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Original Article

Insulin degludec in combination with bolus insulin aspart is safe and effective in children and adolescents with type 1 diabetes

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Insulin degludec (IDeg) once-daily was compared with insulin detemir (IDet) once- or twice-daily, with prandial insulin aspart in a treat-to-target, randomized controlled trial in children 1–17 yr with type 1 diabetes, for 26 wk (n = 350), followed by a 26-wk extension (n = 280). Participants were randomized to receive either IDeg once daily at the same time each day or IDet given once or twice daily according to local labeling. Aspart was titrated according to a sliding scale or in accordance with an insulin:carbohydrate ratio and a plasma glucose correction factor. Randomization was age-stratified: 85 subjects 1–5 yr. (IDeg: 43), 138 6–11 yr (IDeg: 70) and 127 12–17 yr (IDeg: 61) were included. Baseline characteristics were generally similar between groups overall and within each stratification. Non-inferiority of IDeg vs. IDet was confirmed for HbA1c at 26 wk; estimated treatment difference (ETD) 0.15% $[-0.03; 0.32]_{95\%CI}$. At 52 wk, HbA1c was 7.9% (IDeg) vs. 7.8% (IDet), NS; change in mean FPG was −1.29 mmol/L (IDeg) vs. +1.10 mmol/L (IDet) (ETD −1.62 mmol/L $[-2.84; -0.41]_{95\%CI}$, p = 0.0090) and mean basal insulin dose was 0.38 U/kg (IDeg) vs. 0.55 U/kg (IDet). The majority of IDet treated patients (64%) required twice-daily administration to achieve glycemic targets. Hypoglycemia rates did not differ significantly between IDeg and IDet, but confirmed and severe hypoglycemia rates were numerically higher with IDeg (57.7 vs. 54.1 patient-years of exposure (PYE) [NS] and 0.51 vs. 0.33, PYE [NS], respectively) although nocturnal hypoglycemia rates were numerically lower (6.0 vs. 7.6 PYE, NS). Rates of hyperglycemia with ketosis were significantly lower for IDeg vs. IDet [0.7 vs. 1.1 PYE, treatment ratio 0.41 $(0.22; 0.78)_{95\%CI}$, p = 0.0066]. Both treatments were well tolerated with comparable rates of adverse events. IDeg achieved equivalent long-term glycemic control, as measured by HbA1c with a significant FPG reduction at a 30% lower basal insulin dose when compared with IDet. Rates of hypoglycemia did not differ significantly between the two treatment groups; however, hyperglycemia with ketosis was significantly reduced in those treated with IDeg.

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Introduction

The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) study showed conclusively that good glycemic control delays, and may even prevent, the development of long-term complications in type 1 diabetes (T1D) (1–5). Management of T1D in children and adolescents presents particular challenges. Factors that increase the complexity of treating children include hormonal changes during normal growth and development (e.g., rapid growth, pubertal insulin resistance, psychosocial and cognitive development), family dynamics (including socioeconomic status, cultural considerations and parent/caregiver viewpoints) and the provision and quality of care and support outside the home, for example at school/college (6). In recognition of this, the American Diabetes Association and the International Society for Pediatric and Adolescent Diabetes (ISPAD) have published specific guidance for children (7, 8).

Hypoglycemia is one of the main side effects of insulin therapy and is often viewed as the major barrier to achieving good glycemic control by parents and physicians alike. A number of studies have shown that hypoglycemia has a detrimental effect on the cognitive development of young children, and that episodes of hypoglycemia, particularly nocturnal hypoglycemia, can be extremely frightening both for children and their parents/caregivers (9, 10). It can therefore be tempting to set higher glycemic targets to minimize hypoglycemia. In addition, fear of hypoglycemia can lead to reluctance to titrate to appropriate glucose targets, with resultant hyperglycemia and suboptimal HbA1c. However, underinsulinization can place children at-risk of hyperglycemia with ketosis, which, if left untreated, can progress to diabetic ketoacidosis (DKA) (11). The risk of DKA in children with established T1D is up to 10% per patient per year (11). Children who restrict or omit insulin intentionally, or unintentionally due to unstable family circumstances or limited access to supplies, are at greatly increased risk (12, 13). Basal insulin can help reduce the risk of DKA by providing a continual background level of insulin. The long-acting analogs insulin glargine (IGlar) and insulin detemir (IDet) can provide up to 24-h coverage when administered once daily (OD) or twice-daily (BID) in the case of IDet (14, 15). However, because of their action profile, administration should ideally be at the same time each day to prevent periods of insulin insufficiency (14, 15). As children of all ages often have highly variable daily schedules, a basal regimen that provides flexibility in dosing time may be beneficial.

Insulin degludec (IDeg), a new basal insulin for the treatment of T1D and type 2 diabetes (T2D), has been showed to have an ultra-long duration of action and low variability in adults, producing a consistent glucose-lowering activity profile at steady state (16, 17). Pharmacokinetic data have shown that IDeg has a terminal half-life of approximately 25 h, twice that of IGlar, and a duration of action of more than 42 h (18). A phase 3, randomized, controlled trial in adults with T1D confirmed that IDeg OD effectively reduced HbA1c and fasting plasma glucose (FPG), with a lower risk of nocturnal confirmed hypoglycemia than IGlar (19). Furthermore, studies in adults with T1D and T2D have shown that the IDeg injection time may be varied from day to day without compromising efficacy or safety, offering patients greater convenience and flexibility, when needed (20, 21).

The objective of this trial was to investigate the efficacy and safety of IDeg vs. IDet, both in combination with bolus insulin aspart (IAsp), in children and adolescents with T1D (Fig. 1).

Materials and methods

Trial conduct

This was a 26-wk, phase 3b, randomized, controlled, open-label, multinational, parallel-group, treat-to-target non-inferiority trial with a 26-wk extension, comparing the efficacy and safety of IDeg administered OD with that of IDet administered OD or BID, both in combination with mealtime IAsp. The study was conducted at 72 sites in 12 countries (Bulgaria, Finland, France, Germany, Italy, Japan, the Netherlands, Republic of Macedonia, Russian Federation, South Africa, UK and USA). Of these, South Africa did not participate in the 26-wk extension phase as regulatory approval was not granted. The protocol, protocol amendments, consent form, child assent form, subject information sheet and other information provided to the participants and parents/participants' legal representatives were approved by the relevant independent ethics committees or institutional review boards (written informed consent was obtained prior to participant enrolment) and the trial was conducted according to the Declaration of Helsinki (22) and ICH Good Clinical Practice (23). In some countries assent from children themselves ($\leq$17 yr of age, where appropriate) was required in addition to parental consent. Ongoing safety surveillance was performed by a blinded internal Novo Nordisk safety committee and an unblinded independent Data Monitoring Committee (comprising pediatric and endocrine experts). This trial is registered at www.clinicaltrials.gov: NCT01513473.

