A Randomized Trial Comparing Continuous Subcutaneous Insulin Infusion of Insulin Aspart Versus Insulin Lispro in Children and Adolescents With Type 1 Diabetes

STUART A. WEINZIMER, MD[1]
CHRISTINE TERNAND, MD[2]
CAMPBELL HOWARD, MD[3]
CHENG-TAO CHANG, PHD[3]
DOROTHY J. BECKER, MB, BCH[4]
LORI M.B. LAFFEL, MD, MPH[5]
FOR THE INSULIN ASPART PEDIATRIC PUMP STUDY GROUP

OBJECTIVE — The safety and efficacy of insulin aspart continuous subcutaneous insulin infusion (CSII) was compared with that of insulin lispro CSII in children and adolescents with type 1 diabetes.

RESEARCH DESIGN AND METHODS — Children and adolescents aged 4–18 years with diagnosed type 1 diabetes ≥1 year previously and treated with insulin analog in a CSII ≥3 months were randomly assigned 2:1 to 16 weeks of insulin aspart CSII ($n = 198$) or insulin lispro CSII ($n = 100$) in this open-label, parallel-group, multicenter study. Standard diabetes safety and efficacy parameters were assessed.

RESULTS — Baseline demographics, subject characteristics, and diabetes history were similar between treatment groups. After 16 weeks of treatment, insulin aspart CSII was noninferior to insulin lispro CSII as measured by change in A1C from baseline (aspart, $-0.15 \pm 0.05\%$; lispro, $-0.05 \pm 0.07\%$ [95% CI of the treatment difference -0.27 to 0.07]; $P = 0.241$). No significant differences between treatment groups were observed in fasting plasma glucose, hyperglycemia, and rates of hypoglycemic episodes. At week 16, 59.7% of subjects in the aspart group and 43.8% of subjects in the lispro groups achieved age-specific American Diabetes Association A1C goals (<8.5% for subjects aged <6 years; <8% for subjects aged 6–18 years) ($P = 0.040$, corrected for baseline). Daily insulin dose (units per kilogram) was significantly lower at week 16 for subjects treated with aspart compared with those treated with lispro (0.86 ± 0.237 vs. 0.94 ± 0.233, $P = 0.018$).

CONCLUSIONS — Insulin aspart was as safe and effective as insulin lispro for use in a CSII in children and adolescents with type 1 diabetes.

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Intensive management of diabetes can delay the onset/progression of microvascular and cardiovascular complications associated with type 1 diabetes (1). Continuous subcutaneous insulin infusion (CSII) therapy is the method of intensive insulin therapy that most closely mimics physiological insulin release by allowing for administration of 24-h adjustable basal rates and flexible mealtime bolus doses. CSII provides increased convenience and flexibility to patients with type 1 diabetes, enabling insulin delivery modes to be customized to meet the various daily requirements of the individual patient. These features may benefit young children in particular, who may have unpredictable eating and exercise patterns. Recently, an evidence-based consensus statement endorsed by the American Diabetes Association (ADA) and European Association for the Study of Diabetes concluded that CSII (in conjunction with proper support measures) may be appropriate for children of all ages (2).

Insulin pump treatment has become increasingly popular with children and adolescents in recent years owing to technological advances in pumps and their associated catheters and infusion sets. Although there are conflicting comparison studies of the added benefit of CSII versus multiple daily injections (MDIs) in children, there are reports of A1C decreases averaging ~0.5% and a reduction in the frequency of severe hypoglycemia in pediatric subjects treated with CSII compared with their prior therapy or a group receiving MDI therapy (3–12).

Rapid-acting insulin analogs (insulin aspart [NovoLog], insulin lispro [Humalog], and insulin glulisine [Apidra]) are indicated for CSII use in adults (13). The pharmacokinetic and pharmacodynamic properties of insulin analogs (solubility, uniform absorption, and rapid onset of action and short duration of action compared with regular human insulin) make them well suited for use in CSII. In adults with type 1 diabetes, insulin aspart and insulin lispro CSIIs have been shown to be as safe and effective as MDI therapy (14–17). Notably, the ADA and European Association for the Study of Diabetes recommended use of rapid-acting insulin analogs for CSII in pediatric subjects based upon the modest A1C improvements versus regular human insulin observed in adult studies (2).

