Efficacy and safety of a fixed combination of insulin degludec/insulin aspart in children and adolescents with type 1 diabetes: A randomized trial

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Background: Insulin degludec/insulin aspart (IDegAsp) is a fixed soluble co-formulation of basal and bolus insulin.

Objective: To evaluate efficacy and safety of IDegAsp in pediatric patients with type 1 diabetes (T1D).

Subjects: Children and adolescents (aged 1 to <18 years) with T1D.

Methods: A 16-week, phase 3b, treat-to-target, parallel-group, open-label, non-inferiority trial was conducted at 63 sites in 14 countries from October 2013 to November 2014. Patients were randomized 1:1 (age stratified: 1–<6 years; 6–<12 years; 12–<18 years) to IDegAsp once daily (OD) plus insulin aspart (IAsp) for remaining meals (IDegAsp + IAsp), or IDet OD or twice daily plus mealtime IAsp (IDet + IAsp). The primary end-point was HbA1c change from baseline at week 16.

Results: A total of 362 participants were randomized to IDegAsp + IAsp (n = 182) or IDet + IAsp (n = 180). HbA1c decreased from baseline to week 16 by 0.3% in both groups (estimated treatment difference: −0.04%-points [−0.23; 0.15]95%CI (−0.45 mmol/mol [−2.51; 1.60]95%CI), confirming non-inferiority. There were no significant differences between treatment groups in fasting or self-measured plasma glucose. Confirmed hypoglycemia rates did not significantly differ between groups. There was a significant reduction in basal and total insulin dose with IDegAsp + IAsp vs IDet + IAsp (post hoc analysis). Mean number of injections/day was 3.6 and 4.9 with IDegAsp + IAsp and IDet + IAsp, respectively (post hoc analysis). A non-significant higher rate of severe hypoglycemia was observed with IDegAsp + IAsp vs IDet + IAsp. The most frequent adverse events in both groups were hypoglycemia, headache, and nasopharyngitis.

Conclusions: IDegAsp + IAsp was non-inferior to IDet + IAsp regarding HbA1c, had similar hypoglycemia rates and required fewer injections.

KEYWORDS
adolescent, child, insulin degludec/insulin aspart, insulin detemir, type 1 diabetes

Abbreviations: ADA, American Diabetes Association; AE, adverse event; ANOVA, analysis of variance; BID, twice daily; CI, confidence interval; ETD, estimated treatment difference; ETR, estimated treatment ratio; FAS, full analysis set; FDA, US Food and Drug Administration; FPG, fasting plasma glucose; HbA1c, glycosylated hemoglobin; IAsp, insulin aspart; IDeg, insulin degludec; IDegAsp, insulin degludec/insulin aspart; IDegAsp + IAsp, insulin degludec/insulin aspart once daily at the main meal plus insulin aspart for remaining meals; IDet, insulin detemir; IDet + IAsp, insulin detemir once or twice daily plus mealtime insulin aspart; ISPAD, International Society for Pediatric and Adolescent Diabetes; MMRM, mixed model for repeated measurements; OD, once daily; PG, plasma glucose; SAE, serious adverse event; SMPG, self-measured plasma glucose; T1/T2D, type 1/type 2 diabetes

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Despite the known benefits of good glycemic control, achieving it in children and adolescents with diabetes can be extremely challenging due to a complex mix of lifestyle factors and the physiological and developmental changes (e.g., development of insulin resistance during puberty) that occur as they mature. The International Society for Pediatric and Adolescent Diabetes (ISPAD) guidelines recommend that pediatric patients receive basal-bolus therapy to allow titration of individual insulin doses; however, this regimen is complex, which can negatively impact treatment adherence. A third of adolescents with type 1 diabetes (T1D) report omitting insulin doses. In addition, concern surrounding hypoglycemia can cause reluctance to titrate insulin therapy appropriately. This can leave children with T1D at risk of suboptimal glucose control which may have detrimental effects on brain development. Treatments with a more physiological action profile are needed to minimize variation in insulin action and mimic endogenous insulin more closely. Current premixed formulations are not ideal in this respect due to an extended effect of the prandial component, caused by interference between the bolus and prandial components. The ISPAD guidelines acknowledge that premixed analog insulins, commonly used in some countries, may help to reduce the number of injections when adherence is a problem. Insulin degludec/insulin aspart (IDegAsp) is a soluble, ready-to-use co-formulation in the ratio 70% insulin degludec (IDeg) to 30% insulin aspart (IAsp). It is the first co-formulation of basal and bolus insulin that retains the individual pharmacokinetic/pharmacodynamic characteristics of its components, with IDeg providing long-acting insulin coverage and IAsp providing short-acting insulin action. In contrast, available premixed formulations require resuspension. Inadequate resuspension prior to injection decreases dosing precision and increases variability in absorption kinetics, which may increase day-to-day variability in glycemic control. This study aimed to assess the efficacy and safety of IDegAsp administered OD plus IAsp for remaining meals compared with a full basal-bolus regimen in a pediatric population with T1D.

