5/442)
			+0.03 (-0.07, 0.13)						

1.1 Conclusions and Recommendations

In patients with type 1 diabetes, insulin glulisine was noninferior to insulin lispro when used with Lantus (glargine) as basal insulin in GHb change from baseline. For both treatment groups, the mean GHb reduction was 0.14% from a baseline of 7.6%. The upper limit of the 2-sided 95% confidence interval for treatment difference (0%) was 0.1% which is less than the prespecified 0.4% noninferiority margin.

In patients with type 2 diabetes, insulin glulisine was noninferior to regular insulin when used with NPH as basal insulin with or without OHA in GHb change from baseline. Mean GHb changes were -0.46% and -0.30% (Study 3002) and -0.32% and -0.35% (Study 3005) for glulisine and regular insulin, respectively. The upper limits of the 2-sided 95% confidence intervals, -0.05% and +0.13%, for the treatment differences of -0.16% and +0.03% for the 2 studies were within the 0.4% noninferiority margin. The proposed label stated “a larger reduction from baseline A1C was seen in the APIDRA group.” was based on the -0.05% upper limit in study 3002. The upper confidence limit, +0.13% in study 3005, however, was positive.

The 12-week study on timing of glulisine administration compared premeal, postmeal, and regular insulin. The GHb changes from baseline were -0.26%, -0.11% and -0.13% for the 3 treatment groups, respectively. The upper limits of the 98.33% confidence intervals were all within the noninferiority margin (0.4%): 0.01% for the -0.13% difference between premeal glulisine and regular insulin, 0.16% for the +0.02% difference between postmeal glulisine and regular insulin and -0.02% for the -0.15% difference between premeal and postmeal.

In conclusion, glulisine insulin was similar to the comparator insulin in GHb reduction in both type 1 and type 2 diabetes. GHb reductions for premeal or postmeal administration of glulisine were similar in type 1 diabetes patients, and both were similar to regular insulin.

2. INTRODUCTION

2.1 Overview

Apidra (insulin glulisine [rDNA origin]) is a rapid-acting human insulin analog for injection (100 IU/mL) at meals in treatment of adult patients with diabetes mellitus. The indication is for treatment of adult patients with diabetes mellitus for the control of hyperglycemia.

The submission included 3 multinational, multicenter, open-label, randomized, active controlled noninferiority trials. The 26-week study 3001 compared glulisine with insulin lispro in type 1 diabetes patients using insulin glargine as basal insulin. The 26-week study 3002 compared glulisine with regular insulin in type 2 diabetes patients using NPH as basal insulin. The 12-week, 3-arm study 3004 compared premeal and postmeal administration of glulisine to premeal regular human insulin to support a flexible dosing regimen in patients with type 1 diabetes using glargine as basal insulin. Table 1 from the sponsor displays the overview of the study design.

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Table 1 - Overview of completed controlled Phase III studies

	3001	3002	3004
Population	Type I DM adults	Type 2 DM adults	Type I DM adults
Region	Europe, South Africa	North America, Australia	North America, Australia
No. treatment arms	2	2	3
Glulisine dosing	s.c. injection 0–15 min before meals	s.c. injection 0–15 min before meals	s.c. injection 0–15 min before, or immediately after, meals
Comparator	Parallel group Active control (lispro)	Parallel group Active control (regular insulin)	Parallel group Active control (regular insulin)
Blinding	No	No	No
Randomization	Central call-in (1:1) Stratified by prestudy use of insulin glargine vs. other basal insulin	Central call-in (1:1) Stratified by prestudy use of OHAs	Central call-in (1:1:1) Stratified by prestudy use of insulin glargine vs. other basal insulin
Basal insulin	Insulin glargine once daily	NPH insulin twice daily	Insulin glargine once daily
Duration of treatment	26 weeks	26 weeks	12 weeks
Extension study	3011 (26 weeks)	3012 (26 weeks)	–
No. subjects randomized and treated	672	876	860

NPH: neutral protamine Hagedorn insulin; OHA: oral hypoglycemic agent.