The popularity of insulin analog CSII treatment in pediatric patients has increased despite the lack of data from large, randomized clinical trials in this population. Furthermore, it is unclear whether there are any notable differences in efficacy, safety, or tolerability between

From the [1]Yale University School of Medicine, New Haven, Connecticut; the [2]University of Minnesota Physicians, Minneapolis, Minnesota; [3]Novo Nordisk, Princeton, New Jersey; the [4]Children's Hospital of Pittsburgh, Pittsburgh, Pennsylvania; and the [5]Joslin Diabetes Center, Boston, Massachusetts.

Address correspondence and reprint requests to Stuart A. Weinzimer, MD, Yale University School of Medicine, P.O. Box 208064, 333 Cedar St., New Haven, CT 06520-8064. E-mail: stuart.weinzimer@yale.edu.

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Abbreviations: ADA, American Diabetes Association; CSII, continuous subcutaneous insulin infusion; DKA, diabetic ketoacidosis; ITT, intent-to-treat; MDI, multiple daily injection; SAE, severe adverse event; SMPG, self-monitored plasma glucose.

rapid-acting insulin analogs administered via CSII in children and adolescents. Although several studies have compared insulin analog CSII versus MDI therapy and insulin aspart versus insulin lispro CSII in adults (18,19), this is the first large study conducted to date to evaluate and compare the safety and efficacy of two analogs in CSII (insulin aspart versus insulin lispro) in children and adolescents with type 1 diabetes.

RESEARCH DESIGN AND METHODS

— This was a 16-week, open-label, multicenter, parallel-group study. Children and adolescents with type 1 diabetes were randomly assigned in a 2:1 manner to receive either insulin aspart or insulin lispro by CSII via external pump with changes in reservoir, infusion set, and infusion site at least once every 48 h. Subjects were stratified by age (3–5, 6–11, and 12–18 years) before randomization to ensure that the two treatment groups had similar proportions of young children, children, and adolescents, respectively. This study was conducted at 45 sites in the U.S. in accordance with the Declaration of Helsinki and International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use Good Clinical Practice guidelines (20,21). Subjects aged ≥18 years signed informed consent forms. For subjects aged <18 years of age, the caregiver provided written informed consent (including Health Insurance Portability and Accountability Act requirements and child assent) before the initiation of any trial-related activities.

This trial enrolled 298 subjects with type 1 diabetes for ≥1 year and treated for ≥3 months with CSII therapy using either insulin aspart or insulin lispro, who were 3–18 years of age and had an A1C value at screening ≤10.0%. Subjects were excluded from the study if they had impaired hepatic or renal function, abnormal thyroid function, proliferative retinopathy, a history of severe hypoglycemia, or a developmental disorder or had received another investigational drug within 1 month before the trial. Subjects using diluted insulin, or who had basal rates ≤0.05 unit/h or basal rates that were not stable 2 weeks before screening, were excluded. Women were excluded if they were pregnant, breast-feeding, or not using contraception.

Subject-specific basal rates and premealtime bolus doses of insulin were selected at the discretion of the investigator. Self-monitored plasma glucose (SMPG) and dose diary entries were reviewed at each visit and doses were adjusted at the discretion of the investigator.

Efficacy assessments

The primary end point was change in A1C from baseline to the end of the study. A1C measurements were obtained at baseline (week 0) and at weeks 8, 12, and 16 and were analyzed by a central laboratory (Medical Research Laboratories International, Highland Heights, KY). Fasting plasma glucose, eight-point SMPG profiles (readings immediately before and 2 h after meals, at bedtime, and at 2 A.M.), and fasting lipid measurements were obtained at weeks 0 and 16. Eight-point SMPG measurements were recorded in a diary by the subject 2 days before the week 0 and week 16 study visits. Total daily insulin doses were recorded in the diary for 2 days before each office visit (weeks 0, 2, 4, 8, 12, and 16). Weight was measured at each office visit.