2 | METHODS

2.1 | Trial conduct

This was a 16-week, phase 3b, treat-to-target, multinational, multicenter, randomized controlled, parallel-group, open-label, non-inferiority trial comparing the efficacy and safety of IDegAsp OD at the main meal plus IAsp for remaining meals (IDegAsp + IAsp) vs a basal-bolus regimen consisting of insulin detemir (IDet) OD or twice daily (BID; according to local labelling) plus mealtime IAsp (IDet + IAsp) (Figure S1, Supporting Information). Based on available phase 3a data for IDegAsp, 16 weeks of treatment was considered sufficient for assessing the efficacy and safety of IDegAsp + IAsp in a pediatric population with T1D. IDet + IAsp was chosen as a comparator as both components had approval for use in children aged 1 year and above. The trial was conducted at 63 sites in 14 countries (Belgium, Brazil, Canada, Croatia, Czech Republic, Israel, Republic of Macedonia, Poland, Russian Federation, Serbia, Slovenia, South Africa, Spain, and United States), between October 17, 2013 and November 7, 2014. In accordance with local regulations, the protocol, protocol amendments, consent form, child assent form, subject information sheet and all other information provided to participants and parents/legal representatives were approved by the relevant health authorities and independent ethics committees/institutional review boards, and the trial was conducted according to the Declaration of Helsinki and ICH Good Clinical Practice. Ongoing safety surveillance was performed by a blinded internal safety committee and an unblinded independent Data Monitoring Committee, comprising pediatric and endocrinology specialists. This trial is registered at www.clinicaltrials.gov: NCT01835431.

Children and adolescents (1-<18 years of age) with T1D, previously treated with any insulin regimen for ≥3 months at a total daily insulin dose of ≤2 U/kg, and with glycosylated hemoglobin (HbA1c) levels of ≤11% (≤96.7 mmol/mol), were eligible for inclusion.

2.2 | Randomization

A central interactive voice/web response system was used to randomize eligible participants 1:1 to receive either IDegAsp (100 U/mL, Penfill 3-mL cartridge; Novo Nordisk) or IDet (100 U/mL, Penfill 3-mL cartridge; Novo Nordisk), both with mealtime IAsp (100 U/mL, Penfill 3 mL cartridge; Novo Nordisk). Randomization was stratified according to three age groups: 1-<6, 6-<12 and 12-<18 years to ensure an approximately equal distribution of individuals in these different age groups between treatment arms.

2.3 | Procedures

Trial duration, including screening and follow-up visits, was approximately 18 weeks. A treat-to-target protocol was used alongside measurement of self-measured plasma glucose (SMPG) as per ISPAD 2009 guidelines to achieve a prebreakfast SMPG target of 5.0 to 8.0 mmol/L. Participants randomized to IDet received their dose OD or BID in accordance with local labeling. Those participants previously receiving IDet continued with their pretrial regimen. A switch to BID dosing was considered if mean prebreakfast plasma glucose (PG) had reached target but mean predinner PG was >8.0 mmol/L. Investigators were recommended to reduce the daily insulin dose by 20% at initiation and to aim for a basal:bolus ratio of between 50:50 and 30:70. Starting doses of IDegAsp or IDet and IAsp were calculated using the insulin titration guideline, which provided the recommended dose of IDegAsp and total IAsp for patients based on their total daily insulin dose prior to randomization and the abovementioned recommendations; however, all dosing decisions were made at the discretion of the investigator.

Once-weekly titration of IDegAsp OD and IDet OD was conducted according to the lowest prebreakfast SMPG value measured on the 3 days prior to the visit/phone contact. For IDet BID, the morning dose adjustment was based on the lowest predinner SMPG value measured on the 3 days prior to the visit/phone contact. During the trial, the IDegAsp dose could be switched from one meal to another for safety or efficacy reasons at the investigator's discretion.
IAsp was titrated weekly based on the lowest of three SMPG values measured prior to the next meal and bedtime on the 3 days prior to the visit/phone contact. Alternatively, IAsp dosage could be adjusted multiple times daily according to insulin/carbohydrate ratios, preprandial PG values and correction factors, by participants/caregivers with sufficient experience.