2.2 Data Sources

Datasets are located in \\CDSESUB1\N21629\N_000\ of the EDR (electronic document room).

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

Study HMR1964A/3001 – Type 1 diabetes

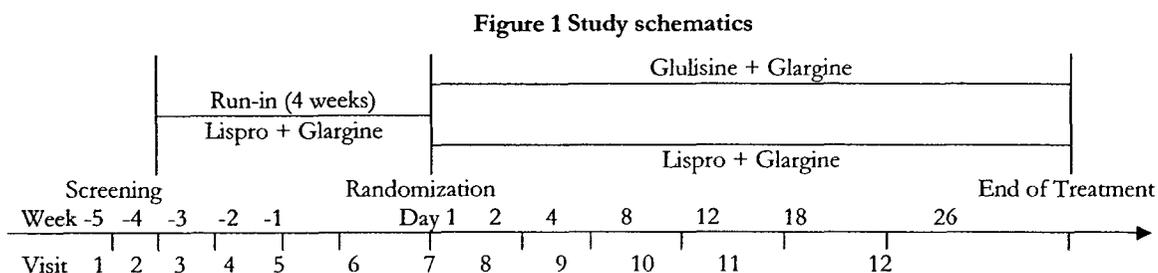
This 26-week, multinational, multicenter (13 European countries and South Africa), randomized, open, active controlled (insulin lispro) study compared glulisine with insulin lispro injected 15 minutes before meals subcutaneously in patients with type 1 diabetes using once daily insulin glargine as basal insulin.

The primary objective was to demonstrate noninferiority of glulisine compared to lispro in the GHb change from baseline to endpoint and to compare the safety of insulin glulisine with insulin lispro in patients with type 1 diabetes.

The study included patients ≥ 18 years of age (19 for Austria) with established type 1 diabetes, more than 1 year of continuous insulin treatment, $HbA_{1c} \geq 6\%$ and $\leq 11\%$ measured at visit 1 (amended from 6.5% to 11%), and a body mass index (BMI) < 35 kg/m².

The study consisted of a screening/run-in phase (4 weeks: lispro+glargine), and a 26-week treatment phase. The screening phase was about 1 week and the run-in phase was 4 weeks (Fig 1). Patients were to be randomized to study medication as soon as possible after reaching the end of the run-in phase, regardless of whether the patient had met the target BG values.

The 2 strata at randomization were the basal insulin use prior to study (glargine or other basal insulin). Pen injection devices were used for the administration of the rapid-acting and basal insulin preparation.



The dose of glargine was titrated based on the fasting (pre-breakfast) blood glucose (FBG) levels. The titration goal was a FBG of 5.0 to 6.7 mmol/L (90 to 120 mg/dL), while avoiding hypoglycemia.

The dose of glulisine or lispro was titrated based on the 2-hour postprandial BG level. The titration goal was a 2-hour postprandial BG of 6.7 to 8.9 mmol/L (120 to 160 mg/dL), while avoiding hypoglycemia.

The dosing schedule for the rapid-acting insulin, glulisine or lispro, was 0 to 15 minutes before a meal. The basal insulin glargine was to be administered once daily in the evening. For those patients who had participated in study HOE901/4007 prior to study HMR1964A/3001, glargine was allowed to be injected in the morning. Glulisine or lispro were not to be mixed with glargine.

Efficacy variables

The primary efficacy variable was GHb change from baseline to endpoint. Endpoint was defined as patient's last available measurement during the treatment phase plus a follow-up period of 14 days (GHb specific).

