Faster-acting insulin aspart provides faster onset and greater early exposure vs insulin aspart in children and adolescents with type 1 diabetes mellitus

Maryam Fath1 | Thomas Danne1 | Torben Biester1 | Lars Erichsen2 | Olga Kordonouri1 | Hanne Haahr3

1Diabetes Centre for Children and Adolescents, Kinder- und Jugendkrankenhaus AUF DER BULT, Hannover, Germany
2Biostatistics, Novo Nordisk A/S, Søborg, Denmark
3Clinical Pharmacology, Novo Nordisk A/S, Søborg, Denmark

Correspondence
Thomas Danne, Diabetes Centre for Children and Adolescents, Kinder- und Jugendkrankenhaus AUF DER BULT, Janusz-Korczak-Allee 12, 30173 Hannover, Germany.
Email: Danne@hka.de

Funding information
Novo Nordisk.

Background: Faster-acting insulin aspart (faster aspart) is insulin aspart (IAsp) in a new formulation with additional excipients (L-arginine and niacinamide). In adults, faster aspart provides faster onset and greater early exposure and action vs IAsp.

Aim: This randomized, double-blind, 2-period crossover trial investigated the pharmacological properties of faster aspart vs IAsp in 12 children (6-11 years), 13 adolescents (12-17 years), and 15 adults (18-64 years) with type 1 diabetes mellitus.

Methods: Subjects received 0.2 U/kg subcutaneous dosing (mean of 8.3, 12.8, and 15.6 U, respectively) immediately prior to a standardized meal (17.3 g carbohydrate/100 mL; amount adjusted by body weight).

Results: Consistently across age groups, onset of appearance occurred approximately twice as fast (5-7 minutes earlier) and early exposure (AUCIAsp,0-30min; area under the IAsp curve from 0 to 30 minutes) was greater (by 78%-147%) for faster aspart vs IAsp, with no treatment differences in total exposure (AUCIAsp,0-t) or maximum concentration ($C_{\text{max}}$). Two-hour postmeal plasma glucose excursion was reduced for faster aspart vs IAsp (although only reaching statistical significance in children). In accordance with the absolute dose administered for each age group, AUCIAsp,0-t for faster aspart was lower in children (estimated ratio children/adults [95% confidence interval]: 0.59 [0.50;0.69], $P < .001$) and adolescents (0.78 [0.67;0.90], $P = .002$) vs adults. No age group differences were seen in $C_{\text{max}}$ (0.91 [0.70;1.17], $P = .445$, and 0.99 [0.77;1.26], $P = .903$). The age effect on AUCIAsp,0-t and $C_{\text{max}}$ did not differ statistically significantly between treatments. Faster aspart and IAsp were well-tolerated.

Conclusion: The current findings in children and adolescents suggest a potential for faster aspart to improve postprandial glycemia over current rapid-acting insulins also in younger age groups. ClinicalTrials.gov identifier: NCT02035371.

KEYWORDS
adolescents, children, pharmacodynamics, pharmacokinetics, type 1 diabetes mellitus

INTRODUCTION

Insulin therapy in childhood and youth is complicated by the continuous changes occurring with respect to weight, body composition, and insulin sensitivity as well as variable physical activity patterns and eating behavior. Approximately 75% of children and young people with type 1 diabetes mellitus (T1DM) do not meet the glycosylated hemoglobin (HbA1c) target of <7.5% (<58 mmol/mol) recommended by the American Diabetes Association (ADA). Regular human insulin (RHI) is used to treat nocturnal hypoglycemia and to control daily insulin requirements. Continuous subcutaneous insulin infusion (CSII) is considered the gold standard for insulin delivery in T1DM patients, but the occurrence of severe hypoglycemia remains an important clinical problem. \[ΔPG_{\text{average}}, \text{Mean plasma glucose excursion}; \ ΔPG_{\text{max}}, \text{Maximum plasma glucose excursion}; ΔE, \text{Energy percent}; E\%_{\text{ERI}}, \text{Energy percent of early insulin action}; \ E\%_{\text{ERI}}; \text{Energy percent of early insulin action}; \text{Faster aspart, Faster-acting insulin aspart; HbA1c, glycosylated hemoglobin; IAsp, Insulin aspart; ISPAD, International Society for Pediatric and Adolescent Diabetes; LLOQ, Lower limit of quantification; PG, Plasma glucose; RHI, Regular human insulin; T1DM, type 1 diabetes mellitus; t\%_{\text{Early 50} \%\text{ of } \text{C}_{\text{max}}}, \text{Time to early } 50\% \text{ of maximum concentration}; \ t_{\text{max}}, \text{Time to maximum concentration; U, Unit(s)}}\]
by the American Diabetes Association (ADA) and the International Society for Pediatric and Adolescent Diabetes (ISPAD). While premixed insulins and self-mixing of rapid-acting and intermediate- or long-acting insulin have received some attention in the younger age groups in order to reduce the number of daily injections, nowadays intensified insulin therapy is the recommended treatment regimen to achieve glycemic targets in children and adolescents with T1DM. In such a treatment regimen, rapid-acting insulin is an important tool to be able to closely match the varying prandial insulin needs during the often irregular daily life of children.