The primary end-point was change from baseline in HbA1c after 16 weeks of treatment. Other efficacy endpoints included fasting PG (FPG), and 4- and 8-point SMPG profiles. SMPG values were measured using capillary blood measurements automatically calibrated to plasma-equivalent values, using a glucose monitor able to capture both blood glucose and blood ketones. Four-point profiles were performed before each scheduled visit, while 8-point profiles were performed at weeks 0 (randomization), 12, and 16. Safety end-points included adverse events (AEs), hypoglycemic episodes, hyperglycemia, hyperglycemia with ketosis (ketones >1.5 mmol/L), insulin dose, body weight, and standard laboratory safety assessments.

Hypoglycemic episodes were classified based on American Diabetes Association (ADA) 2005/ISPAD 2009 guidelines (Figure S2). Confirmed hypoglycemic episodes were defined as episodes with a self-measured PG value of <3.1 mmol/L (Novo Nordisk definition), with or without symptoms, and/or episodes fulfilling the ADA 2005/ISPAD 2009 definition of severe hypoglycemia. Since severe hypoglycemia defined by the ISPAD 2009 guidelines as “the child has altered mental status and cannot assist in their own care, is semiconscious or unconscious, or in coma with/without convulsions and may require parenteral therapy with glucagon or intravenous glucose,” includes a subjective element, all reported severe hypoglycemic episodes were reviewed in a blinded manner by an independent, external pediatric endocrinologist. Hypoglycemic episodes occurring between 11 PM and 7 AM inclusive were classified as nocturnal. Hypoglycemic episodes were considered study treatment-emergent if the onset was on or after the first day of treatment and no later than 7 days after the last day of treatment.

Hyperglycemia was defined as PG >14.0 mmol/L in a participant who looked/felt ill. Hyperglycemia with ketosis was defined when the hyperglycemia criteria were met and capillary blood ketone level exceeded 1.5 mmol/L.

2.4 | Statistical methods

Statistical analyses were carried out for efficacy endpoints derived after 16 weeks of treatment, and included all randomized participants (full analysis set [FAS]), following the intention-to-treat principle. Safety endpoints were summarized using the safety analysis set (all randomized participants exposed to at least one dose of investigational product). Sample size was determined based on the non-inferiority evaluation, using a t-statistic assuming a one-sided test of size 2.5%, a zero mean treatment difference and SD of 1.25%.

The primary objective was to confirm non-inferiority of IDegAsp + IAsp vs IDet + IAsp, as assessed by change from baseline in HbA1c after 16 weeks of treatment, with a non-inferiority limit of ≤0.4% (≤4.4 mmol/mol) for the upper 95% confidence interval (CI) in accordance with US Food and Drug Administration (FDA) guidance. All observed HbA1c measurements available postrandomization at scheduled measurement times were analyzed using a mixed model for repeated measurements (MMRM) with an unstructured covariance matrix. The MMRM method was used to account for missing data of continuous endpoints, and the model included treatment, sex, region (three levels: EU [including Russian Federation and Israel], North America, other), age-group (three levels: 1–<6, 6–<12, and 12–18 years of age) and visit as factors and baseline HbA1c as a covariate. Interactions between visit and all factors and covariates were also included in the model.

Sensitivity analyses included analyses of the per-protocol set and of the set of all completed participants; and an analysis of variance (ANOVA) with missing values imputed using the last observation carried forward method (adjusted by treatment, sex, region and age group as fixed factors, and baseline value of the respective HbA1c as a covariate).

Secondary efficacy end-points were analyzed with a MMRM similar to that applied to the primary end-point, with corresponding baseline values included as covariate.

As prespecified in the trial protocol, P-values were only determined for the primary end-point. The other end-points were considered supportive and explorative in nature.

Hypoglycemic events were modeled using negative binomial regression, with a log-link function and the logarithm of the time period for which a hypoglycemic episode was considered treatment emergent as offset. The model included treatment, sex, region, and age group as fixed factors.

Body weight was expressed as descriptive SD scores, derived from the participant’s age, sex, and body weight together with country-specific reference growth curves (or US Centers for Disease Control and Prevention data where unavailable).

3 | RESULTS

3.1 | Patient characteristics

The participant flow is summarized in Figure 1. In total, 362 participants were randomized to receive either IDegAsp + IAsp (n = 182) or IDet + IAsp (n = 180); one participant from the IDegAsp + IAsp group withdrew consent prior to exposure and one withdrew from the IDet + IAsp group due to randomization in error. Demographics and baseline characteristics were similar across treatment and age groups, apart from some differences in mean FPG and mean duration of diabetes (Table 1). Therapies at screening were: basal-bolus insulin therapy (n = 333 [92.0%]), basal-bolus plus premixed insulin therapy (n = 5 [1.4%]), other antidiabetic regimens (n = 24 [6.6%]); basal insulin, n = 4 [1.1%]; bolus insulin, n = 11 [3.0%]; premix insulin, n = 5 [1.4%]; premix plus bolus insulin, n = 4 [1.1%]). Therapies at screening were also similar across treatment groups.

