Pediatric Diabetes

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Original Article

Treatment with insulin detemir or NPH insulin in children aged 2–5 yr with type 1 diabetes mellitus

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This randomised (1:1), multinational, open-labelled, parallel group trial compared insulin detemir (IDet) with neutral protamine Hagedorn (NPH) insulin, in combination with mealtime insulin aspart, over 1 yr in subjects aged 2–16 yr with type 1 diabetes mellitus. Of 348 randomised subjects, 82 (23.6%) were 2–5 yr (IDet: 42, NPH: 40). This article is a descriptive subgroup analysis of these young children. Baseline characteristics (IDet vs. NPH) were similar: mean age, 4.3 vs. 4.5 yr; diabetes duration, 2.2 vs. 2.1 yr; males, 42.9 vs. 52.5%. Mean haemoglobin A1c (HbA1c) was similar between groups at baseline (8.2 vs. 8.1%), and changed little over 1 yr (8.1 vs. 8.3%). Fasting plasma glucose (FPG) was similar at baseline (8.44 vs. 8.56 mmol/L) and decreased during the study (−1.0 vs. −0.45 mmol/L). A lower rate of hypoglycaemia was observed with IDet compared with NPH (24-h; 50.6 vs. 78.3 episodes per patient-year; nocturnal hypoglycaemia, 8.0 vs. 17.4 episodes per patient-year). No severe hypoglycaemic episodes occurred with IDet, while 3 subjects reported 6 episodes with NPH. Change in weight standard deviation score standardised by age and gender was −0.17 with IDet and +0.03 with NPH. A slightly lower proportion of subjects in this age group reported adverse events with IDet than with NPH (69.0 vs. 77.5%). Serious adverse events were few (5 with IDet, 7 with NPH). In conclusion, long-term treatment with IDet in children aged 2–5 yr suggested similar glycaemic control, greater reduction in FPG, lower rates of hypoglycaemia, no inappropriate weight gain, and fewer adverse events compared with NPH.

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Key words: AE – BMI – DCCT – detemir – FPG – GIR – HbA1c – HPLC – IAsp – IDet – IVRS – NPG – NPH – paediatrics – PG – randomised clinical trial – SAE – safety – SMPG – T1DM

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The Diabetes Control and Complications Trial (DCCT) and other landmark studies have shown that intensive diabetes management in adults and adolescents results in better glycaemic control and delays the onset and slows the progression of vascular and neurological complications (1–4). Studies in preadolescent children have also shown that poor glycaemic control in the young is not harmless and that early intervention is needed to improve prognosis (5).

Intensive insulin therapy is, however, associated with an increased risk of hypoglycaemia and weight gain. The challenge to achieve tight glycaemic control

while reducing the risk of hypoglycaemia is particularly difficult during early childhood due to behavioural and social factors (including variable exercise and eating patterns, dependence on caregivers for injections and blood tests, diabetes care in day care and schools) and physiological consequences of growth, particularly the 'dawn phenomenon', which is a very significant obstacle to optimising glycaemic control in young children, particularly on conventional insulin regimes (6). An ideal treatment would be a physiological, flexible, and predictable insulin regimen protecting against hypoglycaemia (7), and inappropriate weight gain. Continuous subcutaneous insulin infusion is often the most appropriate means of achieving this goal in the very young, but may not be affordable or available, and is not suitable for all children. However, basal–bolus insulin therapy using modern basal and rapid-acting analogues has the potential to offer a more physiological insulin profile, than conventional human insulins, with improved safety.

Insulin detemir (IDet) is a long-acting, soluble acylated analogue of human insulin [Lys^{B29} (N^{ε}-tetradecanoyl) des (B30) human insulin] with a protracted action profile due to the combination of increased self-association at the injection site and buffering of insulin concentration via albumin binding in both the subcutaneous tissue and the blood (8). In adult type 1 diabetes mellitus (T1DM) patients, the metabolic effect in steady-state condition is constant over 24 h, whereas a clear peak is observed with neutral protamine Hagedorn (NPH) insulin after each injection (effects expressed as glucose infusion rate, GIR). Duration of action for IDet is dose dependent and up to 24 h (9, 10). In contrast to NPH human isophane insulin (11, 12), IDet does not require resuspension before injection.