Current rapid-acting insulin analogs (insulin lispro, insulin aspart [IAsp], and insulin glulisine) represent a major improvement in pharmacokinetic properties compared with regular human insulin (RHI). In children and adolescents with T1DM, IAsp and insulin glulisine have shown earlier and greater peak concentration and shorter duration of exposure vs RHI. However, the absorption of current rapid-acting insulins is still not fast enough to achieve sufficient postprandial glucose control. Furthermore, delayed elimination of current rapid-acting insulins, relative to the need for postmeal glucose reduction, increases the risk of late postmeal hypoglycemia, causing children and parents to compensate by introducing snacks. Thus, there is a need for development of ultrafast insulins not only intended for adults but also for children and adolescents with T1DM.

This study is the first to investigate the pharmacokinetic and pharmacodynamic properties of faster-acting insulin aspart (faster aspart), an ultrafast-acting mealtime insulin, in children and adolescents with T1DM. Faster aspart is IAsp in a new formulation with 2 well-known additional excipients, L-arginine and niacinamide, providing a stable formulation with faster initial absorption after subcutaneous administration. Both excipients appear on the US Food and Drug Administration list of approved inactive ingredients in products for injection, with a wealth of human/clinical data available to support safe systemic exposure. In adults with T1DM, faster aspart compared with IAsp demonstrated twice-as-fast onset of appearance, a 2-fold greater early insulin exposure and approximately 50% greater early glucose-lowering effect within the first 30 minutes of administration. The objectives of this study were to assess the overall pharmacokinetic characteristics of faster aspart in children and adolescents compared with those in adults, and to compare the early pharmacokinetic and pharmacodynamic (using a meal test) properties of faster aspart vs IAsp in children and adolescents, using the same comparison in adults as a reference.

2 | METHODS

2.1 | Study design

This was a randomized, double-blind, single-dose, single-centre (Kinder- und Jugendkrankenhaus AUF DER BULT, Hannover, Germany), 2-period, crossover trial in children, adolescents, and adults with T1DM. Review and approval of the protocol were done by the appropriate health authority and ethics committee before initiation of the trial. The trial was performed in accordance with the Declaration of Helsinki, Good Clinical Practice as well as regulatory guidance on pediatric clinical trials. Before initiation of any trial-related activities, adults and adolescents as well as parents or legally accepted representatives of the children and adolescents gave written informed consent. Children gave oral informed assent. The trial was registered at ClinicalTrials.gov (NCT02035371).

2.2 | Participants

Eligible subjects were males and females aged 6 to 11 years (children), 12 to 17 years (adolescents), or 18 to 64 years (adults), who were diagnosed with T1DM ≥12 months before screening, had received multiple daily injection therapy or continuous subcutaneous insulin infusion (CSII) treatment for ≥12 months with a total insulin dose <1.2 (l/I)U/kg/day and bolus insulin dose ≥0.3 (l/I)U/kg/day and <0.7 (l/I)U/kg/day, HbA1c ≤10.0% (86 mmol/mol) and body mass index (BMI) within the 3rd and 97th BMI percentiles (children and adolescents) or ≤28.0 kg/m² (adults). Individuals were excluded if they had clinically significant abnormal values in clinical laboratory screening tests, had clinically significant concomitant diseases, were treated with drug(s) which might interfere with glucose metabolism, were smokers or had unusual meal habits or special dietary requirements. Females who were pregnant or breast-feeding were also excluded from participation.

