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Comparable Efficacy and Safety of Insulin Glulisine and Insulin Lispro When Given as Part of a Basal–Bolus Insulin Regimen in a 26-Week Trial in Pediatric Patients with Type 1 Diabetes

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Abstract

Background: We compared the efficacy and safety of insulin glulisine with insulin lispro as part of a basal–bolus regimen in children and adolescents with type 1 diabetes.

Methods: Overall, 572 children and adolescents (4–17 years old) using insulin glargine or neutral protamine Hagedorn insulin as basal insulin were enrolled in a 26-week, multicenter, open, centrally randomized, parallel-group, noninferiority study. Subjects were randomized to receive glulisine ($n = 277$) or lispro ($n = 295$) 0–15 min premeal.

Results: Baseline-to-endpoint hemoglobin A1c changes were similar between the two insulins: adjusted mean change (glulisine vs. lispro), 0.10% versus 0.16%; between-treatment difference (glulisine–lispro), &minsu;0.06, 95% confidence interval (−0.24; 0.12); and prespecified noninferiority margin, 0.4%. Overall, for all age groups together, the percentage of patients achieving American Diabetes Association age-specific A1c targets at endpoint was significantly higher ($P = 0.039$) with glulisine (38.4%) versus lispro (32.0%). From Month 4 to endpoint, both "all" and "severe" symptomatic hypoglycemia rates were similar (3.10 vs. 2.91 and 0.06 vs. 0.07 events/patient-month, respectively). Frequency and type of adverse events, serious adverse events, or hypoglycemia reported as serious adverse events were similar between both groups.

Conclusions: Glulisine was as effective as lispro in baseline-to-endpoint A1c change, and both treatments were similarly well tolerated.

Introduction

Basal–bolus therapy has become the treatment of choice in all age groups of pediatric patients with type 1 diabetes.[1] The International Society for Pediatric and Adolescent Diabetes Clinical Practice Consensus Guidelines recommends that children/adolescents should attain a target hemoglobin A1c of less than 7.5%, but "each child should have their targets individually determined with the goal of achieving a value as close to normal as possible while avoiding severe hypoglycemia as well as frequent mild-to-moderate hypoglycemia."[2]

Therefore, glycemic targets must be modified owing to the risk of hypoglycemia in children. Young children (under 6 or 7 years of age) often have "hypoglycemic unawareness" owing to a lack of cognitive ability to acknowledge and respond to hypoglycemic symptoms.[3]

Rapid-acting insulin analog (RAIA) products have improved physiochemical properties, resulting in a higher rate and extension of absorption from subcutaneous tissue into the bloodstream compared with regular human insulin (RHI) and, thus, can be administered much closer to mealtimes.[4–6] Cohort studies in pediatric patients have demonstrated significant improvements in average A1c levels across all age groups following the introduction of the RAIA insulin lispro, although achieving target A1c levels still remains problematic in adolescent patients (13–18 years old).[7] Other studies show a

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reduced incidence of nocturnal hypoglycemia using pre-supper lispro.[8,9] In adult type 1 diabetes patients, basal–bolus therapy using RAIAs offers improved glycemic control versus RHI.[10–12]

Insulin glulisine differs from RHI by the replacement of asparagine with lysine at position 3 and of lysine by glutamic acid at position 29 on the B-chain of the human insulin molecule.[13] These substitutions render mono- and dimeric glulisine molecules stable in the drug formulation solution and, therefore, more readily absorbable than other insulin analogs.[6,14] By contrast, lispro has an inversion of the amino acids proline and lysine at positions 28 and 29,[4,15,16] which renders lispro monomers unstable. As a result, zinc is added to the lispro formulation in order to promote self-association into hexamers, which increases stability but offsets some of the gain in rapidity of absorption compared with RHI. This difference in the formulations explains the more rapid absorption and action of glulisine in comparison with lispro observed in lean-to-obese subjects.[13,17]

In adult type 1 diabetes patients, glulisine and lispro have comparable efficacy in terms of glycemic control and rates of symptomatic hypoglycemia when administered as a basal–bolus regimen with insulin glargine (glargine).[18] However, information evaluating the two rapid-acting insulins in a pediatric population is limited. This noninferiority study of insulin therapy, one of the largest, worldwide, in children and adolescents with type 1 diabetes achieving physiological targets, was performed to compare the efficacy and safety of glulisine with lispro as part of a basal–bolus insulin regimen and to establish noninferiority of glulisine versus lispro in terms of A1c.