Children and adolescents (1–17 yr of age) with T1D who had been receiving insulin treatment (any regimen) for at least 3 months, without concomitant oral antidiabetic drugs and with HbA1c levels of $\leq$11%, were eligible for inclusion (Fig. S1, Supporting Information).

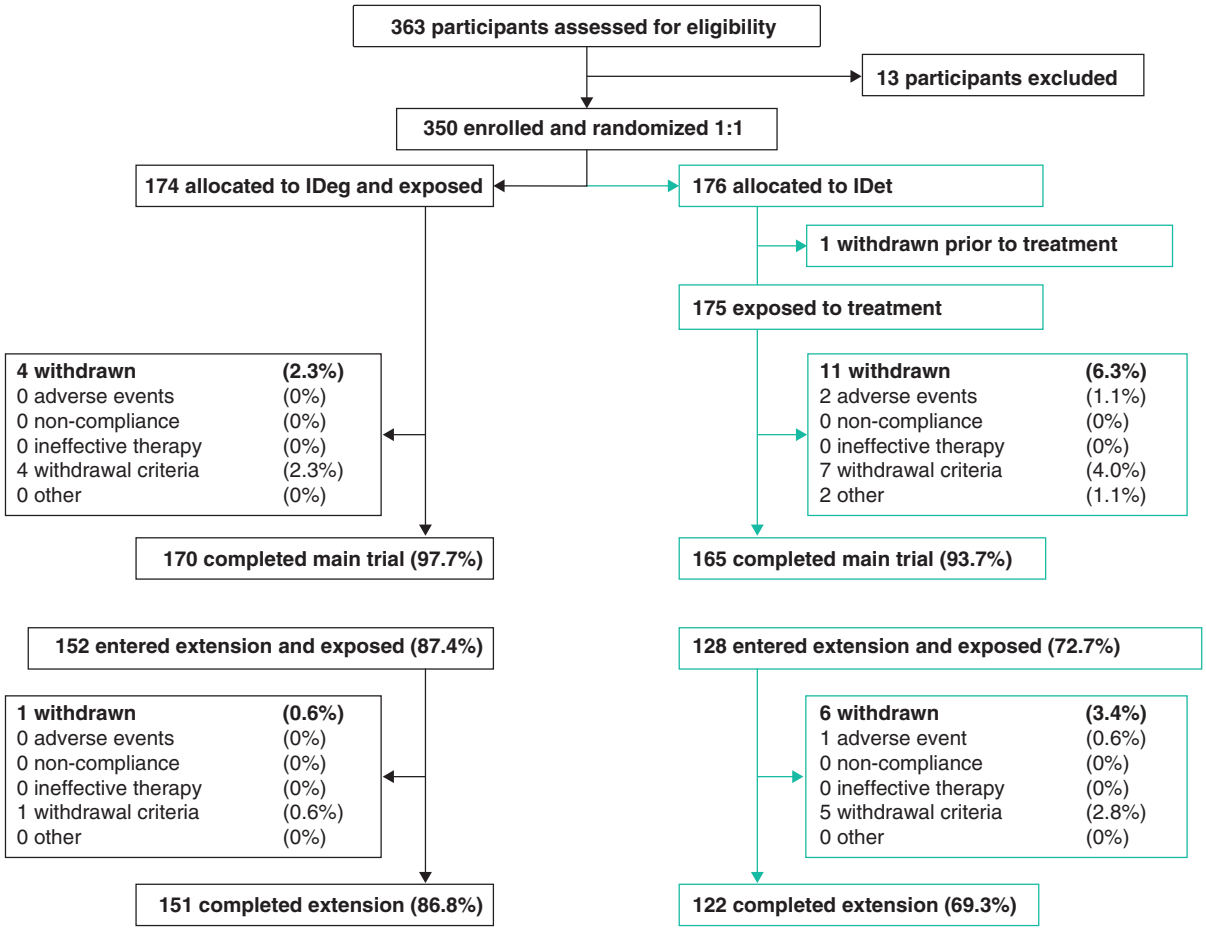

Fig. 1. Participant disposition. IDeg, insulin degludec; IDet, insulin detemir.

Randomization

Following screening, eligible participants were randomized 1:1, using a central interactive voice/web response system, to receive either IDeg (100 U/mL, Penfill® 3-mL cartridge, Novo Nordisk, Bagsværd, Denmark) or IDet (100 U/mL, Penfill® 3-mL cartridge; Novo Nordisk). Randomization was also stratified by age group: 1–5, 6–11 and 12–17 yr, to ensure an approximately equal distribution of participants between treatment arms within each age group.

Procedures

To ensure treatment uniformity between clinics, and to ensure that the patients received optimal treatment, insulin treatment algorithms were developed specifying recommended dose adjustments at different PG levels. Clinical judgment had to be applied to avoid increased risks for the patients. Thus the investigators could overrule the guidelines when necessary. Eligible participants were switched to either IDeg OD or IDet OD or BID with mealtime IAsp at randomization (wk 0). Participants switching to IDet received their dose OD or BID in accordance with local labeling. Participants switching to IDeg received a single dose at the same time each day. The total daily insulin dose was calculated and used to derive the trial bolus and basal doses using the initiation table provided (Table S1), aiming for a basal:bolus ratio of between 50:50 and 30:70 with no basal dose reduction, as this range was generally considered to be appropriate for children with T1D. For example, if the participant's total daily insulin dose prior to the trial was 28 U, the participant would receive a total of 8 U of IDeg or IDet and 20 U of insulin aspart at the ratio of 30:70. The choice of basal:bolus split for each individual was made at the discretion of the investigator. At 26 wk, for those participants not continuing in the extension study, basal insulin was switched to neutral protamine Hagedorn insulin for 7 days to minimize interference with antibody detection at a follow-up visit performed 1 wk later. For those entering the extension study, this was done at 52 wk.