Clinical trials in adults with T1DM have shown that IDet is associated with comparable glycosylated haemoglobin A1c (HbA1c), less variability in fasting plasma glucose (FPG), less nocturnal hypoglycaemia, and less weight gain compared with intermediate-acting NPH (13–16).

In spite of the importance of optimising diabetes care in children, particularly the very young, basal insulin analogues are only approved in children $\geq$6 yr. Few comparative randomised clinical trials have been conducted in this age group comparing these new analogues with traditional insulins. One of these studies, a 26-wk trial in children and adolescents (6–17 yr) with T1DM showed that the treatment with IDet was associated with a similar glycaemic control, a lower and more predictable FPG, lower risk of nocturnal hypoglycaemia, and lower increase in body mass index (BMI), compared with NPH (17). In children younger than 6 yr very few studies with basal insulin analogue therapy have been reported, and none of these have been comparative randomised clinical trials (18–20). Consequently, this study, a multinational, multicentre, randomised clinical trial, is the first to report efficacy and safety data in children as young as 2–5 yr (21).

The trial included 82 children aged 2–5 yr old from 10 European countries. This article presents a comparison of the efficacy and safety of treatment with IDet and NPH in this vulnerable age group after 52 wk of treatment.

Subjects and methods

Subjects

Children with T1DM (n = 82, IDet: 42, NPH: 40) aged between 2 and 5 yr, diagnosed with T1DM for a minimum of 12 month prior to inclusion, receiving a total daily insulin dose $\leq$2.0 U/kg and with HbA1c $\leq$ 11.0%, IDet naïve, and with a maximum BMI $\leq$ 20 kg/m^2 were recruited from diabetes clinics at 32 sites in 10 countries (Bulgaria, the Czech Republic, Finland, France, Hungary, Macedonia, Poland, the Russian Federation, Turkey, and the United Kingdom). Children with clinically significant concomitant diseases or with impaired renal and hepatic function were not included. The study was approved by local ethics committees and health authorities and carried out in accordance with Good Clinical Practice (22) and the Declaration of Helsinki (23). Written informed consent was obtained from all the children's parents or legal representatives before any study-related activities. The trial was registered at ClinicalTrials.gov and carries the following ID number, NCT00435019.

Study design

In this 52-wk, multinational, open-labelled, randomised (IDet:NPH), two-armed parallel group trial, IDet and NPH were administered once or twice daily (according to their pretrial regimen). Both treatment groups received insulin aspart (IAsp) as bolus insulin with main meals and large snacks. The trial consisted of a 2-wk screening period, followed by a 52-wk titration and treatment period, including a total of 10 scheduled visits to the clinical trial sites and 8 telephone contacts. Eligibility was determined at an initial screening visit. Eligible subjects were allocated to treatment with IDet or NPH in a 1:1 ratio and randomisation was carried out using a centralised telephone and web-based randomisation system, the Interactive Voice Response System (IVRS), and performed within 2 wk after the screening visit. IDet and NPH are easily distinguishable by visual inspection, and as the primary end-point, HbA1c is not easily biased, an open-labelled study design was chosen. A double-blind, double-dummy

technique was considered unnecessarily burdensome and invasive for the children as each basal injection would be accompanied by a placebo injection.

Treatment

Children were treated with IDet (Levemir®); Novo Nordisk A/S, Bagsvaerd, Denmark (100 U/mL) or NPH (NPH, human isophane insulin®; Novo Nordisk A/S; 100 IU/mL) once or twice daily, according to pretrial insulin regimen (once-daily basal insulin; or twice or more daily basal insulin injections). Both groups received IAsp (NovoRapid®/NovoLog®; Novo Nordisk A/S; 100 U/mL) two to four times a day, with meals and large snacks.

Children started treatment with basal insulin (IDet or NPH) at a dose equivalent to their pretrial basal insulin dose. During the treatment period, the basal insulin dose was adjusted according to plasma glucose (PG) measurements aiming for a fasting/preprandial PG target of 4.0–7.0 mmol/L (72–126 mg/dL). Parents/carers were asked to measure PG before breakfast and dinner on the 3 d prior to each contact and adjust basal insulin doses according to a simple algorithm titration guideline (Table 1).

Bolus insulin was to be taken with the meal aiming for a postprandial PG of 5.0–11.0 mmol/L (90–198 mg/dL). Bolus insulin doses were adjusted according to local practice.