Safety assessments

Safety was assessed by physical examination findings, clinical laboratory evaluations, and reporting of adverse events, hypoglycemic and hyperglycemic episodes, and diabetic ketoacidosis (DKA) (classified as mild, moderate, or severe according to ADA Clinical Practice Guidelines) (22). Subjects/caregivers were instructed to record the date and time of hypoglycemic symptoms along with the time of the last meal, time and type of last insulin dose, and a plasma glucose value (when available). In this study, minor hypoglycemic episodes were defined as plasma glucose values <56 mg/dl with or without symptoms that were self-treated. Major hypoglycemia was defined as an event with severe central nervous system symptoms consistent with hypoglycemia in which the subject was unable to treat himself or herself and had a plasma glucose value <56 mg/dl and/or reversal of symptoms after food intake or administration of glucagon or intravenous glucose. Hyperglycemia was defined as an event with a plasma glucose value >300 mg/dl and was recorded as an adverse event by the investigator. Subjects were instructed on the signs and symptoms of infusion site reactions and were instructed to record all infusion site reactions in their diary. Diary information (SMPG profiles, episodes of hypoglycemia, hyperglycemia, and DKA, infusion site reactions, and adverse events) was reviewed at each visit.

Statistical analysis

The primary and secondary efficacy analyses were performed on the intent-to-treat population (ITT) (all subjects who received at least one dose of study drug after random assignment and had a post-baseline efficacy assessment). End-of-study values represent mean values for the ITT population using a last observation carried forward imputation approach. The safety population included all subjects receiving at least one dose of study drug.

Comparisons of the A1C change-from-baseline values between treatment groups were made using an ANCOVA model with treatment and age-group as the fixed effects and baseline A1C as covariate; 95% CIs were constructed. Change-from-baseline A1C values are presented as least-squared mean ± SEM values. The primary analysis was the test for noninferiority of aspart to lispro in terms of the change from baseline in A1C to the end of treatment. Noninferiority of aspart to lispro treatment was achieved if the upper limit of the 95% CI of the difference between treatments (least-squared mean aspart – least-squared mean lispro) was not >0.4%. Descriptive statistics (and ANCOVA comparisons between treatment groups) were provided for the primary and secondary efficacy end points. The percentages of subjects who achieved age-specific A1C goals were analyzed using the following 2006 ADA A1C goals: <8.5% for subjects aged <6 years and <8% for subjects aged 6–18 years (23). Statistical significance was defined as $P \leq 0.05$.

BMI was calculated from height and weight measurements obtained at screening and at the end of the study, and National Center for Health Statistics BMIAGE growth curves were used to calculate BMI scores adjusted by age and sex (*z*-BMI scores) (24). *z*-BMI scores are the number of SDs above or below the mean BMI and are commonly used for comparisons between pediatric treatment groups because "normal" BMI varies by age and sex in children and adolescents.

RESULTS

— Baseline demographics and subject characteristics of the 298 enrolled subjects (aspart, $n = 198$; lispro, $n = 100$) were similar between treatment groups (Table 1). The ITT population included 197 subjects in the insulin aspart

Table 1—*Baseline characteristics of enrolled population and subject disposition*

	Insulin aspart CSII	Insulin lispro CSII
Subjects randomly assigned (*n*)	198	100
3–5 years*	7	3
6–11 years	58	30
12–18 years	133	67
Age (years)	13.0 ± 3.30	13.1 ± 3.02
Sex (male/female) (%)	48/52	48/52
Ethnicity (C/B/H/A/O) (%)	85/6/7/1/2	91/2/6/1/0
Weight (kg)	54.3 ± 19.89	55.8 ± 19.13
BMI (kg/m^2)	21.7 ± 4.35	21.8 ± 4.37
z-BMI	0.72 ± 0.780	0.75 ± 0.755
Diabetes duration (years)	6.1 ± 3.36	6.0 ± 2.80
Use of CSII (weeks)	121.3 ± 80.28	132.7 ± 69.99
Insulin at entry (aspart/lispro) (%)	44/56	44/56
TDID before randomization (units)	49.5 ± 24.2	52.8 ± 24.0
Adjusted TDID (units/kg)	0.89 ± 0.26	0.93 ± 0.25
A1C (%)	8.0 ± 0.94	8.1 ± 0.84
Completed study	187 (94.4)	91 (91.0)
Discontinuation from study†	11 (5.6)	9 (9.0)
For adverse event	0	1 (1.0)
Noncompliance	8 (4.0)	6 (6.0)
Other	3 (1.5)	2 (2.0)

Data are mean ± SD or *n* (%). *Although subjects as young as 3 years of age were eligible for inclusion, the youngest child enrolled in this study was 4 years of age (insulin aspart group). †Adverse event withdrawal was due to persistent hyperglycemia attributed to an infusion set problem; "Other" reasons for discontinuation included withdrew consent (2 subjects), request to discontinue CSII (2 subjects), and subject needed a medication not allowed by the study protocol. A, Asian; B, Black; C, Caucasian; H, Hispanic; O, Other; TDID, total daily insulin dose; *z*-BMI, number of SDs above or below the mean BMI (adjusted by age and sex).

group and 99 subjects in the insulin lispro group. Overall, the study completion rate was 93%.