The overall trial duration was approximately 53 wk, including two 26-wk treatment periods and one 7-day basal insulin washout period (Fig. S1). A treat-to-target approach was used to optimize glycemic control and

Table 1. Insulin titration algorithms

Current basal dose		<5 U	5–15 U	>15 U
Pre-breakfast or pre- dinner plasma glucose			Adjustment	
mmol/L	mg/dL	U		
<5.0	<90	−1/2	−1	−2
5.0–8.0	90–145	0	0	0
8.1–10.0	146–180	+1/2	+1	+2
10.1–15.0	181–270	+1	+2	+4
>15.0	>270	+1 1/2	+3	+6
Current bolus dose			≤5U	>5U
Lowest pre-meal or bedtime plasma glucose			Adjustment	
mmol/L	mg/dL		U	U
<5.0	<90		−1	−2
5.0–8.0	90–145		0	0
8.1–10.0	146–180		+1/2	+1
10.1–15.0	181–270		+1	+2
>15.0	>270		+1 1/2	+3

achieve a pre-breakfast self-measured plasma glucose (SMPG) target of 5–8 mmol/L, in accordance with ISPAD guidelines (7). IDeg OD and IDet OD titration was based on the lowest pre-breakfast SMPG value, using glucose meters calibrated to plasma values, on the 3 days prior to each weekly visit/phone contact, and adjusted using a standard titration algorithm (Table 1). Participants receiving IDet OD whose mean pre-breakfast SMPG had reached target but whose mean pre-dinner plasmas glucose (PG) was >8.0 mmol/L (145 mg/dL) commenced an additional morning dose of IDet at 2–4 U, with a pre-dinner titration target of 5–8 mmol/L. If using IDet BID, morning dose titration was based on the lowest pre-dinner SMPG and evening dose titration on the lowest pre-breakfast SMPG on the 3 days prior to visit/phone contact. Titration of IAsp was performed either by use of PG correction factors and insulin:carbohydrate ratios or once weekly, based on the lowest of three SMPG values measured 3 days before a visit/phone contact; pre-meal doses were adjusted according to the lowest post-meal increment observed over the preceding 3 days (Table 1). Carbohydrate counting was only used by those participants and caregivers that had prior experience with this method.

The primary endpoint was change from baseline in HbA1c after 26 wk of treatment. Other efficacy endpoints assessed at both wk 26 and wk 52 included FPG, analyzed by central laboratory, and 4- and 8-point SMPG profiles. Self-measured glucose measurements were performed with capillary blood automatically calibrated to plasma-equivalent glucose values, using a glucose monitor able to capture both blood glucose and blood ketones, which was centrally supplied. Four-point profiles were performed weekly and 8-point profiles were performed at wk 0 (randomization), 12, 26, 38 and 52. Safety variables included adverse events (AEs), hypoglycemic episodes, hyperglycemia, incidence of hyperglycemia with elevated ketones (>1.5 mmol/L), insulin dose, body weight, antibodies and standard laboratory safety assessments. Confirmed hypoglycemia was defined as SMPG <3.1 mmol/L (56 mg/dL) and/or severe episodes as defined by ISPAD [the child has altered mental status and cannot assist in their own care, is semiconscious or unconscious, or in a coma ± convulsions and may require parenteral therapy (glucagon or i.v. glucose)]. The ISPAD definition is very broad and includes a subjective element: 'The child has altered mental status and cannot assist in his own care', and determining whether an episode fulfills the definition can be challenging, especially in young children. Therefore, all reported episodes of severe hypoglycemia were reviewed in a blinded manner by an independent, external pediatric endocrinologist, in order to determine whether the episodes fulfilled the criteria for severe hypoglycemia. Hypoglycemic episodes occurring between 11 pm and 7 am inclusive were classified as nocturnal.

Hyperglycemia was defined as PG values >11.1 mmol/L (200 mg/dL). Hyperglycemia with ketosis was defined when PG exceeded 14.0 mmol/L (252 mg/dL) and the capillary blood ketones exceeded 1.5 mmol/L (27 mg/dL).

Laboratory analyses were conducted at central laboratories (Quintiles Laboratories Europe, Livingston, UK; Quintiles Laboratories South Africa, Centurion, South Africa; Quintiles Laboratories Limited, Marietta, Georgia; Quintiles Laboratories Japan, Tokyo, Japan), with the exception of FPG, which was analyzed at Laboratorium für Klinische Forschung GmbH (Schwentinental, Germany). Antibody analyses were conducted at Celerion Switzerland AG (Fehraltorf, Switzerland), using a validated radioimmunoassay method (24, 25).

Continuous glucose monitoring

Continuous glucose monitoring (CGM) was conducted in a subset of participants in the IDeg group (74 participants) and IDet group (75 participants) at selected sites in Bulgaria, Finland, France, Germany, Italy, the Netherlands, UK, South Africa, Russia and US during the main trial period only. Interstitial glucose (IG) profiles obtained by CGM were performed over a period of 3–6 continuous days. The CGM system (MedTronic International, Switzerland) recorded IG values every fifth minute. CGM was measured between screening and randomization, and again after at least 5 months of treatment.

Statistical methods

The primary objective was to confirm the non-inferiority of IDeg OD to IDet, both with mealtime

IAsp, in controlling glycaemia with respect to change from baseline in HbA1c after 26 wk of treatment. Non-inferiority was confirmed if the upper limit of the two-sided confidence interval (CI) for the treatment difference for mean change in HbA1c was ≤0.4%, in accordance with regulatory guidelines (26). The sample size was determined using a *t*-statistic under the assumption of a one-sided test of size 2.5%, a zero mean treatment difference and standard deviation (SD) of 1.25% for HbA1c. A total of 346 participants had to be randomized to achieve at least 80% or greater power in the evaluation of the per protocol (PP) analysis set, after adjustment for a 10% dropout rate.

Statistical analyses of all efficacy and safety endpoints included all randomized participants [full analysis set (FAS)], following the intention-to-treat principle. No statistical analyses were performed at the stratified age-group data level as the numbers were too low. Descriptive tables and figures were based on FAS for efficacy endpoints and on the safety analysis set (SAS), consisting of all randomized participants exposed to at least one dose of the investigational product, for safety endpoints. Missing values were imputed using last observation carried forward. Comparisons between IDeg and IDet were analyzed at 26 and 52 wk.

Baseline characteristics, demographics, AEs and number of hypoglycemic episodes (including CGM measurements) are presented using descriptive statistics. Treatment differences in change in HbA1c, FPG, body weight and duration of low/high IG measurements by CGM were estimated using analysis of variance (ANOVA), adjusted by treatment, sex, region, age group and baseline value of the respective endpoint. The robustness of the analysis of change in HbA1c from baseline to wk 26 was explored by additional analyses, including analysis of the PP set. Hypoglycemic events and number of low/high IG readings according to CGM were modeled using negative binomial regression, adjusted by treatment, sex, region and age group as fixed factors and with the logarithm of the time period for which a hypoglycemic episode is considered treatment emergent as offset. This time period was defined as the time elapsed from the first day of treatment with investigational product to 7 days after last day of treatment, both inclusive. A *post hoc* analysis examined hypoglycemia rates during the maintenance period (from wk 16 to end of trial), when the majority of participants were anticipated to have achieved stable glycemic control and insulin dose. Analyses were repeated for HbA1c, FPG, SMPG, hypoglycemic episodes, antibodies and central laboratory parameters at 52 wk using the extension trial set (ETS; participants who attended the first visit of the extension period) to assess stability of key results. Data were reported using a 95% CI and p-values for two-sided testing at $\alpha = 0.05$.