Efficacy measures

The primary end-point of this trial was the level of HbA1c measured after 52 wk. At screening, a blood sample for HbA1c was drawn to assess subject eligibility, and at randomisation, a further sample was drawn as a baseline value. Blood samples for FPG were taken at home in the morning at randomisation. Blood samples for HbA1c and FPG were drawn approximately every 3 months (after 12, 26, 38, and 52 wk of treatment). Nine-point self-measured plasma glucose (SMPG) profiles were obtained on a normal weekday 4–7 d prior to randomisation, and after 26 and 52 wk of treatment. Nocturnal plasma glucose (NPG) values were measured at 03 : 00 hours as part of the 9-point SMPG profile.

Hypoglycaemic episodes were classified according to International Society for Paediatric and Adolescent Diabetes (ISPAD) guidelines (24, 25); symptomatic hypoglycaemic episodes with signs/symptoms were divided in three grades (mild, moderate, and severe), with a further category of biochemical hypoglycaemia (glucose < 3.6 mmol/L, without symptoms). Mild hypoglycaemic episodes were defined as episodes where the subjects were able to treat the episode him/herself, whereas moderate episodes were categorised as episodes where the subjects were not able to treat the episode him/herself but responded to oral treatment. In this age group, a very large proportion of symptomatic hypoglycaemic events will be defined as moderate or severe, as young children cannot treat themselves. Severe hypoglycaemic episodes were defined as episodes where the subjects were semiconscious, unconscious, or in coma with or without convulsions.

Body weight

Body weight was measured at all scheduled visits. Body weight was standardised by standard deviation (SD) score in order to allow pooling of data from children of different ages and genders. SD scores were derived from a British reference population from 1990 (26). A positive SD score indicates a higher weight level compared with the population average for a given age.

Safety measures

Standard safety parameters including adverse events (AEs), haematology, biochemistry, physical examination, and vital signs were recorded during the trial. Fundoscopy/fundus photography, physical examination, and vital signs were evaluated at randomisation and after 52 wk of treatment. Height measured in centimetres was recorded before treatment and after 26 and 52 wk of treatment and body weight was measured at all visits.

Table 1. Algorithm for titration of basal insulin dose

Current dose		<5 U	5–15 U	>15 U
Prebreakfast or predinner PG		Adjustment (U)		
<4.0 mmol/L	<72 mg/dL	Reduce according to local practice	Reduce according to local practice	Reduce according to local practice
4.0–7.0 mmol/L	72–126 mg/dL	0	0	0
7.1–10.0 mmol/L	126–180 mg/dL	+0.5	+1	+2
10.1–15.0 mmol/L	181–270 mg/dL	+1	+2	+4
>15.0 mmol/L	>270 mg/dL	+1.5	+3	+5

PG, plasma glucose.

Analytical methods

HbA1c measurements and safety parameters were analysed centrally by Laboratorium für Klinishe Forschung, Germany. HbA1c was measured by ion-exchange high-performance liquid chromatography (HPLC) (Bio-Rad Diamat; Bio-Rad Laboratories, Hercules, CA, USA) and FPG values were assessed using a hexokinase method (Gluco-quant®; Roche Diagnostics GmbH, Mannheim, Germany). SMPG was measured using a glucose meter (Medisense Precision Xtra™ or Optimum Plus™; Abbott Diabetes Care, Delkenheim, Germany). Use of test strips calibrated to PG values ensured that capillary blood concentrations were displayed as PG values. All SMPG values <3.6 mmol/L as well as signs and symptoms of hypoglycaemia were recorded in patients' diaries and included in the analyses of hypoglycaemia. All blood samples were obtained in the morning before administration of insulin.

Statistical analysis

The study was designed as an open-labelled trial with 1:1 randomisation. At randomisation, the children were stratified according to age (age 2–5 and 6–16 yr). Owing to the relative low number of children in the 2–5-yr-old subset, the comparison between treatment with IDet and NPH is based on descriptive statistics. The rate of hypoglycaemia (the number of episodes per subject year of exposure) was calculated for nocturnal, diurnal, and 24-h hypoglycaemic episodes divided in the categories: all, severe, moderate, mild, and biochemical. Hypoglycaemic episodes were categorised as nocturnal if they occurred between 22:00 and 06 : 59 hours (inclusive).

Fig. 1. Subject disposition.