Research Design and Methods

Study population

Subjects were recruited between April 2005 and May 2006 from 65 international sites, including 35 in Europe (Belgium, Denmark, Finland, France, Germany, Hungary, The Netherlands, Norway, Romania, Russia, Sweden, and Switzerland), 18 in the United States, five in both Argentina and South Africa, and two in Australia (see Appendix for participating investigators). Inclusion criteria were as follows: girls or boys, 4–17 years old, with a diagnosis of type 1 diabetes of at least 1 year in duration prior to screening; stable insulin regimen using either neutral protamine Hagedorn insulin (NPH) or glargine as basal insulin at the time of screening, with uninterrupted insulin therapy for at least 1 year prior to screening; A1c 6.0–11.0% at screening; and participants able and willing to complete a subject diary.

Exclusion criteria included the following: diabetes other than type 1; the presence of active proliferative diabetic retinopathy in the 6 months prior to screening; a history of primary seizure disorders or of hypoglycemia unawareness; and prior treatment with any antidiabetes oral agent at any time from diagnosis of diabetes or with pump therapy during the 2 months immediately prior to screening.

Study design and treatment

This was a multicenter, multinational, open-label, stratified, parallel-group, controlled, 1:1 randomized study, with a run-in phase of 4 weeks, a treatment phase of 26 weeks, and a follow-up period of 24 h. The study used a centralized, computerized telephone randomization schedule and was stratified within each site according to the type of basal insulin used at the time of randomization (i.e., glargine or NPH).

The study was conducted in accordance with the Declaration of Helsinki and was in compliance with the local laws and regulations, as well as any applicable guidelines of the countries where the study was performed. All study procedures were reviewed and approved by independent ethics committees/institutional review boards at each participating site. Informed consent from a legally authorized representative (or representatives) was obtained in writing at study enrollment prior to any study-related activities.

During the run-in phase, subjects were treated with subcutaneous lispro as RAIA (0–15 min before meals) in combination with either NPH or glargine as basal insulin. The number of daily RAIA injections (at least two daily injections determined by the investigator) was established during the run-in phase and remained unaltered for the study duration unless deemed necessary by the investigator for safety reasons. Likewise, the basal insulin dose regimen was established during the run-in phase. NPH was administered twice daily (morning and evening) and glargine once daily in the evening (either dinner or bedtime).

After the run-in phase, subjects were centrally randomized to receive either subcutaneous glulisine (0–15 min before meals) or to remain on lispro while continuing their respective basal insulin regimens. The starting dose of glulisine for each subject was equivalent to their previous lispro dose. Blood glucose (BG) targets were adapted to the age of the subjects (under 8 years of age or 8 years and over; Table 1); doses of rapid-acting and basal insulins were individually titrated at the investigator's discretion and were based on self-monitored BG.

Statistical analysis

Analysis sets. The primary analysis population was the modified intent-to-treat (mITT) population, comprising all randomized subjects who received one or more doses of study medication and who had the baseline evaluation and at least one on-treatment efficacy evaluation. Subjects included in the safety population had received one or more doses of study medication.

Primary efficacy endpoint. The study was designed to show noninferiority of glulisine to lispro in terms of A1c

Table 1. Blood Glucose Titration Targets

	Plasma-referenced blood glucose meters	*Blood-referenced blood glucose meters*
Fasting or premeal blood glucose (mg/dL)		
<8 years old	106–150	100–140
≥8 years old	95–150	90–140
2-h postprandial blood glucose (mg/dL)		
<8 years old	128–194	120–180
≥8 years old	106–172	100–160

change from baseline to endpoint with a prespecified noninferiority margin of 0.4%. The same margin was used in glulisine Phase III studies in adult diabetes patients,[12,18–20] as accepted by the European Medicines Agency and the Food and Drug Administration. To assess noninferiority, the two-sided 95% confidence interval (CI) was computed for the adjusted mean difference between groups from an analysis of covariance model, with treatment, type of basal insulin at randomization, and (pooled) center as fixed effects, and baseline A1c as covariate. Centers within each country with fewer than three evaluable subjects per treatment group (per protocol) were pooled, adding the next smallest center until the pooled center had at least three subjects per treatment group.