Results

Patient characteristics

Of the 350 randomized participants, 349 (99.7%) were exposed and most [170/174 (97.7%) for IDeg, 165/175 (93.7%) for IDet] completed the main trial period. The percentage of participants withdrawn during the main period from the IDet group was higher than from the IDeg group (6.3 vs. 2.3%, respectively); see Fig. 1. The majority of withdrawals were because of participants meeting pre-specified withdrawal criteria including withdrawal of consent (Table S2). Of 170 main trial completers in the IDeg group, 152 (87.4%) continued into the extension and 151 (86.8%) of those randomized in the main trial completed the extension period. In contrast, of 165 main trial completers in the IDet group, only 128 (72.7% of participants randomized to IDet) continued into the extension and 122 (69.3% of participants randomized to IDet) completed the extension period (Fig. 1). Baseline characteristics overall and in the stratified age groups were representative for a pediatric population with T1D and both groups were well matched at baseline, with the exception of HbA1c and FPG which were slightly higher in the IDeg arm; Table 2. The pre-trial regimen of most participants (95.7%) comprised basal–bolus therapy. Of those on alternative regimens, 4% were using premix insulin (alone or combined with either basal or bolus insulin), 0.3% were using basal insulin alone and 1.4% were using bolus insulin alone.

Glycemic control

Non-inferiority of IDeg to IDet with respect to change in HbA1c from baseline to wk 26 was confirmed [estimated treatment difference (ETD) IDeg–IDet: 0.15%-points, $(0.03; 0.32)_{95\%\,CI}$ (1.6 mmol/mol, $(0.3; 3.5)_{95\%\,CI}$)]. The robustness of the primary analysis was supported by analysis of the PP set [ETD IDeg–IDet: 0.19%-points, $(0.01; 0.37)_{95\%\,CI}$ (2.0 mmol/mol, $(0.1; 4.0)_{95\%\,CI}$)] and other sensitivity analyses (data not shown). The observed mean decrease in HbA1c from baseline to wk 52 was similar between IDeg [−0.27%-points (3 mmol/mol)] and IDet [−0.22%-points (2.4 mmol/mol)] groups and the trend over time in HbA1c was also similar (Fig. 2A). Similar between-treatment reductions in HbA1c were also observed in children 1–5 yr of age [−0.36 %-points (3.9 mmol/mol) for $IDeg_{1-5}$ and −0.16%-points (1.7 mmol/mol) for $IDet_{1-5}$,], children 6–11 yr of age [−0.35%-points (3.8 mmol/mol) for $IDeg_{6-11,}$ −0.33%-points (3.6 mmol/mol) for $IDet_{6-11}$] and adolescents 11–17 yr of age [−0.10%-points (1.1 mmol/mol) for $IDeg_{11-17}$ and −0.14%-points (1.5 mmol/mol) for $IDet_{11-17}$], respectively, at 52 wk.

Table 2. Participant baseline characteristics

Characteristic	IDeg	IDet
Full analysis set (FAS), n	174	176
1–5	43	42
6–11	70	68
12–17	61	66
Female/Male (%)	44.8/55.2	44.3/55.7
1–5	46.5/53.5	59.5/40.5
6–11	42.9/57.1	39.7/60.3
12–17	45.9/54.1	39.4/60.6
Race: White/Black/Asian/Other (%)	78.2/2.9/13.2/5.7	71.0/2.8/18.2/8.0
1–5	86.0/2.3/2.3/9.3	78.6/2.4/9.5/9.5
6–11	77.1/1.4/14.3/7.2	72.1/1.5/17.6/8.8
12–17	73.8/4.9/19.7/1.6	65.2/4.5/24.2/6.0
Ethnicity: Hispanic or Latin American (%)	4.0	1.7
1–5	9.3	2.4
6–11	4.3	2.9
12–17	0	0
Age (yr)	10.0 (±4.4)	10.0 (±4.4)
1–5	4.3 (±1.1)	4.1 (±1.1)
6–11	9.3 (±1.7)	9.2 (±1.7)
12–17	14.8 (±1.7)	14.6 (±1.8)
Weight (kg)	38.0 (±18.7)	37.8 (±18.9)
1–5	18.0 (±4.0)	17.8 (±3.8)
6–11	32.9 (±7.7)	31.4 (±8.1)
12–17	57.9 (±14.5)	57.2 (±14.2)
BMI (kg/m^2)	18.7 (±3.6)	18.5 (±3.6)
1–5	16.2 (±1.7)	16.3 (±1.7)
6–11	17.7 (±2.6)	17.1 (±2.3)
12–17	21.6 (±3.8)	21.5 (±3.6)
Duration of diabetes (yr)	3.9 (±3.6)	4.0 (±3.4)
1–5	1.4 (±1.0)	1.4 (±1.0)
6–11	3.2 (±2.4)	3.9 (±2.4)
12–17	6.4 (±4.3)	5.7 (±4.2)
HbA1c (%)	8.2 (±1.1)	8.0 (±1.1)
1–5	8.1 (±1.2)	8.0 (±1.3)
6–11	8.1 (±1.0)	8.1 (±1.0)
12–17	8.3 (±1.1)	8.0 (±1.1)
HbA1c (mmol/mol*)	66.1	63.9
1–5	65.0	63.9
6–11	65.0	65.0
12–17	67.2	63.9
FPG, mmol/L [mg/dL]	9.0 (±5.2) [162.1 (±94.4)]	8.4 (±4.9) [151.0 (±87.7)]
1–5	9.3 (±6.0) [167.5 (±107.6)]	9.2 (±5.2) [166.0 (±93.5)]
6–11	9.3 (±4.1) [166.8 (±74.3)]	8.2 (±5.0) [147.6 (±89.4)]
12–17	8.5 (±5.8) [153.5 (±105.1)]	8.1 (±4.6) [145.1 (±82.5)]

*Calculated value.
Data are mean (SD) unless otherwise stated.

At 52 wk, there was a statistically significant difference in laboratory-analyzed FPG, which decreased from baseline in the IDeg group, but increased in the IDet group. With IDeg, the mean FPG decreased from 9.0 to 7.8 mmol/L, corresponding to a change of −1.29 mmol/L. With IDet the mean FPG increased from 8.4 to 9.5 mmol/L, corresponding to a change of +1.10 mmol/L, ETD (IDeg–IDet): −1.62 mmol/L [−2.84; −0.41]$_{95\%CI}$, p = 0.0090, Fig. 2B. Similar changes were observed for the three age groups and for the ETS population, both overall (−1.67 mmol/L in the IDeg group and +0.48 mmol/L in the IDet group) and stratified by age group.