2.3 | Study procedures

The trial included a screening visit, 2 dosing visits separated by 3 to 22 days and a follow-up visit. At the 2 dosing visits, subjects received faster aspart (100 U/mL; Novo Nordisk, Bagsvaerd, Denmark) or IAsp (NovoRapid; 100 U/mL; Novo Nordisk) in a randomized sequence, both administered in a blinded PDS290 pen-injector prefilled pen (Novo Nordisk).

At each dosing visit, a stable glucose level was achieved overnight using an established protocol of variable intravenous infusion of RHI (Actrapid, Novo Nordisk) combined with glucose infusion (if plasma glucose [PG] was <300 mg/dL [16.6 mmol/L] or 0.9% saline infusion (if PG was ≥300 mg/dL [16.6 mmol/L]), according to body weight. Water intake was limited to 200 mL from midnight until 07:00 AM and 100 mL from 07:00 AM until 1 hour prior to dosing, with no water allowed during the last hour prior to dosing.

Subjects were excluded from the dosing visit if they had consumed alcohol or performed physical exercise within 48 hours, if they had received insulin glargine or insulin detemir within 48 hours, intermediate-acting insulin (such as neutral protamine Hagedorn insulin) within 22 hours or IAsp within 12 hours prior to dosing, if they had experienced hypoglycemia (PG ≤70 mg/dL [3.9 mmol/L]) within 24 hours prior to dosing or if they reported gastrointestinal symptoms (such as nausea, vomiting, heartburn, or diarrhea).

In the morning of the dosing visit, the insulin and glucose infusion was terminated when 2 PG measurements done 30 minutes apart were both within the range of 100 to 160 mg/dL (5.6-8.9 mmol/L). Faster aspart or IAsp (0.2 U/kg single-dose) was then injected subcutaneously into a lifted skin fold of the lower abdominal wall above the inguinal area.
Immediately after dosing (within 2 minutes), a standardized liquid meal (BOOST, Nestlé S.A., Vevey, Switzerland: containing 101 kcal per 100 mL, 68 energy percent [E%] carbohydrate, 17 E% protein, and 15 E% fat) was consumed as quickly as possible (within 8 minutes). Adjustment of the volume of the liquid meal was done according to the subject’s body weight (Table S1, Supporting Information).

Blood samples for pharmacokinetic, PG and β-hydroxybutyrate assessment were drawn frequently up to 12 hours as shown in Table S2. In case PG fell below 56 mg/dL (3.1 mmol/L), or at a higher PG level at the discretion of the Investigator for safety reasons, the subject was treated to alleviate hypoglycemia. In case PG was consistently above 342 mg/dL (19 mmol/L) and/or β-hydroxybutyrate levels were above 1.8 mmol/L, RHI (Actrapid) was to be administered intravenously.

Subjects remained in a semi-supine position until 2 hours after dosing and in a supine or semi-supine position thereafter until 12 hours after dosing. Subjects avoided water consumption until 2 hours after dosing to the extent possible and refrained from eating until 6 hours after dosing. From 6 hours postdose, subjects were given meals and snacks. Use of short-acting insulin was limited to RHI from 6 to 12 hours postdose. Subjects remained at the hospital until 12 hours postdose.

2.4 Assessments
A validated IAsp specific enzyme-linked immunosorbent assay was used to measure free serum IAsp concentrations (polyethylene glycol-precipitated). PG levels for pharmacodynamic and safety assessments and β-hydroxybutyrate levels for safety evaluation were measured by a combined blood glucose/β-hydroxybutyrate monitoring system (Precision Xceed Pro, Abbott Diabetes Care, Alameda, California). Additional safety assessments included adverse events, local tolerability at the injection site, hypoglycemic episodes (defined as “confirmed” when they were either “severe” according to ADA criteria, that is, requiring third party assistance, or verified by a PG level of <56 mg/dL [3.1 mmol/L]), laboratory safety parameters, physical examination, and vital signs.