A sample size of 446 subjects (223 in each group) was needed to ensure that the upper bound of the two-sided 95% CI for the adjusted mean difference in A1c between treatments would not exceed 0.4%, with 90% power for a true difference between groups of 0.0%. Considering a nonevaluable rate of 20% owing to a major protocol violation and/or early withdrawal, in total, 560 subjects (280 in each group) were required to be randomized in order to have 446 subjects (223 per group) who were evaluable for the per-protocol analysis.

Secondary efficacy endpoints. As a supplementary analysis of the primary efficacy endpoint, the proportions of subjects who reached target A1c categories were compared between the treatment groups. Other secondary objectives compared glulisine with lispro for the change in A1c from baseline at Weeks 12 and 26: three-point self-monitoring of BG (fasting, before the main meal, and 2 h post-main meal); and insulin doses. Symptomatic hypoglycemia (all, severe, nocturnal, and severe nocturnal episodes) was measured from study start and analyzed in the safety population by time period, focusing on the period "from Month 4 to treatment end," at which time subjects were fully familiarized with the study. A hypoglycemic event was considered severe if the subject required unexpected assistance by a third party, owing to acute neurological impairment as a direct result of the episode, and was associated with either BG lower than 36 mg/dL or prompt recovery following oral carbohydrate, intravenous glucose, or glucagon administration. Secondary efficacy analyses were two-sided and conducted at a significance level of $\alpha = 5\%$. A1c at Week 12 and Week 26, BG values, and insulin doses were analyzed using the same method as described above for the primary efficacy variable. Secondary outcomes were analyzed for the full population and for subgroups of patients according to age group in order to overcome potential effects of age on study outcomes.

Frequency of subjects reaching categories of A1c were compared using a logistic regression model with treatment and (pooled) center as fixed effects and baseline A1c as covariate. Descriptive statistics were provided for the rate of symptomatic hypoglycemia, and groups were compared using an analysis of variance model with treatment and (pooled) center effects applied on the ranked rates. The proportions of subjects with treatment-emergent adverse events (TEAEs) that occurred or worsened during the treatment period and with one or more episodes of serious symptomatic hypoglycemic events were tabulated for each group.

Safety

Safety analyses included the incidence of TEAEs and the monitoring of routine laboratory tests and insulin antibodies. Symptomatic hypoglycemia was classified as a serious adverse event if the event was associated with at least one of the following: (1) loss of consciousness requiring administration of a parenteral countermeasure by a third party; (2) seizure; (3) visit to the Emergency Department or admission to the hospital for treatment; or (4) in the opinion of the investigator, the event met any criterion normally used to define an adverse event as serious.

Results

Study population

Overall, 572 patients were randomized and treated; two subjects given glulisine were excluded from the efficacy analyses performed on the mITT population because post-baseline values for both A1c and BG profile were unavailable. Therefore, the mITT population consisted of 570 subjects (275 treated with glulisine and 295 treated with lispro) (Fig. 1). Of these 570 subjects, eight subjects were under 6 years of age, 240 were between 6 and 12 years old, and 314 were between 13 and 17 years old.

Overall, the mean age was 12.5 years, and demographic and baseline characteristics were comparable between both groups (Table 2). At randomization (baseline), the distribution of subjects administering NPH or glargine as basal insulin was similar between the glulisine and lispro groups: NPH: 30.3% versus 27.1%, respectively; and glargine: 69.7% versus 72.9%.

Efficacy

Changes in A1c from baseline to endpoint. Both groups exhibited similar A1c levels at baseline. The adjusted mean change (mean ± SD) from baseline at endpoint in the mITT population was $+0.10 \pm 0.08\%$ in the glulisine group and $+0.16 \pm 0.07\%$ in the lispro group. The difference in the adjusted means for the change from baseline in A1c between the treatments was equal to -0.06% (95% CI, -0.24, 0.12), confirming noninferiority of glulisine versus lispro based on the upper bound of this 95% CI being below the prespecified noninferiority margin of 0.4%. When A1c was analyzed in subgroups based on age, sex, race, diabetes duration, basal insulin, and baseline A1c, the results in each subgroup were consistent with those seen in the overall population (data not shown).