Table 2. Baseline characteristics

Subjects exposed to treatment, N (%)	Detemir 42 (100.0%)	NPH 40 (100.0%)	All 82 (100.0%)
Gender			
Female	24 (57.1%)	19 (47.5%)	43 (52.4%)
Male	18 (42.9%)	21 (52.5%)	39 (47.6%)
Race			
White	40 (95.2%)	37 (92.5%)	77 (93.9%)
Unknown (*)	2 (4.8%)	3 (7.5%)	5 (6.1%)
Subject by age			
2 yr	8 (19.0%)	3 (8.0%)	11 (13.0%)
3 yr	9 (21.0%)	10 (25.0%)	19 (23.0%)
4 yr	11 (26.0%)	12 (30.0%)	23 (28.0%)
5 yr	14 (33.0%)	15 (38.0%)	29 (35.0%)
Mean age (yr)	4.3 (1.2)	4.5 (1.0)	4.4 (1.1)
Diabetes duration (yr)	2.2 (1.0)	2.1 (0.8)	2.1 (0.9)
BMI (kg/m^2)†	15.4 (13.1–19.1)	16.2 (13.4–19.2)	15.7 (13.1–19.2)
HbA1c (%)†	8.2 (1.1)	8.1 (1.2)	8.2 (1.1)
FPG (mmol/L)†	8.4 (4.9)	8.6 (4.1)	8.5 (4.5)
Pretrial daily insulin dose			
Basal insulin (U/kg)	0.30 (0.13–0.82)	0.34 (0.09–2.82)	0.32 (0.09–2.82)
Bolus insulin (U/kg)	0.47 (0.12–0.75)	0.47 (0.02–0.81)	0.47 (0.02–0.81)
Premix	0.88 (0.14–5.75)	0.50 (0.13–0.77)	0.73 (0.13–5.75)

BMI, body mass index; FPG, fasting plasma glucose; HbA1c, haemoglobin A1c; NPH, neutral protamine Hagedorn.
Numbers are N (%), mean (SD), or median (range).
*The five children of unknown ethnic origin are all from France, where it is illegal to register race.
†HbA1c, FPG, weight, and BMI recorded at or before randomization.

Results

Demographics

A total of 381 children were screened in the study (21), of which, 33 failed to meet all the selection criteria, the majority due to an HbA1c > 11% (Fig. 1). Three hundred and forty-eight (23.6%) children entered the trial of which 82 children were 2–5 yr old. Of these, one child withdrew from the IDet group due to an AE, and one, from the NPH group, due to ineffective therapy.

Baseline characteristics were similar between treatment groups (Table 2), except that the proportion of girls in the IDet group (57.1%) was slightly higher than in the NPH group (47.5%). The majority of the young children were on a basal–bolus insulin regimen before the trial. Most children used an insulin regimen with two basal and three bolus injections daily (36% of subjects in the IDet group and 53% in the NPH group) or a regimen with one basal and three bolus injections daily (26% of subjects in the IDet group and 15% in the NPH group). The others received premixed insulin alone or in combination with basal and/or bolus insulin preparations.

Glycaemic control

Mean HbA1c over the course of the 52-wk treatment period for the 2–5-yr-old children was stable in both treatment groups (Fig. 2A) (IDet: HbA1c 8.2% at baseline vs. 8.1% at 1 yr; NPH: HbA1c 8.1% at baseline vs. 8.3% at 1 yr). Observed mean FPG levels decreased in both groups from baseline to end of trial (IDet: −1.00 mmol/L and NPH: −0.45 mmol/L), but the effect was greater in those receiving IDet (Fig. 2B).

In both treatment groups, the observed mean 9-point SMPG profile values decreased and the profile became flattened during the trial. The observed mean prebreakfast SMPG level at the end of the profile was lower with IDet than with NPH (Fig. 2C). Observed mean NPG (03:00 hours) decreased slightly in the IDet group but did not change in the NPH group.

More subjects in the IDet group (47.6%) than in the NPH group (35.0%) reached the prebreakfast PG target [4.0–7.0 mmol/L (72–126 mg/dL)] during the trial, while the predinner target was reached by a similar proportion of children in both groups (IDet: 21.4% vs. NPH: 22.5%). The NPG target was achieved by similar proportions of children (IDet: 90.5% and NPH: 85.0%).