2.5 Study endpoints
Pharmacokinetic endpoints to evaluate onset of insulin exposure included onset of appearance (time from trial product administration until the first time serum insulin concentration ≥ lower limit of quantification [LLOQ; 10 pmol/L]), time to early 50% of maximum insulin concentration (tEarly 50% Cmax) and time to maximum insulin concentration (tmax). Early partial areas under the curve (AUCs) for serum insulin [AUCIAsp,0-15min, AUCIAsp,0-30min, AUCIAsp,0-1h, AUCIAsp,0-1.5h, and AUCIAsp,0-2h] were included to evaluate early insulin exposure. Overall insulin exposure was assessed from total insulin exposure (AUCIAsp,0-t: primary endpoint) and maximum insulin concentration (Cmax).

Pharmacodynamic endpoints to evaluate early glucose-lowering effect during the standardized meal test included the mean PG excursion from 0 to 1 hour and 0 to 2 hours after trial product administration (ΔPGaverage,0-1h and ΔPGaverage,0-2h) and the maximum PG excursion (ΔPGmax).

All endpoints were derived from the raw profiles. In the derivation of onset of appearance and AUCIAsp endpoints, IAsp concentration was imputed in the time period from dosing until the time of the first observed IAsp concentration above LLOQ, using compartmental modeling. AUCIAsp,0-t was derived by calculating the AUC until the time of last quantifiable IAsp concentration and then extrapolating until 12 hours (the last pharmacokinetic sampling time point) based on the terminal slope.

If the subject was treated to alleviate hypoglycemia, pharmacodynamic profiles and endpoints were derived by carrying forward the last observation before the intervention.

2.6 Statistical analysis
The number of subjects needed to complete the trial was preset to 12 in each of the 3 age groups without any formal sample size calculation. This approach was based on relevant guidance on the conduct of clinical studies, and specifically pharmacokinetic studies, in the pediatric population."13,15 Statistical analyses of pharmacokinetic and pharmacodynamic endpoints were conducted at a 5% significance level including all randomized subjects who received at least 1 dose of trial product. SAS version 9.3 (SAS Institute, Cary, North Carolina) was used for all analyses.

Pharmacokinetic endpoints were log-transformed (except for onset of appearance, tEarly 50% Cmax, and tmax) and analyzed in a linear mixed model with period, age group, treatment, and interaction between age group and treatment as fixed effects, and subject as a random effect. The variance of the random subject effect and the residual variance depended on age group. Pharmacokinetic properties of faster aspart and IAsp were compared within each age group by deriving the treatment ratios and 95% confidence intervals (CIs) for all pharmacokinetic endpoints (treatment differences for onset of appearance, tEarly 50% Cmax, and tmax). Treatment ratios and 95% CIs for onset of appearance, tEarly 50% Cmax, and tmax were calculated by Fieller’s method.18 To compare overall insulin exposure between age groups (children vs adults; adolescents vs adults; primary objective) for both faster aspart and IAsp, age group ratios and 95% CIs were calculated for AUCIAsp,0-1h and Cmax.

Pharmacodynamic endpoints were analyzed on an additive scale using the same model as for pharmacokinetic endpoints and with predose PG included as a covariate. The pharmacodynamic properties of faster aspart and IAsp were compared within each age group by deriving the treatment differences and 95% CIs.

Safety endpoints were summarized by descriptive statistics based on all subjects receiving at least 1 dose of trial product.

3 RESULTS
3.1 Subjects and dosing information
Of the 55 screened individuals, 41 were randomized (13 children, 13 adolescents, and 15 adults) and 40 were exposed to trial product.
One randomized child was withdrawn before first dosing due to occurrence of hypoglycemia within 24 hours of planned dosing. A total of 38 subjects completed the trial (12 children, 13 adolescents, and 13 adults). Two adults were withdrawn after completing the first dosing visit (faster aspart dosing), due to difficulties in drawing predose blood samples at the second dosing visit and inability to attend the second dosing visit, respectively.

Baseline characteristics are presented in Table 1. The mean absolute dose of faster aspart and IA is administered at the dosing visits was 8.3 U in children, 12.8 U in adolescents, and 15.6 U in adults. Thus, the mean absolute dose in children and adolescents was 53% and 82%, respectively, of the dose in adults.

### 3.2 | Treatment differences in pharmacokinetic properties

The mean serum IA concentration-time profiles were shifted to the left for faster aspart vs IA in all 3 age groups (Figures 1 and S1).