Study results

Patient disposition

A total of 67 centers in 13 European countries and South Africa participated in the study. The average number of patients randomized per center was 10 and the range was 3 to 30. A total of 772 patients entered the screening/run-in phase, of which 683 were randomized and received study medication (339 on glulisine and 333 on lispro). Ten (3%) of the glulisine and 13 (4%) of the lispro patients withdrew during the treatment phase. Table 3 displays patient disposition.

Table 3 Patient disposition – 3001, type 1 diabetes

Reason	Glulisine	Lispro	Total
Randomized	342	341	683
Randomized and treated	339	333	672
Withdrawn	10 (2.9%)	13 (3.9%)	23 (3.4%)
Adverse event	3 (0.9%)	3 (0.9%)	6 (0.9%)
Compliance	1 (0.3%)	0	1 (0.1%)
Patient request	4 (1.2%)	5 (1.5%)	9 (1.3%)
Lost to follow-up	1 (0.3%)	2 (0.6%)	3 (0.4%)
Protocol violation	0	2 (0.6%)	2 (0.3%)
Investigator discretion	1 (0.3%)	1 (0.3%)	2 (0.3%)

Demographic and baseline characteristics

58% of patients were male. The mean age was 38.5 in years. The mean BMI was 25 kg/m². The majority of patients were white (97%). Baseline GHb mean (Standard deviation) was 7.6% (0.93%). The 2 treatment groups were similar in these baseline characteristics.

Prior to study entry, 97% and 95% of patients used short-acting insulin and basal insulin, respectively. Short-acting insulin use was 24% regular and 76% rapid-acting analogue. Basal insulin use was 65% NPH, 21% glargine, and 10% Lente.

Primary efficacy results

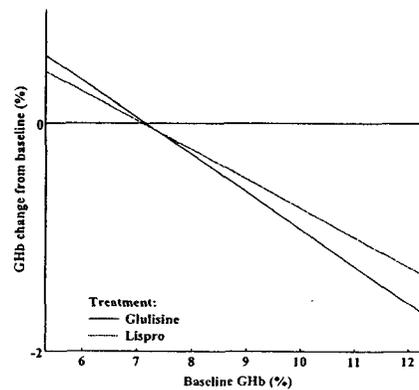
The primary analysis was to test the noninferiority of glulisine compared to lispro in GHb change from baseline to endpoint in the ITT population based on the predefined noninferiority margin of 0.4%. Table 4 displays the analysis results. Both treatment groups showed a GHb reduction from baseline. The difference between the mean changes was 0.00% with an upper limit of the 95%, 2-sided confidence interval of 0.10% that is within the 0.4% noninferiority margin.

Table 4 Primary efficacy analysis, GHb (%) change from baseline (ITT) – Study 3001

	Glulisine (n=331)	Lispro (n=322)
Baseline	7.60	7.58
Endpoint	7.46	7.45
Change from baseline	-0.14 (0.04)	-0.14 (0.04)
Glulisine minus Lispro (CI)	0.00 (-0.09, 0.10)	

Treatment-by-baseline GHb interaction was significant (p=0.06) at the 10% level usually applied to tests of interaction. Figure 2 displays the regressions of GHb change from baseline on baseline GHb for each treatment group. The interaction was qualitative in nature (cross over); however, this finding is not unexpected in noninferiority trials with a zero overall treatment difference for the regression lines must cross unless the slopes are exactly equal. Using analysis of variance without adjusting for baseline as covariate for sensitivity analysis, the results were similar to the Ancova.

Figure 2 Regression of GHb change from baseline on baseline GHb – 3001, type 1 diabetes



Severe symptomatic hypoglycemia

Severe symptomatic hypoglycemia was defined as an event with clinical symptoms that was considered to result from hypoglycemia in which the patient required the assistance of another person and one of the following:

- a BG level below 2.0 mmol/L (36 mg/dL) (amended from 2.8 mmol/L (50 mg/dL)).
- or the event was associated with prompt recovery after oral carbohydrate, intravenous glucose, or glucagons administration.

At the time the amendment was effective, 135 out of the total 683 patients were randomized.