After 52 wk, the change from baseline in the mean of the 8-point SMPG profiles was significantly different for the two treatments. The observed mean change was −0.7 mmol/L with IDeg and +0.3 mmol/L with IDet, ETD (IDeg–IDet): −0.79 mmol/L (−1.32; −0.26)$_{95\%CI}$, p = 0.0036 (Fig. 1C). Similar patterns were seen between age groups. In the IDeg group, post-prandial SMPG values at wk 12, 26, 38 and 52 decreased from baseline, whilst there was no apparent reduction in the IDet group. After 52 wk, there was a statistically significant treatment difference post-breakfast [IDeg–IDet: −1.57 mmol/L (−2.65; −0.49)$_{95\%CI}$, p = 0.0045], post-dinner [IDeg–IDet:

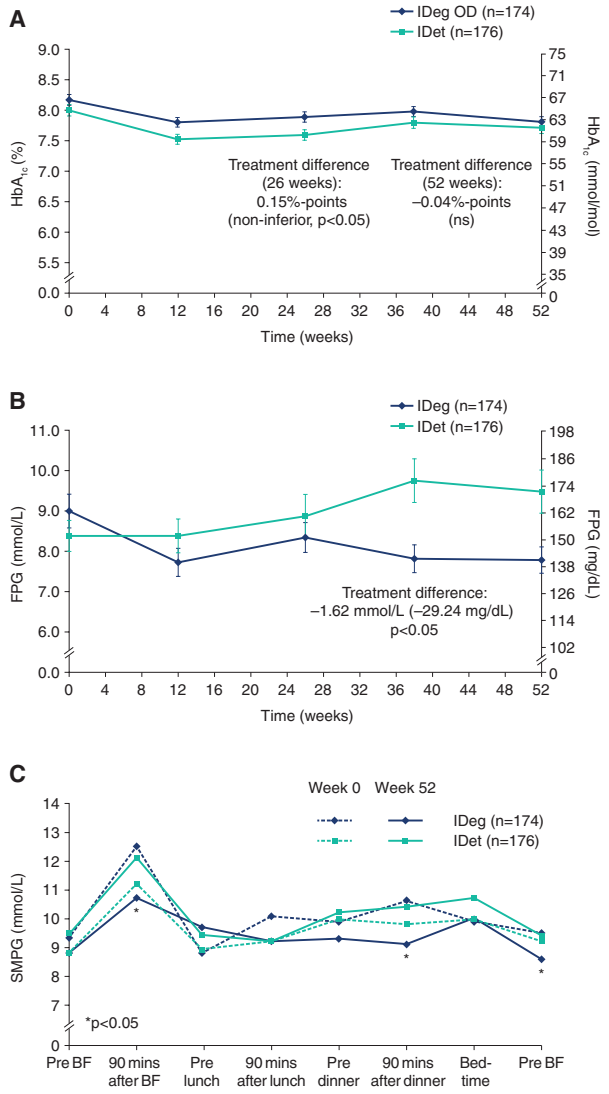

Fig. 2. Mean HbA1c over time (panel A) mean FPG over time (panel B) and mean 8-point SMPG profiles at wk 0 and wk 56 (panel C). Mean values with error bars (standard error of the mean) based on full analysis set and last observation carried forward imputed data. P-values are from an ANCOVA model. IDeg, insulin degludec; IDet, insulin detemir, SMPG, self-measured plasma glucose.

−1.85 mmol/L $(-2.95; -0.75)_{95\%CI}$, p = 0.0011) and pre-breakfast on the second day [IDeg–IDet: −0.94 mmol/L $(-1.77; -0.11)_{95\%CI}$, p = 0.0264]. There were minor profile variations between age groups.

As with the 8-point profile data, pre-breakfast SMPG (based on the 4-point profile) decreased from baseline to wk 2 in the IDeg group and subsequently remained lower than for the IDet group throughout the trial. After 52 wk, the observed mean pre-breakfast value was significantly lower with IDeg compared with IDet [8.7 vs. 9.4 mmol/L, respectively; ETD IDeg–IDet: −0.76 mmol/L $(-1.46; -0.05)_{95\%CI}$, p = 0.0354]. Within-subject variability in pre-breakfast SMPG after 52 wk was similar for the two treatment arms; ETD (IDeg–IDet): 1.04, $(0.93; 1.16)_{95\%CI}$.

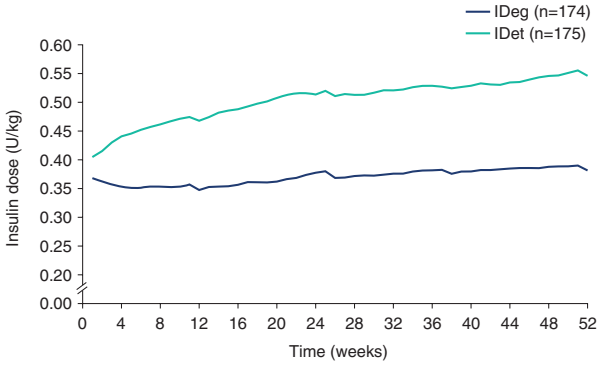

Fig. 3. Mean basal insulin dose over time. Mean values based on full analysis set and last observation carried forward imputed data. IDeg, insulin degludec; IDet, insulin detemir.

Insulin dose

At baseline, the mean daily basal dose was slightly lower in the IDeg group compared with the IDet group (0.37 vs. 0.40 units/kg, respectively) and remained fairly constant throughout the trial, reaching 0.38 U/kg by wk 52. By contrast, the mean daily basal dose in the IDet group increased over the study duration (Fig. 3). The mean daily dose of IDeg remained lower than that of IDet throughout the trial and across the three age groups (Table 3). The overall pattern was similar in the ETS, apart from a slightly lower basal insulin dose at wk 1 in participants 6–11 yr of age in the IDet group compared with the SAS (0.39 vs. 0.42 U/kg). After 52 wk, 112 (64%) participants were using IDet BID. Mean daily IAsp dose increased gradually during the trial in both treatment groups. After 52 wk, mean daily IAsp dose was marginally lower in the IDeg group compared with the IDet group (0.55 vs. 0.58 U/kg) (Table 3). After 52 wk of treatment, participants receiving IDeg required 30% less basal insulin, and 18% less insulin overall, and the basal:bolus ratios were 41:59 with IDeg vs. 48:52 with IDet. The mean basal (IDeg:IDet) dose ratio (U/kg) was 0.70. In contrast, the bolus insulin dose ratio (IAsp:IAsp) was ~1, indicating that participants in both groups received comparable doses of IAsp.

Table 3. Mean insulin doses

Mean insulin dose	IDeg	IDet
Number of patients (n)	174	175
Basal, U/kg (U)		
Baseline	0.37 (15)	0.40 (16)
End of trial	0.38 (17)	0.55 (24)
Bolus, U/kg (U)		
Baseline	0.50 (20)	0.52 (20)
End of trial	0.55 (24)	0.58 (24)
Total, U/kg (U)		
Baseline	0.87 (35)	0.93 (36)
End of trial	0.93 (41)	1.13 (48)

IDeg, Insulin degludec; IDet, insulin detemir.