Changes in A1c at Weeks 12 and 26. Similar effects on A1c levels were reported in both groups after 12 and 26 weeks. For the glulisine and lispro groups, the adjusted mean change (mean ± SD) from baseline to Week 12 was $-0.01 \pm 0.07\%$ and $-0.03 \pm 0.06\%$, and that from baseline to Week 26 was $0.08 \pm 0.08\%$ and $0.17 \pm 0.08\%$, respectively.

Changes in A1c according to age group. For all age groups together, the percentage of subjects achieving the American Diabetes Association (ADA)-recommended A1c target (7.5–8.5% for children under 6 years of age, <8% for children 6–12 years old, and <7.5% for children/adolescents over 12 years of age) was significantly higher ($P = 0.039$) with

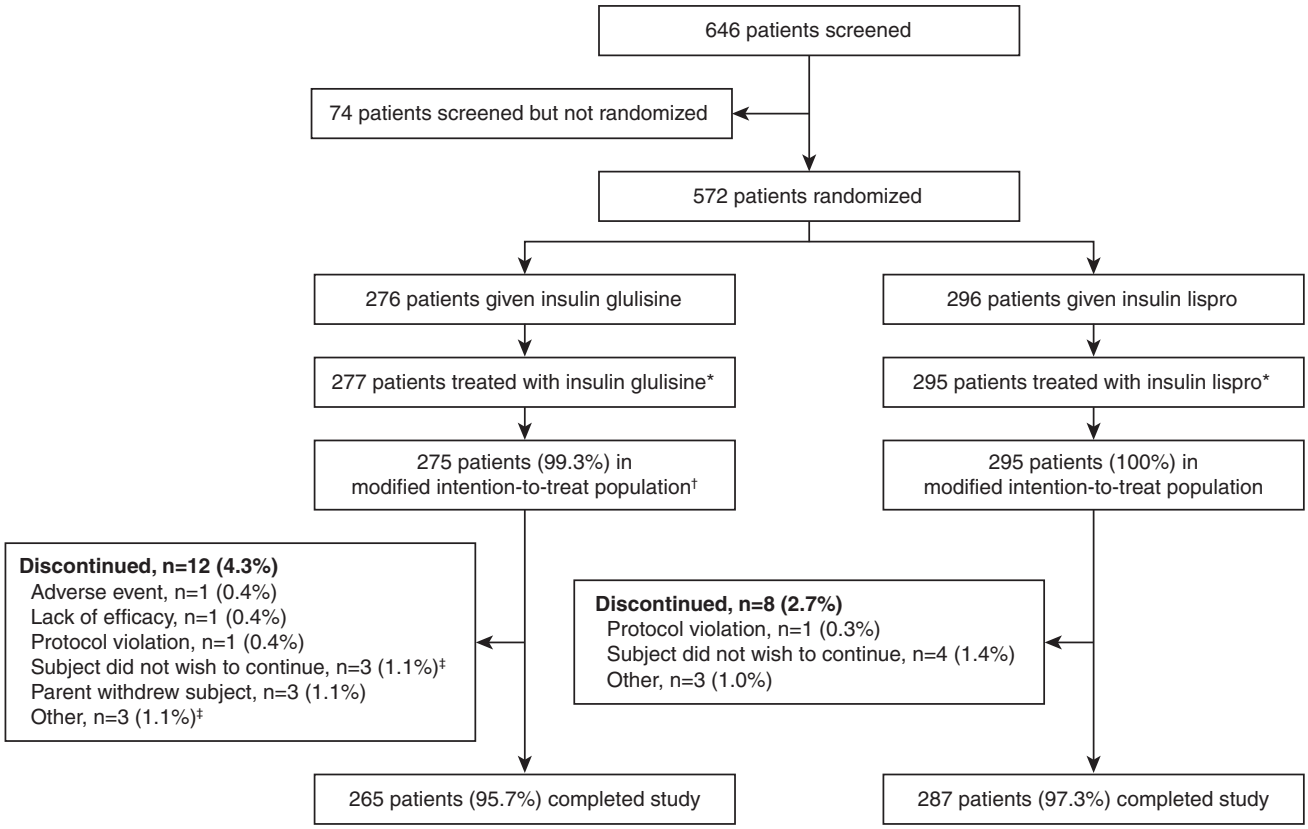

FIG. 1. Summary of subject disposition. *One subject was randomized to insulin lispro but was treated with insulin glulisine. †Two subjects were excluded from the efficacy analysis performed on the modified intent-to-treat population owing to missing endpoint/on-treatment A1c measurements. ‡These decisions were not made because of an adverse event.

glulisine (38.4%) than with lispro (32.0%) (Table 3). This difference was most pronounced in adolescents (13–17 years): 31.1% of subjects receiving glulisine achieved their ADA age-specific A1c target of less than 7.5% at endpoint versus 21.1% of those receiving lispro ($P = 0.025$).