3.2 | Glycemic control

IDegAsp + IAsp and IDet + IAsp were associated with similar changes in HbA1c from baseline. The estimated mean decrease in HbA1c was 0.27%-points (2.98 mmol/mol) for IDegAsp + IAsp and 0.23%-points
(2.53 mmol/mol) for IDet + IAsp at week 16 (Figure 2A). The estimated treatment difference (ETD) for IDegAsp + IAsp - IDet + IAsp at week 16 was $-0.04\%$-points $[-0.23; 0.15]_{95\%CI} (-0.45 \text{ mmol/mol} [-2.51; 1.60]_{95\%CI})$. This finding confirmed the non-inferiority of IDegAsp + IAsp vs IDet + IAsp, with respect to change in HbA1c from baseline. This was supported by the per-protocol analysis set (ETD IDegAsp + IAsp - IDet + IAsp: $-0.04\%$-points $[-0.23; 0.15]_{95\%CI}; -0.39 \text{ mmol/mol} [-2.46; 1.68]_{95\%CI})$ and all other sensitivity analyses. Within each treatment group, the trend for decreased mean HbA1c over time was similar for all age groups (Figure S3).

After 16 weeks, mean FPG was 8.4 mmol/L in the IDegAsp + IAsp group and 8.3 mmol/L in the IDet + IAsp group (Figure 2B). The ETD (IDegAsp + IAsp - IDet + IAsp) was $0.31 \text{ mmol/L} [-0.70; 1.33]_{95\%CI}$ (not significant). Within the IDegAsp + IAsp group, mean FPG decreased from baseline to week 16 for children aged 1 to 5 years and adolescents aged 12 to 17 years, but tended to increase from week 12 to week 16 in children aged 6 to 11 years, due to a few outliers with elevated FPG levels at week 16. Within the IDet + IAsp group, mean FPG followed the overall trend across all age groups (Figure S4).

No differences were observed in the mean 8-point SMPG profile between treatment groups at any time point. Fluctuation in PG followed the overall trend across age categories in both treatment groups with no significant difference observed in fluctuation of 8-point SMPG profiles (estimated treatment ratio [ETR] IDegAsp + IAsp/IDet + IAsp: 1.09 [0.98; 1.22]$_{95\%CI}$).

Similarly, there were no significant differences between treatment groups in 4-point SMPG profiles at 16 weeks, within treatment groups; within-participant variability in prebreakfast SMPG was similar for the treatment groups (ETR IDegAsp + IAsp/IDet + IAsp: 1.02 [0.91; 1.14]$_{95\%CI}$).

### 3.3 Insulin dose

Insulin doses at weeks 1 and 16 are given in Table 2. After 16 weeks, 54.2% participants in the IDet + IAsp group were using IDet BID. The mean total daily insulin dose (U/kg) ratio (IDegAsp + IAsp/IDet + IAsp) was 0.86, reflecting a numerically lower dose (by 14%) of IDegAsp + IAsp vs IDet + IAsp. Post hoc analysis of the difference between daily doses using a MMRM analysis confirmed a statistically significant reduction with IDegAsp + IAsp vs IDet + IAsp of 26% for basal dose (IDeg component vs IDet, ETR: 0.74 [0.66; 0.82]) and 15% for total insulin dose (ETR: 0.85 [0.78; 0.92]).
The mean number of injections per day at the end of the trial was 3.6 for IDegAsp + IAsp, and 4.9 for IDet + IAsp (post hoc analysis; P < 0.0001), using Wilcoxon two-sample test.

In terms of adherence to titration protocol, prescribed minus actual dose was similar between treatment groups.