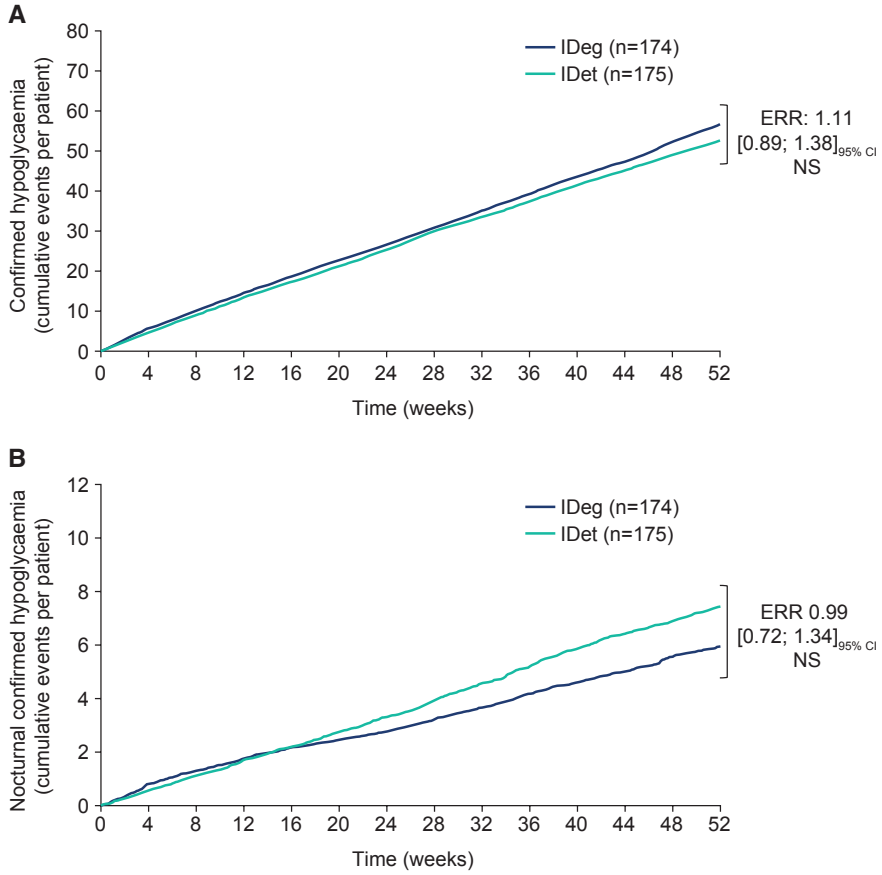

Fig. 4. Cumulative rates of confirmed (A) and nocturnal confirmed (B) hypoglycaemia. Mean values based on safety analysis set and last observation carried forward imputed data. IDeg, insulin degludec; IDet, insulin detemir.

Hypoglycemia

At 52 wk, rates of confirmed hypoglycemia [i.e., PG <3.1 mmol/L and/or severe (altered mental status, cannot assist in own care, semiconscious/unconscious, or in coma ± convulsions)] were similar for IDeg and IDet [57.7 vs. 54.1 events/exposure year, estimated rate ratio (ERR): 1.11 (0.89; 1.38)$_{95\%CI}$, NS] (Fig. 4A and Table 4), as were rates of nocturnal hypoglycemia [6.0 vs. 7.6 events/exposure year, ERR 0.99 (0.72; 1.34)$_{95\%\,CI}$, NS; Fig. 4B and Table 4]. Incidence and rates of severe hypoglycemia were numerically higher with IDeg than IDet, but the difference was not statistically significant: 17.8 vs. 13.7%; 0.51 vs. 0.33 events/exposure year [ERR 1.30 (0.64; 2.64)$_{95\%\,CI}$, NS; Table 4]. Rates of severe hypoglycemia, including only episodes of semi consciousness/unconsciousness and coma ± convulsions, were 0.09 and 0.14 events/exposure year for IDeg and IDet, respectively [ERR 0.62 (0.24; 1.60)95% CI, NS; *post hoc* analysis based on external classification of severe hypoglycemic episodes; Table 4].

Participants in the IDet group continuing in the extension had markedly lower rates of both confirmed (0.31 vs. 0.63 events/exposure year) and severe (50 vs. 80 events/exposure year), but not nocturnal confirmed (7.3 vs. 6.9 events/exposure year) hypoglycemia at 26 wk compared with those discontinuing after the main trial period. In the IDeg arm, those continuing into the extension had higher rates of severe hypoglycemia (0.48 vs. 0.11 events/exposure year) and lower rates of nocturnal confirmed hypoglycemia (5.5 vs. 9.3 events/exposure year), whereas rates of confirmed hypoglycemia were similar (58 vs. 55 events/exposure year) at 26 wk irrespective of continuation or not (data not shown).

Hyperglycemia with ketosis

The rate of hyperglycemic episodes (>14 mmol/L) with ketosis (>1.5 mmol/L) was significantly lower for IDeg vs. IDet [0.7 vs. 1.1 events/exposure year, treatment ratio 0.41 (0.22; 0.78)$_{95\%\,CI}$, p = 0.0066; Fig. 5], and lower rates were observed for IDeg compared to IDet for all age groups. The same pattern was also observed in the ETS population. When stratified by age, children 1–5 yr of age had a higher rate of episodes of hyperglycemia with ketosis in both treatment groups (1.34 vs. 1.61 events/exposure year for IDeg vs. IDet, respectively) compared with the two older age groups

Table 4. Hypoglycemia

	IDeg (n = 174)				IDet (n = 175)			
	n	%	E	R	n	%	E	R
All confirmed hypoglycemia	171	98.3	9317	5771	168	96.0	7967	5405
Nocturnal confirmed hypoglycemia	133	76.4	973	603	125	71.4	1120	760
All reported severe hypoglycemia	31	17.8	82	51	24	13.7	48	33
Externally classified severe episodes	28	16.1	61	38	22	12.6	38	26
Altered mental status and cannot assist in own care	21	12.1	46	28	11	6.3	18	12
Semiconscious or unconscious	7	4.0	7	4	6	3.4	10	7
Coma ± convulsions	6	3.4	8	5	7	4.0	10	7
Not severe hypoglycemia	5	2.9	13	8	5	2.9	8	5
Not possible to classify	5	2.9	8	5	1	0.6	2	1

E, number of events; IDeg, Insulin degludec; IDet, insulin detemir; n, number of participants; %, percentage of participants; R, event rate per 100 patient-years of exposure; SAS, safety analysis set.