Self-monitored BG (three-point profile). At baseline, the mean BG profiles (±SD) were comparable for all three time points in both groups. At endpoint, only the mean pre-breakfast BG was significantly lower in the glulisine group (Table 4).

Table 2. Subject Demographics and Baseline Characteristics

	Insulin glulisine (n = *277*)	*Insulin lispro* (n = *295*)
Gender		
Female [*n* (%)]	131 (47.3)	156 (52.9)
Male [*n* (%)]	146 (52.7)	139 (47.1)
Age (years)	12.5 (3.05)	12.6 (2.92)
Subjects by age group		
<8 years [*n* (%)]	22 (7.9)	19 (6.4)
≥8 years and <12 years [*n* (%)]	78 (28.2)	71 (24.1)
≥12 years [*n* (%)]	177 (63.9)	205 (69.5)
BMI (kg/m^2)	20.8 (3.4)	20.5 (3.3)
Time since diagnosis of diabetes (years)	5.31 (3.61)	5.16 (3.22)
A1c at baseline (%)	8.20 (1.04)	8.17 (1.02)
Basal insulin at randomization		
NPH insulin [*n* (%)]	84 (30.3)	80 (27.1)
Insulin glargine [*n* (%)]	193 (69.7)	215 (72.9)
Insulin dose at baseline		
Total daily insulin dose [U (U/kg)]*	51.30 (23.75) [0.98 (0.02)]	50.86 (22.07) [0.98 (0.02)]
Daily basal insulin dose [U (U/kg)]*	27.20 (13.96) [0.52 (0.01)]	26.55 (14.14) [0.51 (0.01)]
Daily prandial insulin dose [U (U/kg)]*	24.26 (14.64) [0.47 (0.01)]	24.34 (14.72) [0.48 (0.01)]

Data are mean (SD) values, except where indicated and for daily insulin dose per body weight (*), which are adjusted mean (SE) values. A1c, hemoglobin A1c; BMI, body mass index; NPH, neutral protamine Hagedorn.

Table 3. Number of Subjects Reaching American Diabetes Association–Recommended Age-Specific Hemoglobin A1c Categories

Age class and A1c category, time point	*Insulin glulisine* n/N	%	*Insulin lispro* n/N	%	P *value for difference between treatment at endpoint*
Subjects <6 years old with A1c >7.5 and <8.5%					
Baseline	1/3	33.3	2/5	40.0	—
Endpoint	1/3	33.3	2/5	40.0	
Subjects 6–12 years old with A1c <8.0%					
Baseline	53/120	44.2	55/120	45.8	
Endpoint	57/120	47.5	56/120	46.7	0.505
Subjects 13–17 years old with A1c <7.5%					
Baseline	36/148	24.3	40/166	24.1	
Endpoint	46/148	31.1	35/166	21.1	0.025
All ages combined with A1c in the targeted interval					
Baseline	90/271	33.2	97/291	33.3	
Endpoint	104/271	38.4	93/291	32.0	0.039

A1c, hemoglobin A1c; n = number of subjects reaching American Diabetes Association–recommended age-specific hemoglobin A1c categories; N = total number of subjects in the specified age class.

Insulin dose. Most subjects had three to four bolus insulin injections at baseline (glulisine [58.0%] and lispro [60.5%]), which remained stable throughout the study (Table 5). Mean daily total, basal, and prandial insulin doses were comparable in both groups at baseline (Table 2).

At study end, the daily total dose of insulin for the glulisine and lispro groups was 53.85 ± 24.09 U (1.00 ± 0.32 U/kg) and 55.80 ± 23.70 U (1.04 ± 0.31 U/kg), respectively. From baseline, both groups showed an increase in daily total insulin doses, which was greater in the lispro group ($+4.91 \pm 0.65$ and $+2.53 \pm 0.68$ U/day; $P = 0.0074$ [$+0.05 \pm 0.01$ and $+0.01 \pm 0.01$ U/kg; $P = 0.0045$] for the glulisine and lispro groups, respectively) (details on basal and prandial insulin doses are in Fig. 2).