3.4 | Hypoglycemia

Confirmed hypoglycemia (PG <3.1 mmol/L or severe as defined by ADA 2005/ ISPAD 2009 guidelines\textsuperscript{21,22}) was experienced by 92.8% of IDegAsp + IAsp and 91.6% of IDet + IAsp participants. Rates of confirmed hypoglycemia were 46.23 and 49.55 per patient year for IDegAsp + IAsp and IDet + IAsp respectively, and were not statistically different between treatments (ETR IDegAsp + IAsp/IDet + IAsp: 0.95

![FIGURE 3](image-url) Cumulative rates of confirmed (A) and nocturnal confirmed (B) hypoglycemia using the Novo Nordisk classification (PG <3.1 mmol/L or severe hypoglycemia). Mean values based on safety analysis set. IAsp, insulin aspart; IDegAsp, insulin degludec/insulin aspart; IDet, insulin detemir

TABLE 1  Patient baseline characteristics (all patients stratified by age groups)

| Characteristic                        | IDegAsp + IAsp | IDet + IAsp |
|---------------------------------------|----------------|-------------|
| Full analysis set (FAS), n            | 182            | 180         |
| 1-<6                                  | 41             | 41          |
| 6-<12                                 | 61             | 61          |
| 12-<18                                | 80             | 78          |
| Female %                              | 51.1           | 52.2        |
| 1-<6                                  | 48.8           | 58.5        |
| 6-<12                                 | 52.5           | 44.3        |
| 12-<18                                | 51.3           | 55.1        |
| Race: White/Black/Asian/other, %      | 92.9/4.4/0.2/7.9 | 93.3/2.2/0.6/3.9 |
| 1-<6                                  | 92.7/2.4/0.4/9.9 | 90.2/4.9/0.4/9.9 |
| 6-<12                                 | 96.7/3.3/0/0   | 95.1/1.6/0/3.3 |
| 12-<18                                | 90.0/6.3/0.3/8.6 | 93.6/1.3/1.3/3.8 |
| Ethnicity: Hispanic or Latin American, % | 8.2            | 7.2         |
| 1-<6                                  | 12.2           | 9.8         |
| 6-<12                                 | 6.6            | 4.9         |
| 12-<18                                | 7.5            | 7.7         |
| Age, y                                | 10.5 (±4.3)    | 10.8 (±4.6) |
| 1-<6                                  | 4.6 (±1.1)     | 4.3 (±1.1)  |
| 6-<12                                 | 9.2 (±1.7)     | 9.4 (±1.9)  |
| 12-<18                                | 14.5 (±1.6)    | 15.2 (±1.7) |
| Weight, SD score                      | 0.40 (±1.12)   | 0.47 (±0.94) |
| 1-<6                                  | 0.41 (±1.24)   | 0.16 (±1.05) |
| 6-<12                                 | 0.15 (±1.18)   | 0.53 (±0.86) |
| 12-<18                                | 0.58 (±0.99)   | 0.60 (±0.92) |
| BMI, kg/m$^2$                          | 19.2 (±4.2)    | 19.6 (±4.0) |
| 1-<6                                  | 16.4 (±2.2)    | 16.2 (±1.6) |
| 6-<12                                 | 17.4 (±3.3)    | 18.1 (±2.8) |
| 12-<18                                | 22.0 (±3.9)    | 22.5 (±3.8) |
| Duration of diabetes, y               | 4.4 (±3.7)     | 3.8 (±3.2)  |
| 1-<6                                  | 1.8 (±1.2)     | 1.5 (±0.8)  |
| 6-<12                                 | 3.4 (±2.5)     | 3.2 (±2.4)  |
| 12-<18                                | 6.4 (±4.2)     | 5.6 (±3.5)  |
| HbA1c, %                              | 8.1 (±1.2)     | 8.1 (±1.2)  |
| 1-<6                                  | 7.9 (±1.4)     | 8.1 (±1.1)  |
| 6-<12                                 | 8.1 (±1.1)     | 7.8 (±1.1)  |
| 12-<18                                | 8.3 (±1.3)     | 8.2 (±1.4)  |
| HbA1c, mmol/mol                       | 65.4 (±13.6)   | 64.6 (±13.6) |
| 1-<6                                  | 62.8 (±15.0)   | 65.1 (±11.9) |
| 6-<12                                 | 64.6 (±12.3)   | 61.6 (±12.3) |
| 12-<18                                | 67.3 (±13.7)   | 66.6 (±15.0) |
| FPG, mmol/L [mg/dL]                   | 8.6 (±4.4) [155.6 (±80.2)] | 8.1 (±4.2) [146.5 (±74.9)] |
| 1-<6                                  | 8.8 (±4.8) [158.5 (±86.4)] | 8.2 (±4.2) [148.1 (±75.1)] |
| 6-<12                                 | 8.0 (±3.9) [144.7 (±70.0)] | 8.1 (±4.2) [146.0 (±75.3)] |
| 12-<18                                | 9.0 (±4.7) [162.4 (±84.3)] | 8.1 (±4.2) [146.1 (±75.5)] |

The mean number of injections per day at the end of the trial was 3.6 for IDegAsp + IAsp, and 4.9 for IDet + IAsp (post hoc analysis; P < 0.0001), using Wilcoxon two-sample test.