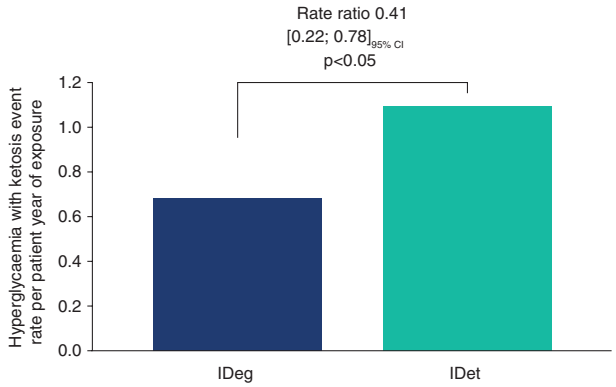

Fig. 5. Rate of hyperglycemia with ketosis. Mean values with error bars (standard error of the mean) based on full analysis set and last observation carried forward imputed data. *P*-values are from an ANCOVA model. IDeg, insulin degludec; IDet, insulin detemir.

Table 5. Summary of AEs

	IDeg	IDet
All patients	174	175
Number of patients with events	161	157
Percentage of patients with events	92.5%	89.7%
Number of events	1462	1266
Adverse event rate per 100 PYE	906	859
Number of patients with serious AEs	18	16
Percentage of patients with serious AEs	10.3%	9.1%
Number of events	25	24
Serious adverse event rate per 100 PYE	15	16
Number of patients withdrawn due to AEs	0	3
Percentage of patients withdrawn due to AEs	0.0%	1.7%

AEs, adverse events; IDeg, Insulin degludec; IDet, insulin detemir; PYE, patient-years of exposure.

(0.50 vs. 0.92 events/exposure year for $IDeg_{6–11}$ vs. $IDet_{6–11}$, and 0.43 vs. 0.95 events/exposure year for $IDeg_{12–17}$ vs. $IDet_{12–17}$, respectively).

Other safety endpoints

At 52 wk, mean body weight SD scores had increased in the IDeg group but remained relatively unchanged in the IDet group [change: +0.11 vs. −0.06 kg, ETD: 0.17 $(0.10; 0.25)_{95\%\,CI}$, $p < 0.0001$].

AE profiles were similar for IDeg and IDet (Table 5). The majority of reported AEs for both groups were mild or moderate in severity and considered unlikely to be related to trial product. Of those considered possibly or probably related to trial product, ~97% were resolved by the end of the trial. The observed rates of serious AEs (SAEs) were also similar for IDeg and IDet (Table 5) and the most common SAEs were infections, hypoglycemia and hyperglycemia for both groups. The rate of SAEs considered possibly or probably related to the investigational medicinal product was five events per 100 PYE with IDeg and 3 events per 100 PYE with IDet, respectively. Only three participants, all from the IDet group, withdrew from the trial due to AEs (wrong trial drug administration, hypoglycemic seizure and anxiety disorder). Two cases of DKA were reported, both in the IDeg group, but were considered unlikely to be related to trial product.

The mean level of insulin antibodies cross-reacting between insulin analogs and human insulin decreased slightly with IDeg and increased slightly with IDet during the trial period (data not shown). No clinically relevant differences either from baseline to end of treatment or between the two treatment groups were observed for vital signs, physical examination, electrocardiograms, fundoscopy or laboratory measurements.

CGM subgroup analysis

In the subgroup of participants who performed CGM assessment before and during treatment with IDeg (74 participants) and IDet (75 participants) in the main trial period, the event rates for low IG and high IG generally reflected the pattern for hypo-

and hyperglycemic episodes. At wk 26, there were no significant differences between the IDeg and IDet groups for either IG <3.1 mmol/L [IDeg:IDet ratio: 1.50 (0.97; 2.32)$_{95\%CI}$] or IG <3.9 mmol/L [IDeg:IDet ratio: 1.29 (0.98; 1.71)$_{95\%CI}$]. Nocturnally, observed rates with IDeg and IDet were 2.49 vs. 3.13 events per 100 PYE for IG < 3.1 mmol/L and 5.16 vs. 5.22 events per 100 PYE for IG ≤3.9 mmol/L. Owing to the low number of nocturnal events, no statistical analysis was conducted. The duration of low IGs was not significantly different between IDeg and IDet for either IG <3.1 mmol/L [IDeg–IDet contrast: 0.12 h (−0.33; 0.56)$_{95\%CI}$, NS] or IG <3.9 mmol/L [IDeg–IDet contrast: 0.30 h (−0.37; 0.97)$_{95\%CI}$, NS].

The observed rate of high IGs after 26 wk was 11.20 (IDeg) vs. 10.66 (IDet) events per 100 PYE, respectively, with no significant difference between treatments [IDeg–IDet contrast: 1.03 (0.91; 1.17)$_{95\%CI}$, NS]. Nocturnal observed high IG rates after 26 wk were 12.05 (IDeg) vs. 10.61 (IDet) events per 100 PYE, respectively. There was no significant difference between treatments in the observed duration of high IGs overall [8.07 vs. 7.40 h; IDeg–IDet contrast: 0.47 (−0.69; 1.64)$_{95\%CI}$, NS] or nocturnally (2.92 vs. 2.12 h for IDeg vs. IDet, respectively).

Discussion

Intensive insulin therapy is associated with reduced long-term complications compared with non-intensive therapy in people with T1D and as such has become the standard of care. Treating intensively to reach glycemic targets can be particularly challenging in children, as their needs are in constant flux during their growth and development toward adulthood. Although a basal–bolus regimen containing basal insulin analogs enables many patients to achieve their glycemic targets, issues associated with variability of action, and an action profile requiring strict administration timing, can reduce the likelihood of attaining good glycemic control, particularly for children and adolescents, whose daily routine (and/or that of their parent/caregiver) can vary substantially. Poor glycemic control can result in persistent hyperglycemia and increasing risk of DKA. IDeg has a duration of action exceeding 42 h and a reduced intra-patient variability in glucose-lowering effect, and thus may offer a desirable alternative to other insulin analogs by enabling a degree of flexibility in dosing time when needed (17, 27).

This study has showed that IDeg OD provides effective long-term improvements in glycemic control, when compared with IDet OD or BID, both with mealtime IAsp in children with T1D as young as 1 yr of age. In this study, the titration guideline recommended that IDeg be dosed at the same time each day and IDet in accordance with local labeling. Throughout the trial, IDet doses were consistently higher than IDeg doses, showing that improvements in FPG were achieved with lower daily insulin doses in the IDeg group. On the basis of insulin dose ratios at 52 wk, the IDeg group required less basal insulin and less insulin overall compared with the IDet group. The higher IDet dose is probably in part due to 64% of the group receiving IDet BID, which is well-documented to increase basal doses (28, 29). The fact that IDeg ensures basal insulin coverage with one daily injection for all is an important benefit, particularly in children, as this reduces the burden of insulin injections.