Symptomatic hypoglycemia. No relevant differences between the two treatment arms were reported for the monthly rate per patient (events per patient-month) of all (3.10 ± 4.33 vs. 2.91 ± 4.35), severe (0.06 ± 0.24 vs. 0.07 ± 0.27), nocturnal (0.21 ± 0.50 vs. 0.20 ± 0.80), or severe nocturnal symptomatic hypoglycemia (0.01 ± 0.07 vs. 0.01 ± 0.09) from Month 4 to treatment end for glulisine and lispro, respectively. Analysis of the safety population for all categories of symptomatic hypoglycemia in subgroups of subjects based on age, duration of diabetes, basal insulin, and baseline A1c yielded results that were consistent with those seen in the population as a whole (data not shown).

Safety

The frequency and type of TEAEs, serious TEAEs, or hypoglycemia reported as serious TEAEs were similar between both groups. Withdrawal due to a TEAE occurred in only one (0.4%) subject treated with glulisine because of a non-serious TEAE of injection site swelling. Similar percentages of subjects in the two groups had TEAEs that were possibly related to medication (9.0 vs. 9.5% for glulisine vs. lispro). Among them, the most common were related to the underlying disease or to the treatment of the disease, injection site hypertrophy, hypoglycemic seizure, hypoglycemia not otherwise specified, and hypoglycemic coma. Similar proportions of subjects in the two groups experienced these possibly related TEAEs.

Discussion

This worldwide study in children and adolescents with type 1 diabetes shows that glulisine is noninferior to lispro in terms of A1c change. Despite equipotency to RHI for both analogs, as shown in previous pharmacokinetic/pharmacodynamic studies,[21] the total insulin dose in the glulisine group was significantly lower compared with the lispro group. This

Table 4. Change in Self-Monitored Three-Point Profile Blood Glucose Values in the Modified Intent-to-Treat Population

Time point	*Insulin glulisine* n	*Adjusted mean (SE)*	*Insulin lispro* n	*Adjusted mean (SE)*	P *value for difference between treatment*
Baseline (mg/dL)					
Pre-breakfast	272	171.0 (3.7)	292	172.1 (3.6)	0.810
Before main meal	272	184.9 (4.8)	292	186.5 (4.6)	0.782
2-h post-main meal	259	159.8 (4.3)	285	163.6 (4.1)	0.505
Endpoint (mg/dL)					
Pre-breakfast	272	158.0 (3.8)	292	170.5 (3.7)	0.014
Before main meal	272	175.9 (4.4)	292	176.6 (4.2)	0.894
2-h post-main meal	259	165.8 (4.0)	285	162.9 (3.8)	0.564

Table 5. Average Number of Daily Rapid-Acting Insulin Injections

	Number (%) of subjects	
	Glulisine [n (%)]	*Lispro* [n (%)]
Baseline		
Total number of evaluable subjects	274 (100)	294 (100)
Number of injections		
1 to <2 daily	3 (1.1)	5 (1.7)
2 to <3 daily	69 (25.2)	68 (23.1)
3 to <4 daily	159 (58.0)	178 (60.5)
4 to <5 daily	38 (13.9)	35 (11.9)
≤5 daily	5 (1.8)	8 (2.7)
Endpoint		
Total number of evaluable subjects	274 (100)	294 (100)
Number of injections		
1 to <2 daily	6 (2.2)	5 (1.7)
2 to <3 daily	57 (20.8)	53 (18.0)
3 to <4 daily	168 (61.3)	186 (63.3)
4 to <5 daily	35 (12.8)	41 (13.9)
≤5 daily	8 (2.9)	9 (3.1)

lower insulin requirement with glulisine may be linked to the specific glulisine features and may also explain the lower pre-breakfast (fasting) blood glucose values at endpoint in the glulisine group.

Despite the improvements in the number of patients reaching their A1c targets, there was a very modest increase in baseline to endpoint A1c values in both groups. This is not entirely unexpected, as comparable trials in children and adolescents show similar increases as a result of lispro treatment, and the results of the present study are consistent with these trials.[8,22–24] These findings are suggestive of the importance of factors other than insulin, such as patient attitude and lifestyle, in achieving and maintaining good glycemic control.