For all 3 age groups, onset of appearance occurred approximately twice-as-fast (5–7 minutes earlier; \( P < .01 \)), and \( t_{\text{Early 50% Cmax}} \) was also shorter (by 6–11 minutes; \( P < .05 \)), with faster aspart vs IA (Table 2). While \( t_{\text{max}} \) occurred statistically significantly earlier for faster aspart than for IA in adults (\( P = .029 \)), the earlier \( t_{\text{max}} \) for faster aspart vs IA in children and adolescents did not reach statistical significance (\( P = .300 \) and \( P = .093 \), respectively). The effect of treatment on onset of exposure did not differ statistically significantly between age groups. \( P \)-values for treatment by age group interaction were .365, .326, and .395 for onset of appearance, \( t_{\text{Early 50% Cmax}} \), and \( t_{\text{max}} \), respectively.

In all 3 age groups, early insulin exposure was statistically significantly greater for faster aspart than for IA within 30 minutes postdosing (AUCIA\textsubscript{IA} \( 0-15\) min and AUCIA\textsubscript{IA} \( 0-30\) min). The effect of treatment on early exposure was not statistically significantly different between age groups. \( P \)-values for treatment by age group interaction were .351, .356, .789, .927, and .962 for AUCIA\textsubscript{IA} \( 0-15\) min, AUCIA\textsubscript{IA} \( 0-30\) min, AUCIA\textsubscript{IA} \( 0-1\) h, AUCIA\textsubscript{IA} \( 0-1.5\) h, and AUCIA\textsubscript{IA} \( 0-2\) h, respectively.

AUCIA\textsubscript{IA} \( 0-t \) and \( C_{\text{max}} \) were both similar for faster aspart and IA, irrespective of age group (Table S3).

### 3.3 | Treatment differences in early glucose-lowering effect

Glucose intervention to alleviate hypoglycemia within the first 6 hours after dosing occurred in 8 subjects for both faster aspart (1 child and 7 adults) and IA (2 children, 1 adolescent, and 5 adults). No glucose interventions occurred during the first hour postdosing and only 2 glucose interventions occurred during the second hour postdosing (1 child for IA and 1 adult for faster aspart). All other
glucose interventions occurred later than 2 hours postdosing and thus have no impact on the reported pharmacodynamic endpoints. No interventions occurred to alleviate hyperglycemia.

Mean predose adjusted PG profiles for faster aspart vs IAsp during the first 2 hours after the standardized meal are shown for all 3 age groups in Figure 3. The overall PG excursion appeared to be reduced for faster aspart compared with IAsp, particularly in children and adults. In children, ΔPGaverage,0-1h, ΔPGaverage,0-2h, and ΔPGmax were all reduced for faster aspart vs IAsp (by approximately 21-28 mg/dL [1.2-1.6 mmol/L]; P = .005, P = .028 and P = .044, respectively), while in adolescents and adults pharmacodynamic endpoints did not differ statistically significantly between treatments (Figure 3 and Table S4). The effect of treatment did not differ statistically significantly between age groups. P-values for treatment by age group interaction were .149, .316, and .474 for ΔPGaverage,0-1h, ΔPGaverage,0-2h, and ΔPGmax, respectively.

### 3.4 | Age-group differences in overall insulin exposure

AUC_{C_{max},0-1} for faster aspart was lower in children compared with adults (estimated age group ratio children/adults [95% CI]: 0.59 [0.50;0.69], P < .001) and in adolescents compared with adults (adolescents/adults: 0.78 [0.67;0.90], P = .002). C_{max} for faster aspart did not differ statistically significantly between children and adults (0.91 [0.70;1.17], P = .445) or between adolescents and adults (0.99 [0.77;1.26], P = .903). Similar results were observed for IAsp (data not shown). Accordingly, the effect of age did not differ statistically significantly between treatments. P-values for treatment by age group interaction were .481 and .755 for AUC_{C_{max},0-1} and C_{max}, respectively.

### 3.5 | Safety

Both faster aspart and IAsp were well-tolerated in all 3 age groups, and no safety issues were identified during the trial. There were no serious adverse events and the majority of adverse events were mild (13 of 15 events). A total of 3 confirmed hypoglycemic episodes occurred during the trial (1 with faster aspart and 2 with IAsp; all in adult subjects). No injection site reactions were observed. No clinically significant findings were reported in safety laboratory assessments or vital signs.