Nocturnal hypoglycemia was defined as an event which occurred while the patient was asleep, between bedtime and before getting up in the morning. By definition, episodes of severe symptomatic nocturnal hypoglycemia were a subset of severe symptomatic hypoglycemic episodes.

The percentages of patients reporting at least one episode of severe symptomatic hypoglycemia were 11% (38/339) for glulisine group and 8.7% (29/333) for lispro group. Of the severe hypoglycemia, the severe nocturnal hypoglycemia percentages were 6.2% (21/339) and 3.0% (10/333), respectively for glulisine and lispro.

Table 5 displays the number and percent of the severe symptomatic hypoglycemia and severe nocturnal symptomatic hypoglycemia.

Table 5 Severe symptomatic hypoglycemia and severe nocturnal symptomatic hypoglycemia – 3001 type 1 diabetes

	Glulisine n=339		Lispro n=333	
	# of patients	# of episodes	# of patients	# of episodes
Severe symptomatic hypoglycemia				
Screening/run-in phase	13 (3.8%)	13	14 (4.2%)	16
Treatment phase	38 (11.2%)	61	29 (8.7%)	47
Nocturnal				
Screening/run-in phase	4 (1.2%)	4	7 (2.1%)	8
Treatment phase	21 (6.2%)	25	10 (3.0%)	15

The incidences of severe nocturnal symptomatic hypoglycemia were significantly different between glulisine and lispro. Note that more than half of the incidences of severe symptomatic hypoglycemia were nocturnal in the glulisine group and only 1/3 of the total number of incidences in the lispro group.

Study 3004 – Type 1 diabetes (12 weeks)

This 12-week study assessed the safety and efficacy of glulisine injection immediately after meals compared with injecting either regular insulin 30 to 45 minutes before meals, or glulisine 0 to 15 minutes before meals. In addition, premeal glulisine was compared with regular insulin.

The primary efficacy analysis was conducted using an analysis of covariance model with change in GHb from baseline to endpoint as the dependent variable, treatment and (pooled) center as fixed effects, and the baseline GHb value as a covariate. To adjust for multiplicity, the noninferiority of postmeal glulisine to premeal glulisine, postmeal glulisine to regular insulin and premeal glulisine to regular insulin was tested using 98.33% 2-sided confidence intervals.

Study results

A total of 860 (286 premeal glulisine, 296 postmeal glulisine, and 278 regular insulin) patients were randomized and treated at 93 centers in 3 countries, US, Canada, and Australia (added in Amendment 1) between September 22, 2001 and September 6, 2002. The mean age was 40.3 years, and 94.3% patients were white. A total of 797 patients completed the study (267 premeal glulisine, 278 postmeal glulisine, and 252 regular insulin). The number of withdrawals was 19, 18, and 26 for the 3 treatment groups, respectively.

The noninferiority of postmeal glulisine to premeal glulisine and to regular insulin as well as of premeal glulisine to regular insulin was demonstrated by the 98.33% CI values (Table 6).

Table 6 GHb(%) change from baseline analysis results – 3004 type 1 diabetes

	Premeal glulisine (n=268)	Postmeal glulisine (n=276)	Regular insulin (n=257)	LSM Difference (98.33% CI)
Mean baseline	7.73	7.70	7.64	
Mean endpoint	7.46	7.58	7.52	
LSM change from baseline	-0.26	-0.11	-0.13	
Postmeal glulisine vs. Regular				0.02(-0.11, 0.16)
Premeal glulisine vs. regular				-0.13 (-0.26, 0.01)
Postmeal vs. premeal glulisine				0.15 (0.02, 0.29)

The difference between postmeal and premeal glulisine in GHb change from baseline to endpoint was statistically significant (lower bound CI above zero). However, the 0.29% upper bound of the CI was within the 0.4% noninferiority margin; therefore, postmeal glulisine was not inferior to premeal glulisine according to the pre-defined criterion for assessing non-inferiority.