Glulisine was well tolerated and showed a safety profile similar to that of lispro, with hypoglycemia and injection site reactions being the most commonly reported TEAEs. This trial extends the findings of a previous study comparing glulisine with RHI in children and adolescents with type 1 diabetes,[25] which confirmed that the rapid onset of glulisine observed in adults[6,26–28] is also seen in the pediatric population.

Pharmacokinetic studies comparing glulisine and lispro in lean-to-obese subjects without diabetes showed comparable glucodynamic efficacy between both insulins.[13,17] However, the time to action of lispro became more attenuated with increasing body mass index and skin thickness.[13] By contrast, glulisine had a consistently faster and earlier onset of action than lispro across a range of body mass index.[13,17] As obesity rates in children with type 1 diabetes continue to increase,[29] this observation could be a potential advantage for the use of glulisine in such children.

A potential limitation of this study is that changes in insulin doses were not adjusted for sex, age, or pubertal status, which are factors known to affect insulin requirements because of differences in metabolic requirements.[30,31] Also, patients were using one of two different basal insulins (NPH or glargine), which limits extrapolation of the results. However, the authors felt that this was appropriate because both insulins are commonly used in the age group of patients in this study, and insulin glargine is only recommended for patients 6 years of age and over. Very few patients under 6 years of age participated in this study, which precluded meaningful analysis of those under 6 years of age.

In conclusion, the results of the present study demonstrate that glulisine is well tolerated and is as effective as lispro in the

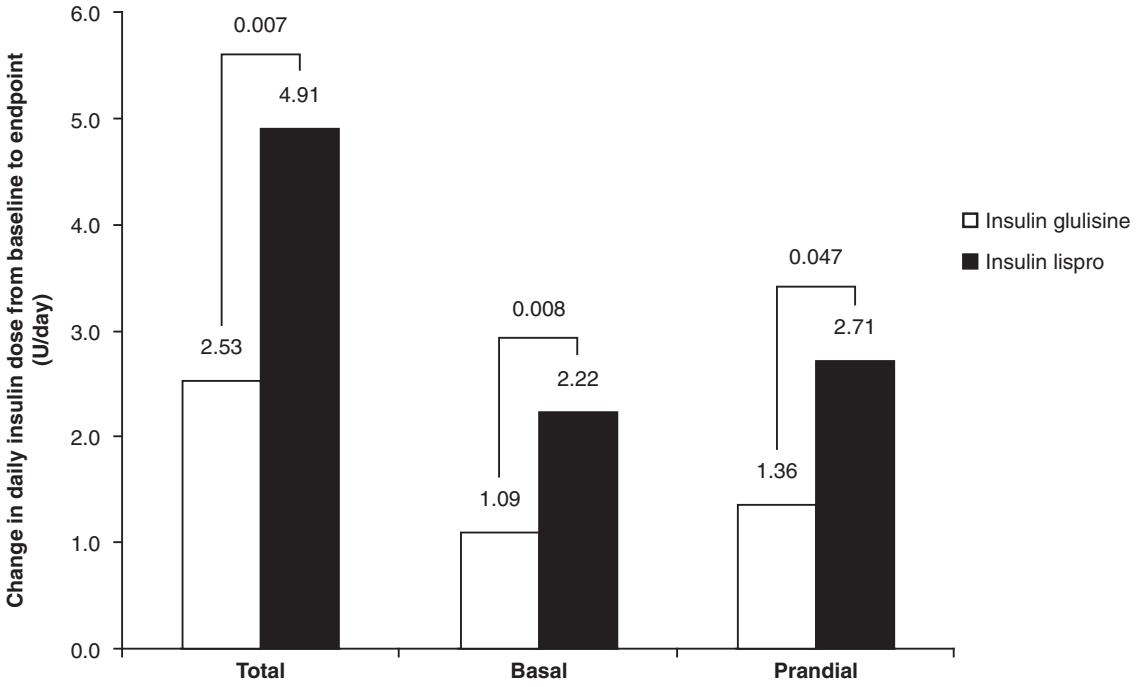

FIG. 2. Difference between the baseline to endpoint change in daily insulin dose for the treatment groups. Data are mean change (95% confidence interval).

treatment of type 1 diabetes in children and adolescents. Moreover, a greater proportion of adolescents 13–17 years of age achieved ADA-recommended A1c targets with glulisine than with lispro.

Appendix

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