### 4 | DISCUSSION

The key findings of this study were the faster onset of appearance and the greater early exposure observed for faster aspart compared with IAsp in children and adolescents. These results are in line with those observed in adults in this study as well as in a previous study. The pharmacokinetic results translated into a statistically significant reduction in 2-hour postprandial PG excursion with faster aspart vs IAsp in children. Statistically non-significant trends in the same direction were seen in adolescents and adults. However, in a larger phase 3 study, mealtime faster aspart was shown to be superior vs mealtime IAsp in adult subjects with T1DM with respect to change from baseline in 2-hour postprandial glucose excursion in a meal test.

In younger age groups, where eating behavior is known to vary considerably, postmeal insulin administration might facilitate a better match between meal carbohydrate content and insulin dose. Postmeal dosing of insulin glulisine or IAsp resulted in greater blood glucose levels for 2 hours after the meal compared with premeal dosing in children and adolescents with T1DM. Thus, a need remains for insulins with pharmacological properties better suited for postmeal dosing when this is needed. Results in adults with T1DM suggest that faster aspart may be administered up to 20 minutes postmeal with no impact on overall glycemic control or hypoglycemia risk as compared to IAsp dosed at mealtime. Postmeal dosing of faster aspart has not been tested in children or adolescents so far, but a clinical trial is currently being conducted to investigate this option.
An insulin with improved pharmacological properties vs current rapid-acting insulins may be useful in insulin pump therapy. In a CSII setting in adults with T1DM, faster aspart provided earlier onset and greater early exposure and glucose-lowering effect vs IAsp. In children and adolescents with T1DM, CSII has advantages over multiple daily injections in terms of improved glycemic control and reduced risk of hypoglycemia. Over the last 2 decades, use of insulin pump therapy in youth with T1DM has increased substantially, although large geographical variation exists. Using CSII, the faster absorption of faster aspart should shorten the lag time following adjustments of the insulin infusion rate. In closed-loop systems, the ultrafast properties of faster aspart may be even more relevant, as a faster insulin response to variations in measured blood glucose would be a very important step toward fully functional artificial pancreas systems. These potential applications of faster aspart remain to be investigated in pediatric patients with T1DM.

Total exposure of faster aspart and IAsp was lower in children and adolescents than in adults in this study. For IAsp, this contradicts a study with the combination product insulin degludec/insulin aspart, where total exposure of the IAsp component was statistically significantly higher in children than in adults. This discrepancy between studies may be due to the fact that we measured free IAsp in the current study, whereas total IAsp was measured in the previous study. Higher levels of insulin antibodies in children, potentially interfering with the total IAsp assay, could provide an explanation for the previous observations. A possible explanation for the lower total exposure of faster aspart and IAsp in children and adolescents compared with adults in the current study is that subjects received the same dose per kg body weight. As the volume of distribution does not change directly in proportion to the increase in body weight during growth in children and adolescents, a similar total exposure may not be expected when children, adolescents, and adults are dosed according to body weight. Interestingly, in the present study the age group differences in total exposure (41% and 22% lower in children and adolescents vs adults) were very close to the age group differences in absolute dose (47% and 18% lower in children and adolescents vs adults).

A limitation of this study was the relatively low number of subjects in each age group. This is important to bear in mind both when assessing the age group differences in overall exposure and when comparing early pharmacokinetic and pharmacodynamic properties between treatments. It is notable that most treatment differences in early pharmacological properties reached statistical significance.
Despite the fact that the study was not powered to detect these differences, another limitation was that a meal test rather than a glucose clamp was used to assess early pharmacodynamic properties. While acknowledging its possible weaknesses, this approach was taken in order to reduce the invasive procedures and required blood volume and thereby the burden on the pediatric subjects in accordance with relevant guidance on the conduct of pediatric clinical trials. The clinical interpretation of the results from the meal test may be difficult due to its experimental nature: a standardized liquid meal, with subjects staying in a supine position, and adjustment of the insulin dose and meal size relative to body weight rather than being individualized. The latter implies that between-subject comparison (ie comparison between age groups) of pharmacodynamic properties should be made with caution. Consequently, our focus with respect to early pharmacodynamic properties has been on the treatment comparison, taking advantage of the similar study conditions for faster aspart and IAsp dosing within each subject.