Efficacy

In the ITT population, observed mean A1C values were 8.0 ± 0.94 and 8.2 ± 0.84% at baseline and 7.9 ± 0.93 and 8.1 ± 0.85% at the end of the study (last observation carried forward) for insulin aspart and insulin lispro, respectively. The change in A1C from baseline at the end of the study was −0.15 ± 0.05% in the insulin aspart group and −0.05 ± 0.07% in the insulin lispro group. Insulin aspart CSII was demonstrated to be noninferior to insulin lispro CSII (as measured by the change in A1C from baseline to the end of the study) as the upper limit of the 95% CI for the treatment difference did not exceed 0.4 (95% CI −0.27 to 0.07).

At baseline, 50.3% of the subjects in the aspart group were at age-specific A1C goals compared with 40.4% of subjects in the lispro group ($P = 0.138$). At week 16, 59.7% of subjects in the aspart group and 43.8% of the subjects in the lispro group achieved ADA age-specific recommendations for A1C ($P = 0.040$, corrected for baseline percentage).

Mean fasting plasma glucose values were comparable between treatments at baseline (aspart 170.8 ± 77.39 mg/dl; lispro 177.8 ± 67.61 mg/dl, $P = 0.455$) and at the end of the study (aspart 166.5 ± 67.28 mg/dl; lispro 180.2 ± 82.58 mg/dl, $P = 0.113$). Self-measured eight-point plasma glucose profiles showed similar patterns between treatments at baseline and at the end of the study (Fig. 1). The eight-point SMPG profiles collected before weeks 0 and 16 showed a similar pattern for both treatment groups. Plasma glucose values were generally highest 2 h after breakfast for both insulin aspart and insulin lispro. In general, week 16 values were lower than week 0 values. No statistically significant differences between treatment groups in mean SMPG values were observed at any of the eight time points at week 16. All mean lipid values were within normal limits and were not significantly different between the insulin aspart and insulin lispro treatment groups at baseline and at the end of the study.

As expected for a pediatric trial, mean body weight increased from baseline for both treatment groups during the trial but was comparable between treatment groups (aspart 1.8 ± 2.07 kg; lispro 1.6 ± 2.09 kg, $P = 0.387$). At the end of the study, mean *z*-BMI was 0.75 ± 0.768 in the insulin aspart groups and 0.72 ± 0.780 in the insulin lispro group, a mean change in *z*-BMI from baseline of 0.03 ± 0.241 and −0.02 ± 0.204, respectively. The difference between treatments in the change in *z*-BMI score from baseline at the end of study was not significant.

The mean weight-adjusted daily insulin dose at week 0 was similar between treatment groups (aspart 0.89 ± 0.259 unit/kg, lispro 0.93 ± 0.247 unit/kg, $P = 0.344$). By week 16, the mean weight-adjusted daily dose was significantly lower in the aspart group compared with the lispro group (0.86 ± 0.237 vs. 0.94 ± 0.233 unit/kg, respectively, $P = 0.018$).