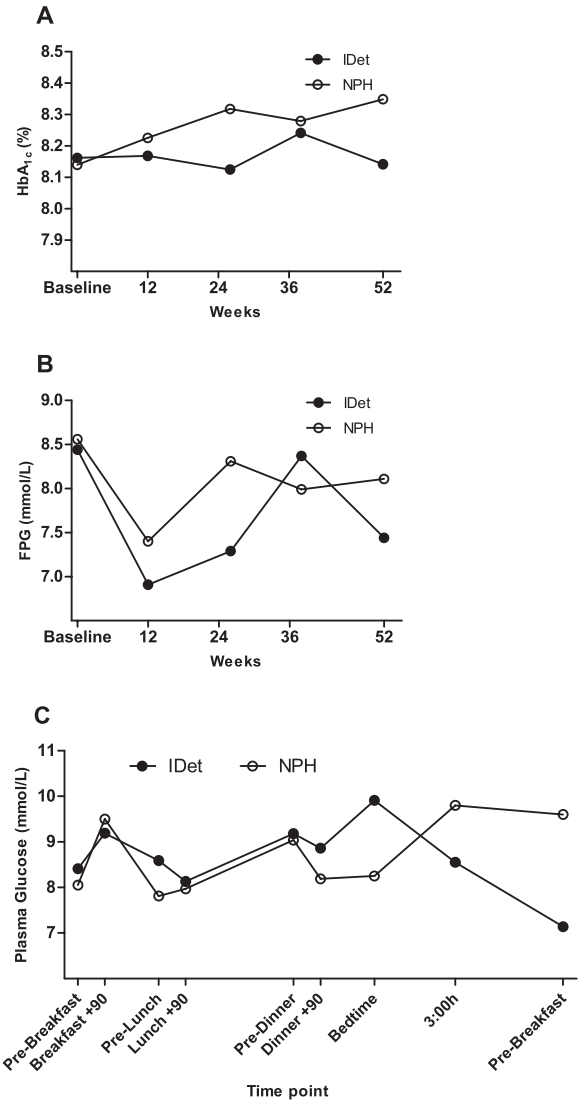

Fig. 2. Change in mean glycosylated haemoglobin A1c (HbA1c) (A), fasting plasma glucose (FPG) (B), and 9-point self-measured plasma glucose (SMPG) (C) over time.

The total median daily insulin dose per kilogram body weight was similar in the two treatment groups after 52 wk. As would be expected in growing children, median daily doses of IDet and NPH increased during the trial. The ratios (IDet/NPH) of the median daily insulin doses at the end of trial were 1.09 (0.47/0.43 U/kg) for basal insulin and 1.05 (0.50/0.48 U/kg) for bolus insulin. At baseline, 14 children were on a once daily IDet regimen and at the end of trial this was reduced to 9 children.

Hypoglycaemic episodes

The percentage of children with hypoglycaemic episodes was similar between treatments, but children treated with IDet had fewer episodes than those treated with NPH. Two thousand seventy-two hypoglycaemic episodes were reported for 40 (95%) children with IDet and 3050 episodes for 39 (98%) children with NPH. No severe hypoglycaemic episodes were reported in the IDet group, whereas six episodes (in three subjects) were reported for NPH (Table 3). The mean rate (episodes per patient-year of exposure) of hypoglycaemia was lower with IDet for total hypoglycaemic events (50.6 vs. 78.3), and nocturnal (22 : 00–06 : 59 hours) episodes (8.0 vs. 17.4) (Fig. 3; Table 3).

Mean SD score of body weight

The observed mean weight SD score at baseline was lower with IDet than with NPH, and decreased slightly with IDet compared with a slight increase in the NPH group during the trial. Change in observed mean weight SD score standardised by age and gender was −0.17 with IDet and 0.03 with NPH (Fig. 4).

Adverse events

A slightly lower proportion of subjects reported AEs with IDet than with NPH (69.0 vs. 77.5%). None of these events were severe with IDet and the majority was considered unlikely related to trial product, whereas three severe events (in three children) were reported for NPH. The rate (the number of events/1000 exposure years) of AEs with IDet (2949) was lower than with NPH (4324).

Five serious adverse events (SAEs) were recorded for five (12%) children in the IDet group and seven SAEs were recorded for six (15%) children in the NPH group. The rate of SAEs was lower with IDet (122/1000 exposure years) compared with NPH (179/1000 exposure years). The most common SAEs were infections (gastroenteritis) and gastrointestinal disorders (dyspepsia) in both treatment groups. Furthermore, one case of T1DM inadequate control was reported in the IDet group and two cases of hypoglycaemic unconsciousness were reported in the NPH group. No deaths were reported in this trial.