The treatment-by-stratum interaction was not significant (p=0.9), but the treatment-by-center or country interaction as well as the treatment-by-baseline interaction were significant (p≤0.1). Figure 3 displays the GHb change by baseline GHb and Figure 4 displays the median change of GHb by country. The interactions were primarily attributable to the US data which had 64% of patients (525/822). The greatest median GHb change was -0.4% for the premeal glulisine group in the US.

Figure 3 GHb change from baseline by baseline GHb (%) – Study 3004 type 1 diabetes

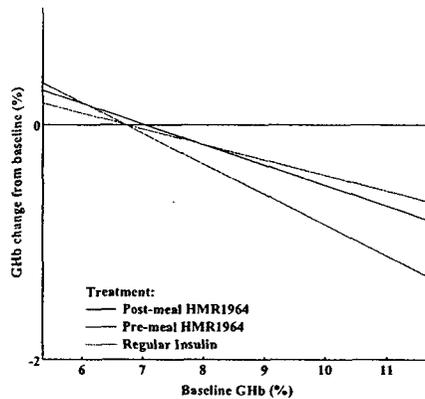
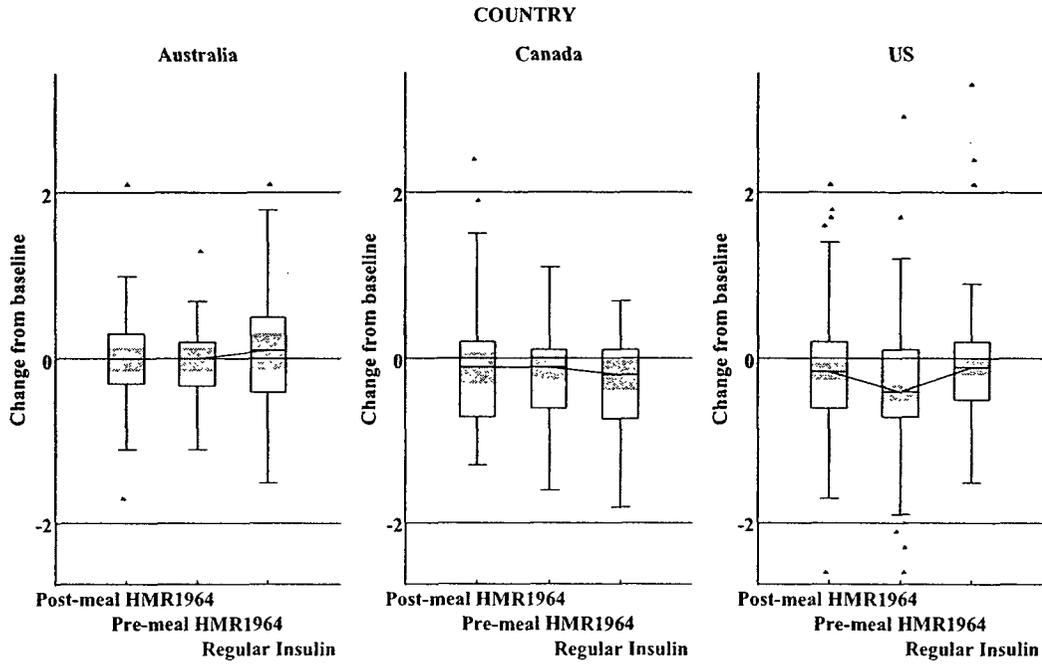


Figure 4 Median of GHb change from baseline by country – Study 3004 (type 1 diabetes)



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Study 3002 – Type 2 diabetes (26 weeks)

Study design

The study design was similar to study 3001 which had a 1 week screening period and a 4 week run-in period to confirm the inclusion criteria and to establish the standard insulin regimen (regular insulin at mealtime and twice daily NPH insulin). Patients randomized to glulisine began glulisine treatment at Day 1 of the treatment phase. Those patients who were randomized to regular insulin were to continue on regular insulin as in the run-in phase.