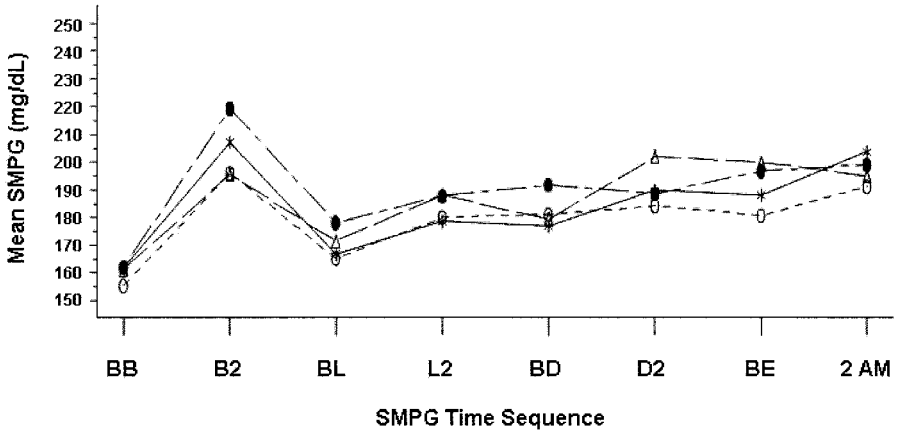

Figure 1—*Eight-point SMPG profiles for insulin aspart CSII and insulin lispro CSII at weeks 0 (*, aspart; ●, lispro) and 16 (○, aspart; △, lispro) (ITT population). BB, before breakfast; B2, 2 h after breakfast; BL, before lunch; L2, 2 h after lunch; BD, before dinner; D2, 2 h after dinner; BE, at bedtime; 2 AM, at 2 A.M. ± 60 min.*

Table 2—*Hypoglycemia episodes*

Type of episode	Insulin aspart CSII			Insulin lispro CSII			*P* value†
	Subjects	Episodes	Rate	Subjects	Episodes	Rate	
n	198			100			
Total							
All	190 (96.0)	5,547	92.2	97 (97.0)	2,418	81.3	0.209
Major	19 (9.6)	25	0.4	8 (8.0)	9	0.3	0.482
Minor	188 (94.9)	4,643	77.2	94 (94.0)	1,961	66.0	0.129
Symptoms only	149 (75.3)	722	12.0	82 (82.0)	394	13.3	0.603
Unclassified	24 (12.1)	157	2.6	18 (18.0)	54	1.8	0.586
PG ≤36 mg/dl	94 (47.5)	301	5.0	41 (41.0)	117	3.9	0.307
Nocturnal*							
All	118 (59.6)	340	5.7	56 (56.0)	184	6.2	0.645
Major	3 (1.5)	4	0.1	1 (1.0)	1	0.0	0.590
Minor	112 (56.6)	293	4.9	47 (47.0)	157	5.3	0.694
Symptoms only	25 (12.6)	33	0.6	19 (19.0)	23	0.8	0.288
Unclassified	6 (3.0)	10	0.2	1 (1.0)	3	0.1	0.659
PG ≤36 mg/dl	18 (9.1)	25	0.4	8 (8.0)	19	0.6	0.376

Data are *n* (%) unless otherwise indicated. Rate represents number of hypoglycemic events per subject year. Major represents a hypoglycemic episode with severe central nervous system symptoms consistent with hypoglycemia in which the subject was unable to treat himself/herself and had a plasma glucose (PG) <56 mg/dl and/or reversal of symptoms after food intake, or administration of glucagon or intravenous glucose. Minor represents a hypoglycemic episode with PG <56 mg/dl with or without symptoms that were self-treated. Symptoms represent symptoms related to hypoglycemia that were not meter confirmed or PG ≥56 mg/dl. *Nocturnal events were hypoglycemic events that occurred between midnight and 5:59 A.M. Events with missing times were excluded. †*P* value from Poisson regression testing whether rates were similar between treatments (rate ratio = 1).

Hypoglycemia, hyperglycemia, and DKA

The incidence and rates of hypoglycemic episodes are presented in Table 2. Rates of minor hypoglycemic episodes were similar between the two treatment arms, and the rate of major hypoglycemic episodes was also similar between treatment groups with a relatively small but similar percentage of subjects reporting at least one major hypoglycemic event during the study period (9.6 and 8.0% in the aspart and lispro groups, respectively). Rates of nocturnal hypoglycemic events were also similar between treatment groups.

Hyperglycemic episodes were reported as adverse events for 21 (11%) subjects in the CSII insulin aspart group compared with 17 (17%) subjects in the CSII insulin lispro group. Most of the events were classified as mild or moderate. During the study, a total of three episodes that met the study criteria for DKA (21) were reported by three subjects (one in the aspart group and two in the lispro group). All subjects with DKA recovered and went on to complete the study.