Discussion

To our knowledge this is the first randomised trial using IDet for treatment of children with T1DM younger than 6 yr old. Although no formal statistical analyses have been made between the two treatment groups due to the low number of subjects, the descriptive statistics presented in this article provide important information on the efficacy and safety of treatment with IDet and NPH in this age group, where very limited data is available. The results from the trial showed that glycaemic control measured by mean HbA1c was

Table 3. Summary of all hypoglycaemic episodes

	IDet				NPH			
	N	(%)	E	R	N	(%)	E	R
All 24-h episodes								
Severe 24 h	0	0	0	0.0	3	8	6	0.2
Moderate 24 h	17	40	239	5.8	16	40	562	14.4
Mild 24 h	28	67	519	12.7	27	68	980	25.1
Biochemical 24 h	37	88	1314	32.1	36	90	1502	38.5
All nocturnal								
Severe nocturnal	0	0	0	0.0	2	5	3	0.1
Moderate nocturnal	7	17	38	0.9	8	20	57	1.5
Mild nocturnal	13	31	63	1.5	20	50	193	5.0
Biochemical nocturnal	24	57	228	5.6	24	60	424	10.9

%, percentage of subjects; E, the number of episodes; IDet, insulin detemir; N, the number of subjects; NPH, neutral protamine Hagedorn; R, episodes per subject year of exposure.

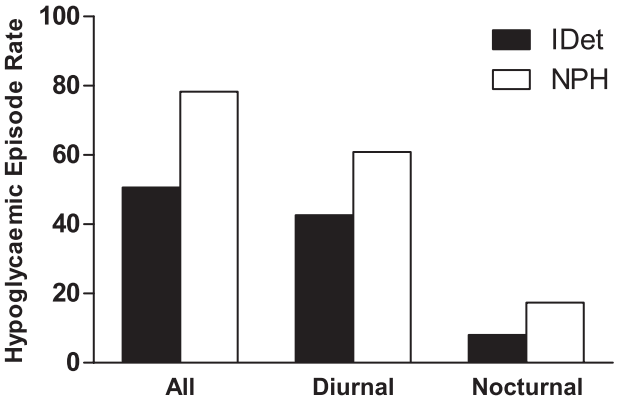

Fig. 3. The mean rate of hypoglycaemic episodes. Nocturnal: 22 : 00–06 : 59 hours.

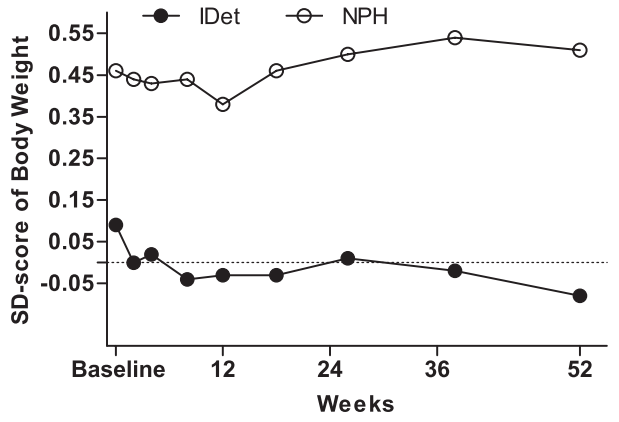

Fig. 4. Change in mean weight SD score over time.

similar with IDet and NPH. However, IDet was associated with a lower mean FPG, a lower rate of overall and nocturnal hypoglycaemia, a decreasing weight SD score, and fewer AEs compared with NPH. The 9-point SMPG profile values decreased similarly from baseline to end of trial with IDet and NPH. However, the mean prebreakfast SMPG level at the end of the profile tended to be lower with IDet than with NPH, and also mean NPG over time had a slight net decrease in the IDet group compared with no change in the NPH group.