TABLE 2  Insulin dose—basal and bolus doses

| Mean insulin dose | IDegAsp + IAsp | IDet + IAsp |
|-------------------|----------------|-------------|
| Safety analysis set, n | 181            | 179         |
| Basal, U/kg       |                |             |
| Week 1            | 0.31           | 0.38        |
| Week 16           | 0.36           | 0.49        |
| Total bolus, U/kg |                |             |
| Week 1            | 0.49           | 0.52        |
| Week 16           | 0.52           | 0.52        |
| Total, U/kg       |                |             |
| Week 1            | 0.79           | 0.89        |
| Week 16           | 0.88           | 1.01        |
TABLE 3 Hypoglycemia—Severe, confirmed, nocturnal confirmed

| Incidence % patients | Rate Episodes/PYE | Rate ratio (IDegAsp + IAsp/IDet + IAsp) |
|----------------------|------------------|----------------------------------------|
| Severe               | 6.1% (11/181)    | 0.26                                   |
| Confirmed            | 92.8% (168/181)  | 46.23                                  |
| Nocturnal confirmed  | 55.8% (101/181)  | 5.77                                   |

Abbreviations: % patients, proportion of patients with events; #, number of patients with events; IDegAsp, insulin degludec/insulin aspart; IDet, insulin detemir; n, number of patients in treatment group; PYE, patient-years of exposure.

The rate of hyperglycemic episodes was similar for IDegAsp + IAsp and IDet + IAsp (10.9 and 8.33 events/exposure year, respectively). The proportion of patients experiencing hyperglycemic episodes with ketosis (ketones >1.5 mmol/L) and the rate of these episodes were numerically lower for IDegAsp + IAsp vs IDet + IAsp (2.2% vs 4.5% of patients; 0.11 vs 0.22 events/exposure year, ns, ETR 0.46 [0.12; 1.79]95% CI; Figure 4).

3.5 | Hyperglycemia with ketosis

The rate of hyperglycemic episodes was similar for IDegAsp + IAsp and IDet + IAsp (10.9 and 8.33 events/exposure year, respectively). The proportion of patients experiencing hyperglycemic episodes with ketosis (ketones >1.5 mmol/L) and the rate of these episodes were numerically lower for IDegAsp + IAsp vs IDet + IAsp (2.2% vs 4.5% of patients; 0.11 vs 0.22 events/exposure year, ns, ETR 0.46 [0.12; 1.79]95% CI; Figure 4).

3.6 | Change in body weight

Analysis of change from baseline in weight SD score showed a statistically significant difference between groups after 16 weeks of treatment (+0.06 with IDegAsp + IAsp vs −0.02 with IDet + IAsp; and the ETD for IDegAsp + IAsp−IDet + IAsp: 0.07 [0.02; 0.12]95% CI).

3.7 | Adverse events

AE profiles were similar for IDegAsp + IAsp and IDet + IAsp (Table 4). The majority of reported AEs for both groups were mild or moderate in severity and resolved by the end of the trial. Except for hypoglycemia, the most commonly reported AEs in both treatment groups were headache, nasopharyngitis, upper abdominal pain, pyrexia, and vomiting (Table S2). The observed rate of serious AEs (SAEs) was low, although numerically higher in the IDegAsp + IAsp treatment group than with IDet + IAsp (14 vs 7 events; 0.26 vs 0.13 events/patient-year) (Table 4). One participant in the IDegAsp + IAsp group withdrew from the trial due to an AE (hypoglycemic seizure) and one participant...
in the IDet + IAsp group withdrew due to "other" safety reasons "intermittent but recurrent hypoglycemia attributed to trial product." All other SAEs were single occurrences in both treatment groups. No clinically relevant differences from baseline to end of treatment or between treatment groups were observed for vital signs, physical examination and laboratory values.

4 | DISCUSSION

This study has demonstrated that IDegAsp OD provides comparable glycemic control to IDet OD or BID, both with mealtime IAsp in children with T1D aged 1 to <18 years. Similar glycemic control in the IDe-
gAsp + IAsp treatment arm was achieved with a lower insulin dose and number of daily injections vs the IDet + IAsp arm. Throughout the trial, doses were numerically lower for IDegAsp + IAsp than IDet + IAsp and after 16 weeks there was a statistically significant reduction with IDe-
gAsp + IAsp compared with IDet + IAsp. Specifically, the daily dose of the IDeg component of IDegAsp was 26% lower than that of IDet in the comparator arm and the total daily dose of insulin was 15% lower with IDegAsp + IAsp vs IDet + IAsp. This is in agreement with previous results from treat-to-target trials, which demonstrated a lower end-of-
trial daily insulin dose requirement with IDeg vs IDet and vs insulin glargine 100 units/mL (Iglar U100) and with Iglar U100 vs IDet.