In conclusion, the current findings of a faster onset and greater early exposure for faster aspart vs IAsp in children and adolescents are in line with those in adults and suggest that the ultrafast insulin, faster aspart, may induce better mealtime glucose control relative to current rapid-acting insulins, also in pediatric patients with T1DM.

**FIGURE 3** Plasma glucose (PG) profiles (mean predose adjusted) and PG excursion endpoints in a meal test after administration of faster aspart vs insulin aspart (0.2 U/kg) in (A) children, (B) adolescents, and (C) adults with T1DM. P-values are for the treatment comparison of faster aspart vs insulin aspart. ΔPG_average, mean plasma glucose excursion; ΔPG_max, maximum plasma glucose excursion; CI, confidence interval; T1DM, type 1 diabetes mellitus.
ACKNOWLEDGMENTS

This study was funded by Novo Nordisk. The involvement of the Kinder- und Jugendkrankenhaus AUF DER BULT, Diabetes Centre for Children and Adolescents, Hanover, Germany, is gratefully acknowledged. The authors would like to thank Theis Gondolf, MD, Novo Nordisk, for his review and input to the manuscript and Carsten Roepstorff, PhD, CR Pharma Consult. Copenhagen, Denmark for providing medical writing support, which was funded by Novo Nordisk. The study was coordinated by Novo Nordisk and all data processing and statistical analyses were performed by Novo Nordisk.

Disclosure of interest

T.D. has received speaker honoraria and research support and has consulted for Abbott, Bayer, BMS, AstraZeneca, Boehringer Ingelheim, DexCom, Eli Lilly, Medtronic, Novo Nordisk, Sanofi, and Roche. He is a shareholder of DreaMed Ltd. T.B. has received speaker honoraria and scientific support from Medtronic. O.K. has received research support and has consulted for Novo Nordisk and Sanofi. She is a shareholder of DreaMed Ltd. L.E. and H.H. are employees and shareholders of Novo Nordisk. M.F. declares no conflict of interest.