The study enrolled male and female type 2 diabetes patients ≥ 18 years of age, with more than 6 months on insulin treatment immediately prior to study entry, GHb from 6 to 11% measured at visit 1 (amended to 6.5 to 11%).

Study Results

The study was conducted in 89 centers: US (65), Canada (14), and Australia (10). Of the 1186 patients in the screening/run-in phase, 878 were randomized. Two patients randomized to glulisine treatment were not treated and 876 received study medication: 435 on glulisine and 441 on regular insulin. Approximately 93% (n=812) of the patients completed the 26-week study (407 on glulisine and 405 on regular insulin). Table 7 is a summary of patient disposition.

Table 7 Patient disposition – Study 3002 (Type 2 diabetes)

Reason for withdrawal	Glulisine	Regular insulin	Total
Randomized	437	441	878
Randomized but not treated	2 (0.5%)	0	2 (0.2%)
Randomized and treated	435	441	876
Completers	407 (93.6%)	405 (91.8%)	812 (92.7%)
Withdrawn in treatment phase	28 (6.4%)	36 (8.2%)	64 (7.3%)
Reason for withdrawal			
Patient died	1 (0.2%)	2 (0.5%)	3 (0.3%)
Adverse event	5 (1.1%)	6 (1.4%)	11 (1.3%)
Patient did not wish to continue	12 (2.8%)	13 (2.9%)	25 (2.9%)
Patient lost to follow-up	5 (1.1%)	6 (1.4%)	11 (1.3%)
Investigator discretion	4 (0.9%)	1 (0.2%)	5 (0.6%)
Lack of efficacy	0	1 (0.2%)	1 (0.1%)
Poor compliance	0	3 (0.3%)	3 (0.7%)
Protocol violation	0	2 (0.2%)	2 (0.5%)
Patient no longer meets criteria	0	1 (0.2%)	1 (0.1%)
Other reason	1 (0.2%)	1 (0.2%)	2 (0.2%)

Baseline demographic and characteristics

There were more female patients in the regular insulin group (50%) than in the glulisine group (44%). The mean age was 58.9 years in the glulisine group and 57.7 years in regular insulin patients. Treatment groups were similar in baseline BMI and race distribution. The mean BMI was 34.6 (kg/m²). 85% of patients were white, 11% black, 2% asian/oriental and 1.4% multiracial. The percent of patients using OHA were 58% at baseline and 58.4% at endpoint. Of the 508 patients on OHAs at randomization, 133 (26%) were on a sulfonylurea.

Primary efficacy analyses – GHb (%) change from baseline

The primary analysis on GHb change from baseline was conducted using an ANCOVA model with treatment, (pooled) center and stratum as fixed effects, and baseline GHb as a covariate. Table 8 displays the primary analysis. The upper 2-sided confidence interval was less than the noninferiority margin of 0.4%.