There was a statistically significant increase in weight SD score with IDegAsp + IAsp vs IDet + IAsp, confirming the weight sparing properties of IDet observed in previous studies. Increasing obesity in a sub-population of children is a major challenge in managing pediatric diabetes. As such, clinicians may consider the weight-sparing effect of IDet compared with the ketosis benefit of IDegAsp when choosing appropriate treatments for this patient population.

Hypoglycemia was evaluated in this trial using two classifications: ADA 2005/ISPAD 2009 classifications and a Novo Nordisk classification (PG <3.1 mmol/L) which aims to capture hypoglycemia at the PG level at which symptoms are experienced. Rates of confirmed hypoglycemia and nocturnal confirmed hypoglycemia were similar between treatment groups irrespective of the classification used. There was no statistically significant difference in the number of episodes meeting the ISPAD 2009 definition of severe hypoglycemia, although numerically more were reported for the IDegAsp + IAsp group. External blinded review of severe hypoglycemia showed that this was predominantly driven by episodes classified as severe based on the criterion "the child is having altered mental status and cannot assist in their care." This criterion can be difficult to assess in very young children and can be subjective. It should be noted that the open-label trial design may have influenced the reporting of severe hypoglycemia, especially for those who continued previous treatment regimens (approximately half of the participants in the IDet + IAsp group). Of note, episodes classified as severe based on more objective symptoms: "semiconscious or unconscious and coma ± convulsions" were similarly spread among the two treatment arms: five patients reported six events with IDegAsp + IAsp and three patients reported four events with IDet + IAsp.

The overall rate of nocturnal confirmed hypoglycemia was highest in the oldest age group (12-<18 years old). This may be attributed to the adolescent lifestyle, as this population tends to be more active than the younger age groups during the period defined as "nocturnal" (23:00-07:00) in this study.

Similar to the results reported by Thalange et al., who investigated the safety and efficacy of IDeg OD in a pediatric trial of similar design, we observed a numerical reduction in the rates of hyperglyce-
mia with ketosis with IDegAsp + IAsp vs IDet + IAsp; however, this difference did not reach statistical significance.

At baseline, patients in the IDegAsp treatment group had a numeri-
cally longer mean diabetes duration and slightly higher FPG, overall. The effect of this on outcomes is unclear but it is unlikely to impact results since (1) the differences are not substantial and (2) randomization was stratified by the three different age groups and differences in FPG and diabetes duration were not observed for all three age groups.

Limitations of this trial include its open-label design and its short duration, which was based on ethical considerations and phase 3a data available for adults with T1D or T2D at the time of trial design.

This trial was strengthened by its use of both Novo Nordisk and ADA 2005/ISPAD 2009 classifications for hypoglycemia. In addition, severe hypoglycemia was captured using a broad definition and inde-
pendently reviewed. Furthermore, the multinational nature of the study population and the broad age range of participants make these results highly relevant to the global pediatric population with T1D.

In conclusion, IDegAsp + IAsp was non-inferior to IDet + IAsp in reducing HbA1c in a pediatric population with T1D. IDegAsp, as the first fixed soluble co-formulation insulin, could offer the potential bene-
fit of fewer injections compared with a traditional basal-bolus regimen, and may therefore represent an addition to the treatment options for pediatric individuals with T1D for whom a treatment option with fewer injections is important or where adherence may be a challenge.

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Conflict of interest

T.B. served on advisory boards of Novo Nordisk, Sanofi, Eli Lilly, Boehringer, Medtronic and Bayer Health Care. T.B.’s Institution received research grant support, with receipt of travel and accommod-
ation expenses in some cases, from Abbott, Medtronic, Novo Nor-
disk, GluSense, Sanofi, Sandoz and Diamyd. T.B. received honoraria for participating on the speaker’s bureaux of Eli Lilly, Bayer, Novo Nordisk, Medtronic, Sanofi and Roche. T.B. owns stocks of DreamMed. L.C.D. has received research support from Novo Nordisk. M.E. is an employee of Novo Nordisk A/S. O.K. was an employee of Novo Nordisk A/S at the time of writing. O.K. owns shares in Novo Nordisk and is now an employee of Boehringer Ingelheim. G.J.K. receives research grant funding from Novo Nordisk through an unrestricted grant to the Jaeb Center. Mi.K. has received grants from...
Novo Nordisk and Medtronic for scientific meetings. Ma.K. has nothing to declare. N.S. has received honoraria for lectures and advisory board participation from Novo Nordisk. A grant was made from Novo Nordisk to NS’s hospital for patient education.