Safety

Adverse events were reported by 82% (162 of 198) of subjects in the aspart CSII group (498 events) and 83% (83 of 100) of the subjects in the lispro treatment group (293 events). The numbers and types of reported adverse events were similar for the two treatment groups. The five most frequently occurring adverse events for the aspart and lispro groups, respectively, were upper respiratory tract infection (18 and 20%), hyperglycemia (11 and 17%), nasopharyngitis (10 and 10%), pharyngolaryngeal pain (7 and 11%), and vomiting (8 and 10%). The majority of adverse events were mild in severity (aspart 82%; lispro 77%). Thirty (15%) subjects in the aspart group and 16 (16%) subjects in the lispro group experienced adverse events that were considered to have a probable or possible relationship to the study drug by the investigator. Only one subject withdrew from the study because of an adverse event (persistent hyperglycemia due to an infusion set problem by a subject in the lispro group).

Seven serious adverse events (SAEs) were reported for six subjects (five subjects [2.5%] in the aspart group and one subject [1.0%] in the lispro group). Hypoglycemic seizure, DKA, hypoglycemia with accidental overdose of insulin, hyperglycemia, and skin lacerations were SAEs reported by subjects in the aspart treatment group; hypoglycemia was the SAE reported by one subject in the lispro group. All subjects recovered, and none of these subjects withdrew from the study as a result of their SAE.

The following adverse events were classified as infusion site reactions: catheter site–related reaction, infusion site erythema, induration, irritation, pruritus, rash, reaction, swelling, or vesicles. The percentages of subjects who reported an infusion site reaction were similar between groups (aspart 17%, lispro 21%, $P = 0.43$). Treatment with either insulin aspart CSII or insulin lispro CSII did not appear to have any adverse effects on physical examination findings, vital signs, or hematology, biochemistry, or urinalysis parameters.

CONCLUSIONS — Results from this study indicate that insulin aspart CSII is as effective as insulin lispro CSII in children and adolescents aged 4–18 years. Mean fasting plasma glucose, SMPG, and A1C values were comparable from baseline to the end of the study for both treatment groups. This finding was not surprising considering that subjects enrolled in the trial were not naive to CSII treatment with insulin analogs, as 44% of subjects had used insulin aspart and 56% had used insulin lispro before study entry with mean durations of CSII use of 121 and 132 weeks, respectively.

This study was not a treat-to-target study with defined dosing guidelines. Investigators reviewed subject diaries and subject-specific basal and bolus doses were determined at their discretion. For this reason, the baseline and end of study data provide insight into the safety and

glycemic control achieved with insulin analog CSII therapy in children and adolescents in a "real-world" clinical setting.

Notably, the weight-adjusted mean daily dose of insulin aspart was significantly less than that of insulin lispro. Although subjects in the aspart group used less insulin, they were able to achieve comparable levels of glycemic control at the end of the study. The mean total daily dose of insulin aspart at the end of the study (0.86 unit/kg) was similar to the dose reported at the end of another insulin aspart CSII study of 16 subjects aged 8–21 years (0.9 unit/kg) (25).

Nocturnal hypoglycemia is a serious concern for the pediatric population. The rates of major nocturnal hypoglycemic episodes or episodes of plasma glucose ≤36 mg/dl were very low in this study for both treatment groups, consistent with observations from an earlier CSII study in adults (18). Most hypoglycemic events occurred during the daytime, more consistent with the impact of daytime exercise/activity or inaccurate bolus dosing than with improper basal rate. Insulin aspart was shown previously to be associated with a lower risk of symptomatic, major, or minor hypoglycemia compared with MDI in adults (14). In this study, the rates of all classifications of hypoglycemia were comparable between insulin aspart and insulin lispro, suggesting a similar hypoglycemic risk for both analogs when used in CSII for pediatric subjects.

In this study, the incidence of hyperglycemia for both treatment groups was lower (aspart,11%; lispro 17%) than in previous adult studies of insulin aspart CSII (18,26). However, the lower rate of hyperglycemic episodes in this study may be due to the fact that investigators had to report hyperglycemia as an adverse event and not merely as any instance when plasma glucose is >300 mg/dl.

In summary, insulin aspart CSII provides glycemic efficacy noninferior to that of insulin lispro CSII at a significantly lower total daily dose, with no increased risk of hypoglycemia over 16 weeks of therapy in pediatric subjects familiar with pump therapy. Overall, insulin aspart CSII was shown to be safe and tolerable in pediatric subjects aged 4–18 years. The results of this study confirm that insulin analog CSII therapy is efficacious in appropriately selected children and adolescents with type 1 diabetes. Insulin analog CSII therapy provides a safe and effective insulin delivery option for pediatric patients with type 1 diabetes and their caregivers who desire the convenience and flexibility associated with CSII.

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