REFERENCES

1. Wood JR, Miller KM, Maahs DM, et al. Most youth with type 1 diabetes in the T1D Exchange Clinic Registry do not meet American Diabetes Association or International Society for Pediatric and Adolescent Diabetes clinical guidelines. Diabetes Care. 2013;36:2035–2037.
2. Chiang JL, Kirkman MS, Lafell LM, Peters AL. Type 1 diabetes through the life span: a position statement of the American Diabetes Association. Diabetes Care. 2014;37:2034–2054.
3. Reeves MJ, Pillay K, de Beaufort C, et al. Assessment and monitoring of glycemic control in children and adolescents with diabetes. Pediatr Diabetes. 2014;15(suppl20):102–114.
4. Petit-Bibal C, Rothenbuhler A, Lucchini P, et al. Decrease in clinical hypoglycemia in young children with type 1 diabetes treated with free-mixed aspart and detemir insulin: an open labelled randomized trial. Pediatr Diabetes. 2015;16:345–353.
5. Danne T, Bangstad HJ, Deeb L, et al. ISPAD Clinical Practice Consensus Guidelines 2014. Insulin treatment in children and adolescents with diabetes. Pediatr Diabetes. 2014;15(suppl20):115–134.
6. Danne T. Flexibility of rapid-acting insulin analogues in children and adolescents with diabetes mellitus. Clin Ther. 2007;29(suppl D):S145–S152.
7. Mortensen HB, Lindholm A, Olsen BS, Hylelberg B. Rapid appearance and onset of action of insulin aspart in paediatric subjects with type 1 diabetes. Eur J Pediatr. 2000;159:483–488.
8. Danne T, Becker RH, Heise T, Bittner C, Frick AD, Rave K. Pharmakokinetik, prandial glucose control, and safety of insulin glulisine in children and adolescents with type 1 diabetes. Diabetes Care. 2005;28:2100–2105.
9. Boland E, Monsod T, Delucia M, Brandt CA, Fernando S, Tamborlane WW. Limitations of conventional methods of self-monitoring of blood glucose: lessons learned from 3 days of continuous glucose sensing in pediatric patients with type 1 diabetes. Diabetes Care. 2001;24:1858–1862.
10. Cengiz E. Undeniable need for ultrafast-acting insulin: the pediatric perspective. J Diabetes Sci Technol. 2012;6:797–801.
11. Food and Drug Administration. Inactive ingredient search for approved drug products. http://www.accessdata.fda.gov/scripts/cder/igi/index.cfm. Accessed January 23, 2017.
12. Heise T, Hövelmann U, Brandsted L, Adrian CL, Nosek L, Haahr H. Faster-acting insulin aspart: earlier onset of appearance and greater early pharmacokinetic and pharmacodynamic effects than insulin aspart. Diabetes Obes Metab. 2015;17:682–688.
13. ICH Harmonised Tripartite Guideline E11. Clinical investigation of medicinal products in the pediatric population. 20 July 2000. http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E11/Step4/E11_GuideLine.pdf. Accessed January 23, 2017.
14. European Medicines Agency. Committee for Medicinal Products for Human Use. Guideline on the Role of Pharmacokinetics in the Development of Medicinal Products in the Paediatric Population. 28 June 2006. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003066.pdf. Accessed January 23, 2017.
15. U.S. Food and Drug Administration. Guidance for Industry. General Considerations for Pediatric Pharmacokinetic Studies for Drugs and Biological Products November 1998. http://www.fda.gov/ohrms/dockets/ac/03/briefing/39278B1_04_GFI-Pharmacokinetic2OGuidance.pdf. Accessed January 23, 2017.
16. Biester T, Danne T, Bläsig S, et al. Pharmacokinetic and prandial pharmacodynamic properties of insulin degludec/insulin aspart in children, adolescents, and adults with type 1 diabetes. Pediatr Diabetes. 2016;17:642–649.
17. American Diabetes Association. Defining and reporting hypoglycemia in diabetes: a report from the American Diabetes Association Workgroup on hypoglycemia. Diabetes Care. 2005;28:1245–1249.
18. Fieller EC. Some problems in interval estimation. J R Stat Soc Series B Stat Methodol. 1954;16:175–185.
19. Russell-Jones D, Bode B, de Block C, et al. Double-blind mealtime fast-acting insulin aspart vs insulin aspart in basal–bolus improves glycemic control in T1D: the onset61 trial. Diabetes. 2016;65(suppl1):A77.
20. Cobry E, McFann K, Messer L, et al. Timing of meal insulin boluses to achieve optimal postprandial glycemic control in patients with type 1 diabetes. Diabetes Technol Ther. 2010;12:173–177.
21. Danne T, Aman J, Schöber E, et al. A comparison of postprandial and preprandial administration of insulin aspart in children and adolescents with type 1 diabetes. DiabetesCare. 2003;26:2359–2364.
22. Heise T, Zijlstra E, Nosek L, Rikte T, Haahr H. Pharmacological properties of faster-acting insulin aspart vs insulin aspart in patients with type 1 diabetes receiving continuous subcutaneous insulin infusion: A randomized, double-blind, crossover trial. Diabetes Obes Metab. 2016. doi: 10.1111/dom.12803 [Epub ahead of print]
23. Pozzilli P, Battelino T, Danne T, Havorka R, Jarosz-Chobot P, Renard E. Continuous subcutaneous insulin infusion in diabetes: patient populations, safety, efficacy, and pharmacoeconomics. Diabetes Metab Res Rev. 2016;32:21–39.
24. Phillip M, Battelino T, Rodríguez H, Danne T, Kaufman F. Use of insulin pump therapy in the pediatric age-group. Diabetes Care. 2007;30:1653–1662.
25. Sherr JL, Hermann JM, Campbell F, et al. Use of insulin pump therapy in children and adolescents with type 1 diabetes and its impact on metabolic control: comparison of results from three large, transatlantic paediatric registries. Diabetologia. 2016;59:87–91.
26. Danne T, Tamborlane WW. Insulin pumps in pediatrics: we have the technology. We have the evidence. Why are still so few kids using it? Pediatr Diabetes. 2006;7(suppl 4):2–3.
27. Kovatchev B, Tamborlane WW, Cefalu WT, Cobelli C. The artificial pancreas in 2016: a digital treatment ecosystem for diabetes. Diabetes Care. 2016;39:1123–1126.

SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

How to cite this article: Fath M, Danne T, Biester T, Erichsen L, Kordonouri O, Haahr HFaster-acting insulin aspart provides faster onset and greater early exposure vs insulin aspart in children and adolescents with type 1 diabetes mellitus. Pediatr Diabetes. 2017;18:903–910. https://doi.org/10.1111/pedi.12506