Table 8 GHb (%) change from baseline (ITT) – Study 3002 type 2 diabetes

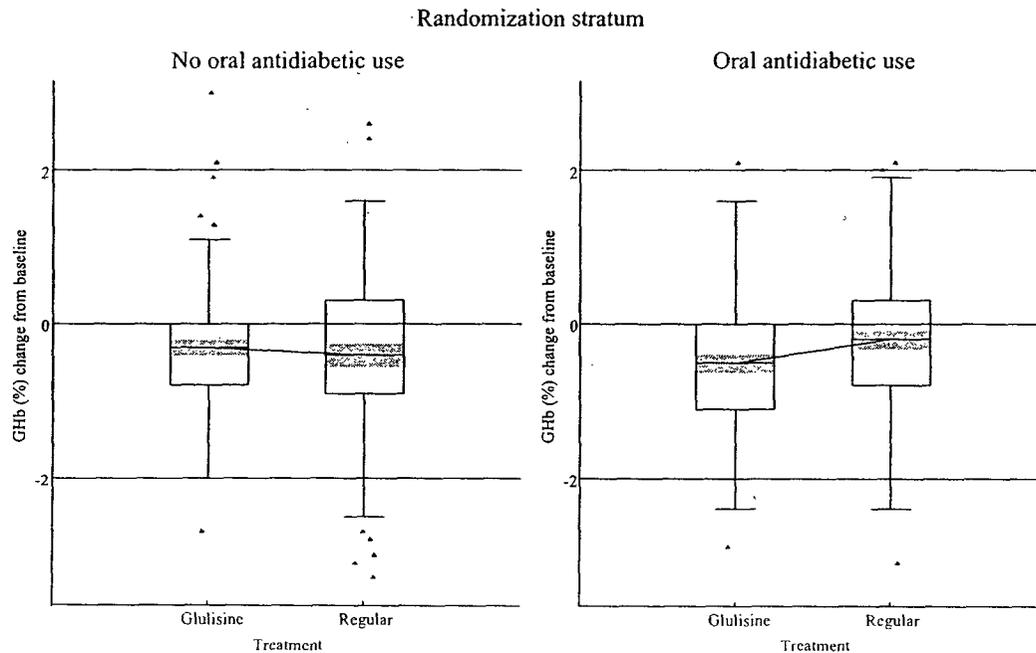
	Glulisine (n=404)	Lispro (n=403)
Mean baseline (SD)	7.57 (0.93)	7.50 (0.95)
Mean endpoint (SD)	7.11 (0.94)	7.22 (1.01)
LSM change from baseline (SE)	-0.46 (0.05)	-0.30 (0.05)
Glulisine minus Lispro (CI)	-0.16 (-0.26, -0.05)	

The treatment-by-oral agent use interaction was examined (p=0.14). The descriptive statistics of GHb (%) by treatment group and oral antidiabetic use are displayed in Table 9.

Table 9 Descriptive statistics of GHb (%) by stratum (ITT) – Study 3002 type 2 diabetes

	Glulisine		Regular	
	No oral (n=173)	Oral (n=231)	No oral (n=162)	Oral (n=241)
Mean baseline (SD)	7.50 (0.89)	7.62 (0.96)	7.59 (1.00)	7.45 (0.91)
Mean endpoint (SD)	7.12 (0.93)	7.10 (0.95)	7.22 (1.11)	7.21 (0.93)
LSM change from baseline (SE)	-0.38 (0.76)	-0.52 (0.80)	-0.37 (0.96)	-0.23 (0.85)
Median change from baseline	-0.30	-0.50	-0.40	-0.20
Treatment median	-0.40		-0.30	

Figure 5 Median GHb (%) change from baseline by stratum



4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race and Age

4.2 Other Special/Subgroup Populations

Gender

On the primary endpoint, the treatment-by-gender interaction was not significant for study 3001 ($p=0.4$), study 3004 ($p=0.7$). It was borderline for study 2 ($p=0.1$). However, the treatment-by-gender interaction for baseline GHb was significant ($p=0.02$). Table 10 displays the least squared mean and standard error of HbA_{1c} by gender for study 3002.

Table 10 Mean (SD) of baseline and change from baseline HbA_{1c} by gender – Study 3002 type 2 diabetes

	HMR1964			Regular Insulin		
	F (n=183)	M (n=234)	Difference	F (n=212)	M (n=209)	Difference
Baseline	7.48 (0.08)	7.46 (0.07)	-0.13 (0.09)	7.59 (0.07)	7.40 (0.07)	0.19 (0.09)
Change from baseline	-0.31 (0.06)	-0.49 (0.05)	0.18 (0.08)	-0.25 (0.06)	-0.27 (0.06)	0.02 (0.07)

Race

Treatment-by-race interaction for GHb change from baseline was not significant for Study 3001 ($p=0.88$) where 96% patients were White (634/657). For Study 3004 the interaction was significant ($p=0.07$) based on subgroups White (94%) and non-White. Table 11 displays the least square means for GHb. The treatment-by-race interaction was attributable to the difference in response between the post meal and pre meal HMR1964 groups.