Furthermore, although not formally tested in this study, flexibility in administration timing of IDeg was shown to be possible without compromising glycemic control in adults (20, 21). Owing to the preserved pharmacokinetic properties of IDeg across pediatric and adult populations (30), the potential for flexibility in dosing time when needed may make IDeg a very useful option for children and their caregivers.

In this trial, hypoglycemia was evaluated using both ISPAD classifications and a Novo Nordisk definition of confirmed hypoglycemic episodes PG <3.1 mmol/L and/or severe hypoglycemia). Whereas severe hypoglycemia in adults is defined based on ability to self-treat (31), the ISPAD definition contains a broader, more subjective component: 'The child is having altered mental status and cannot assist in their care' (10). On the basis of external classification, the majority of hypoglycemic episodes were deemed severe based on this most subjective component. For severe episodes 'accompanied by either (semi) unconsciousness or coma ± convulsion', *post hoc* analysis showed that the observed rates were either numerically lower with IDeg compared with IDet or similar between treatments, respectively. Thus, rates of severe hypoglycemia in this trial cannot be directly compared to rates of severe hypoglycemia in other pediatric trials where a narrower definition of severe hypoglycemia (e.g. episodes accompanied by seizure/loss of consciousness/coma) may have been used. Most severe episodes occurred during the day and in most cases, bolus insulin was the last insulin administered (results not shown). Moreover, incidence of severe hypoglycemia was low with <1% of hypoglycemic episodes classified as severe with either treatment using the ISPAD criteria.

Nocturnal hypoglycemia represents a pivotal parameter; as these episodes are usually independent of bolus doses, exercise or food intake, they provide the most relevant comparison standard for basal insulins. IDeg has consistently been showed to be associated with lower nocturnal hypoglycemia rates in adults compared with other basal insulins (19, 32–35). In this trial, there was a numerical reduction in nocturnal hypoglycemia in favor of IDeg, although statistical

significance was not achieved. The ultra-long, flat action profile and reduced intrapatient variability of IDeg facilitate improvements in FPG without increasing nocturnal hypoglycemic episodes. This property is especially beneficial for young children, where nocturnal hypoglycemia is of particular concern (36, 37). It should be noted that in this trial participants were transferred from pre-trial basal insulin to IDeg or IDet without specific dose reduction recommendations. However, evidence from the phase 3 trial program has led to the recommendation that the dose of both basal and bolus insulin should be reduced upon initiation of IDeg (38), and a similar recommendation would seem appropriate for children, based on the lower pre-breakfast, post-breakfast and post-dinner glucose levels observed in the IDeg arm in this trial. The values for pre- and post-breakfast in particular reflect the effect of greater basal control, which could be explained by the ultra-long duration of IDeg; a lower pre-breakfast, leading to a reduction in post-breakfast by default, although bolus insulin certainly will also play a role. The effect on post-lunch glucose values may be confounded by the availability (or lack of) medical assistance to administer bolus insulin during school/nursery hours.

At the opposite end of the glycemic spectrum, inadequate treatment can lead to hyperglycemia and if left untreated, rising ketone levels may progress to DKA, which is associated with increased morbidity and mortality (11). Prevention of DKA is of particular importance in children and adolescents, whose continuous cognitive and physical development place them at particular risk (11). In this trial, IDeg treatment led to a significant reduction in the rates of hyperglycemia with ketosis when compared with IDet. This reduction may be attributed to the ultra-long and flat pharmacokinetic profile of IDeg.

The CGM data from a subset of participants generally confirmed the patterns of hypo- and hyperglycemia (but not hyperglycemia with ketosis) discussed above, and showed that the duration of low IGs was not significantly longer for IDeg than IDet. In general, IDeg and IDet were both well tolerated and there were no clinically meaningful differences in relation to AEs, antibodies and standard safety parameters.

Limitations of this trial include the greater extent of discontinuation following the main study of participants in the IDet group compared with the IDeg group. Those participants from the IDet group who discontinued had a higher confirmed and severe hypoglycemia rate than those who continued. Secondly, this was an open-label trial and investigators may have been more vigilant in their management of the IDeg arm, including reporting of AEs. Furthermore, as 46% of those enrolled received IDet as part of their prior therapy, familiarity may have affected both the dosing and hypoglycemia rates observed, especially during the initial part of the trial.

The multinational nature of the trial population, covering 12 countries and a range of racial backgrounds, and the broad age range of participants who were all characteristic of patients with T1D, make these findings highly generalizable to the global pediatric population with T1D. Moreover, this study has provided a comprehensive assessment of severe hypoglycemia in a pediatric population.

Conclusion

In conclusion, this trial has showed that IDeg offers a valuable new addition to the treatment of T1D in children, with the potential to deliver similar glycemic control to IDet, achieved with comparable safety, but reduced hyperglycemia with ketosis in a single daily injection.

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Author contributions

N. T. acts as guarantor for the contents of this article. All authors (N. T., L. D., V. I., T. K., G. K., A. P., J. S., S. T., A. M. O. F., O. K. and T. D.) were involved in critical analysis and interpretation of the data, drafting/critically revising the article, and shared in the final responsibility for the content of the manuscript and the decision to submit it for publication.

Conflict of interest

N. T. has participated in advisory boards for Novo Nordisk, Eli Lilly and Lifescan. He has acted as a paid consultant to Novo Nordisk in the capacity of an external speaker at international meetings and his institution has received financial support for the delivery of clinical research trials from Novo Nordisk, Sanofi Aventis and Eli Lilly. L. D. has participated in advisory boards for Sanofi and received research support from Novo Nordisk. G. K. has acted as a consultant to Novo-Nordisk, providing consultation on the definition of hypoglycemia in children. A. P. has participated in advisory boards and speakers' bureau for Novo Nordisk and has also received research support from Novo Nordisk. J. S. has received grant funding from Daiichi Sankyo. S. T. has participated

in advisory boards for Novo Nordisk, Sanofi Aventis, Eli Lilly and Lifescan. He has also received speaker honoraria from Roche Diagnostics, Novo Nordisk and Sanofi Aventis. A. M. O. F. and O. K. are employees of Novo Nordisk and own stock in the company. T. D. has received speakers' honoraria, research support and has consulted for Eli Lilly, Medtronic, Novo Nordisk, Roche, Bristol-Myers Squibb (BMS)/AstraZeneca, Boehringer, Bayer, Abbott, DexCom and Sanofi. V. I. and T. K. have no conflicts of interest to disclose.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Fig. S1. Trial design schematic.

Table S1. Titration guideline for insulin dose at initiation.

Table S2. Withdrawals according to prespecified criteria.

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