These results are in line with the results for the trial as a whole where the results are based on formal statistical analyses (21), as well as with previous findings in adults (27, 28), and from a previous children study comparing treatment with IDet and NPH (17). However, the results from the total group (21) showed that HbA1c increased slightly with both IDet and NPH. This increase was, however, largely attributable to suboptimal glycaemic control in the subgroup of adolescents aged 13–16 yr, and may partly be explained by the influence of puberty with hormonal changes, growth, variable exercise and eating patterns, and the psychological burdens of adolescence (7, 21, 29). Importantly, no severe nocturnal hypoglycaemia was observed in the IDet group, a finding which was replicated in the study as a whole (21), implying that it would be possible to further reduce HbA1c by a more aggressive IDet titration. However, it is important to bear in mind that this study was not a treat-to-target design.

As would be expected in growing children, the median daily doses of both IDet and NPH increased during the trial for the 2–5 yr olds.

The rates of all 24-h hypoglycaemic episodes and all nocturnal hypoglycaemic episodes were lower with IDet than with NPH. These results corresponded with both the result of the group as a whole (21) and with previous findings in adults (27, 28), while only a lower rate of all nocturnal hypoglycaemic episodes was reported in the previous paediatric trial (17). However, the definition of hypoglycaemic episodes in this trial is based on the updated ISPAD guideline (21, 22) and differs from the previously used definition, so the findings are not directly comparable.

The safety results from the trial showed that the overall rate of AEs was lower with IDet compared to NPH, and fewer SAEs were reported with IDet than with NPH. The difference in SAEs was primarily due to the fewer hypoglycaemic episodes reported as SAEs with IDet compared to NPH. There was no difference between subjects treated with IDet and NPH with respect to exposure, clinical laboratory values, and vital signs. No deaths or episodes of diabetic ketoacidosis were reported in this subset and the fundoscopy/fundus photography examinations were normal in all these children. Overall, these findings are in line with the results of the total group (21).

As with the total group (21), the weight SD score after 1 yr was lower with IDet than with NPH, indicating that weight returned towards the mean value for the reference population instead of increasing inappropriately. However, the actual difference in weight SD score between IDet and NPH was not clinically significant. The lower weight SD score with IDet corresponds to the lower BMI reported in the previous trial in children (17) and is consistent with the general observation of less weight gain in adults treated with IDet in comparison with other basal insulins. As accurate and detailed growth standards were not available in all 10 participating countries, British standards (26) were used. These standards allow very accurate calculation of SD scores, as data are available for monthly time intervals and gender. This was not the case for other available population data. Although the derivation of the SD scores was based on growth curves from one specific country, the difference between the treatment arms is independent.

There is little experience with basal insulin analogue treatment in children with T1DM below 6 yr of age, and only very few trials have been performed in this age group. Three non-randomised clinical trials including very young children have been reported (18–20). A prospective 6-month study including 80 patients aged 2–19 yr, including 14 children younger than 6 yr old receiving insulin glargine once daily plus regular human insulin or rapid analogue before meals, showed that the average HbA1c level dropped in the preschool children without increasing the number of severe episodes of hypoglycaemia (18). In addition, in a study of 71 children and adolescents (including 9 children younger than 7 yr old), it was also shown that HbA1c levels improved and hypoglycaemic episodes decreased (19). Furthermore, a recent study comparing diabetes control in children younger than 6 yr ($n = 10$) using basal/bolus regimen showed that insulin glargine and rapid-acting analogues resulted in an overall control comparable to treatment with NPH insulin plus regular and/or rapid-acting analogues. Insulin glargine and rapid-acting analogues decreased episodes of symptomatic hypoglycaemia, and resulted in lower fasting glucose (20). This study is in line with the present trial although it only included a very limited number of patients ($n = 10$) compared with the 82 children in the present trial.

Intensive insulin therapy in adults has been shown to reduce the complications of T1DM; however, this was at the cost of high rates of hypoglycaemia and inappropriate weight gain (30, 31), leading to caution in extending intensive insulin therapy to children, especially to the very young. This study has shown the practicality and safety of basal–bolus insulin therapy, even in this age group. An ideal insulin regimen in very young children should be flexible, while protecting against hypoglycaemia and inappropriate weight gain. IDet, in combination with a rapid-acting insulin analogue, would appear to address these requirements.

In conclusion, the present study indicates that IDet is as safe and efficacious as NPH for the treatment of 2–5-yr-old children with T1DM. Children treated with IDet appeared to have less hypoglycaemia, less undesirable weight gain, and fewer AEs than children treated with NPH. However, a large-scale confirmatory trial is necessary to corroborate the results from this subanalysis of 2–5-yr-old children.

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Conflict of interest

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