Table 11 Least square means (SE) by race – Study 3004

HbA _{1c}	Postmeal HMR1964			Premeal HMR1964			Regular Insulin		
	Non White (n=14)	White (n=266)	Diff	Non White (n=15)	White (n=261)	Diff	non White (n=17)	White (n=249)	Diff
Baseline	7.54(0.25)	7.72(0.06)	-0.18(0.25)	8.19(0.24)	7.71(0.06)	0.48(0.24)	7.84(0.22)	7.63(0.06)	0.21(0.23)
Change	0.00 (0.17)	-0.08 (0.04)	0.09 (0.17)	-0.66 (0.17)	-0.19 (0.04)	-0.47 (0.17)	-0.27(0.16)	-0.08(0.04)	-0.19(0.16)

Study 3002 had 15% non White patients (127/838). The treatment-by-race interaction was not significant ($p=0.4$).

Age group

No treatment-by-age group (65 or above vs. less than 65) interaction was detected for the 2 studies (2 & 5) in patients with type 2 diabetes which had 37% and 47%, respectively, of patients 65 years of age or above ($p=0.7$). In the 2 studies in patients with type 1 diabetes only 2% of patients were ≥ 65 years in age, therefore; no treatment-by-age group interaction was conducted due to lack of power.

5. SUMMARY AND CONCLUSIONS

5.2 Conclusions and Recommendations

Insulin glulisine was noninferior to lispro in GHb (%) change from baseline in patients with type 1 diabetes. Insulin glulisine was noninferior to regular insulin in GHb change from baseline in patients with type 2 diabetes. The mean GHb at baseline was 7.6% and the reduction from baseline was 0.14% in the type 1 patient study. The mean GHb at baseline was 7.6% for glulisine and 7.5% for regular insulin and the reduction from baseline was 0.30% for regular and 0.46% for glulisine.

APPENDICES

For financial disclosure, one of the Medical Officer requested examination of patients at the _____ site (3%). The Descriptive statistics for GHb in the subgroup and in the ITT population are displayed in Tables 12 and 13 for studies 3002 and 3004, respectively.

Table 12 Descriptive statistics of GHb – Study 3002 type 2 diabetes

					ITT		
		n	mean	S.D.	n	mean	S.D.
HMR1964	Baseline Value	12	7.19	0.89	417	7.58	0.94
	Endpoint Value		7.05	0.96		7.13	0.95
	Change From Baseline		-0.14	0.83		-0.45	0.78
Regular Insulin	Baseline Value	14	7.63	0.85	421	7.52	0.96
	Endpoint Value		7.51	0.95		7.25	1.02
	Change From Baseline		-0.12	0.69		-0.27	0.88

Table 13 Descriptive statistics of GHb – Study 3004 type 1 diabetes

					ITT		
		n	mean	S.D.	n	mean	S.D.
Post meal HMR1964	Baseline Value	5	7.56	0.55	280	7.70	0.91
	Endpoint Value		8.28	0.97		7.59	0.99
	Change From Baseline		0.72	0.73		-0.12	0.67
Pre meal HMR 1964	Baseline Value	5	8.40	0.77	276	7.73	0.91
	Endpoint Value		8.00	1.08		7.46	0.92
	Change From Baseline		-0.40	0.48		-0.26	0.67
Regular Insulin	Baseline Value	6	7.45	0.44	266	7.63	0.92
	Endpoint Value		7.20	0.78		7.51	1.02
	Change From Baseline		-0.25	0.58		-0.12	0.65

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/s/

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