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REFERENCES
1. The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group. Effect of intensive therapy on the microvascular complications of type 1 diabetes mellitus. JAMA. 2002;287:2563-2569.
2. Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) Study Research Group. Intensive diabetes treatment and cardiovascular outcomes in type 1 diabetes: the DCCT/EDIC study 30-year follow-up. Diabetes Care. 2016;39:686-693.
3. Halvorsen M, Yasuda P, Carpenter S, Kaiserman K. Unique challenges for paediatric patients with diabetes. Diabet Spectr. 2005;18:167-173.
4. Rewers M, Pihoker C, Donaghe K, Hanas R, Swift P, Klingensmith GJ. ISPAD Clinical Practice Consensus Guidelines 2014 Compendium. Assessment and monitoring of glycaemic control in children and adolescents with diabetes. Pediatr Diabetes. 2014;15(suppl. 20):102-114.
5. Vijan S, Hayward RA, Ronis DL, Hofer TP. Brief report: the burden of diabetes therapy: implications for the design of effective patient-centered treatment regimens. J Gen Intern Med. 2005;20:479-482.
6. Peyrot M, Rubin RR, Kruger DF, Travis LB. Correlates of insulin injection omission. Diabetes Care. 2010;33:240-245.
7. Wisting L, Freisland DH, Skrivarhaug T, Dahl-Jørgensen K, Ra Ø. Disturbed eating behavior and omission of insulin in adolescents receiving intensified insulin treatment. Diabetes Care. 2013;36:3382-3387.
8. Desrocher M, Rovet J. Neurocognitive correlation of type 1 diabetes mellitus in childhood. Child Neuropsychol. 2004;10:36-52.
9. Mauers N, Mazaike P, Buckingham B, et al. Longitudinal assessment of neuroanatomical and cognitive differences in young children with type 1 diabetes: association with hyperglycemia. Diabetes. 2015;64:1770-1779.
10. Mazaike P, Weinzimer S, Mauers N, et al. Variations in brain volume and growth in young children with type 1 diabetes. Diabetes. 2016;65:476-485.
11. Onishi Y, Ono Y, Rabøl R, Endahl L, Nakamura S. Superior glycemic control with once-daily insulin degludec/insulin aspart versus insulin glargine in Japanese adults with type 2 diabetes inadequately controlled with oral drugs: a randomized, controlled phase 3 trial. Diabetes Obes Metab. 2013;15:826-832.
12. Heise T, Nosek L, Roepstorff C, Chenji S, Klein O, Haahr H. Distinct prandial and basal glucose-lowering effects of insulin degludec/insulin aspart (IDegAsp) at steady state in subjects with type 1 diabetes mellitus. Diabetes Ther. 2014;5:255-265.
13. Humulin SmPC. https://www.medicines.org.uk/emc/m medicine/3425. Accessed December 2017.
14. Novomix 30 SmPC. https://www.medicines.org.uk/EMC/medicines/8591/SPC/NovoMix30+Penfill+100+U+ml+NovoMix30+FlexPen+100+U+ml/. Accessed December 2017.
15. Haak T, Tiengo A, Draeger E, Suntum M, Waldhäusl W. Lower within-subject variability of fasting blood glucose and reduced weight gain with insulin detemir compared to NPH insulin in patients with type 2 diabetes. Diabetes Obes Metab. 2005;7:56-64.
16. Levemir SmPC. https://www.medicines.org.uk/emc/medicines/14584. Accessed December 2017.
17. NovoRapid SmPC. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000258/WC00030372.pdf. Accessed December 2017.
18. World Medical Association Inc. Declaration of Helsinki. Ethical principles for medical research involving human subjects. J Indian Med Assoc. 2009;107:403-405.
19. ICH Harmonised Tripartite Guideline. Guideline for good clinical practice. J Postgrad Med. 2001;47:199-203.
20. Rewers M, Pihoker C, Donaghe K, Hanas R, Swift P, Klingensmith GJ. ISPAD Clinical Practice Consensus Guidelines 2009 Compendium: Assessment and monitoring of glycemc control (Chapter 7). Pediatr Diabetes. 2009;10:71(suppl 12):71-81. Errata included in file. http://c. ymcdn.com/sites/www.isp_ad.org/resource/resmgr/Docs/isp_ad_CPCG_2009-CHAPTER_7.pdf. Accessed December 2017.
21. ADA - 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.
22. Clarke W, Jones T, Rewers A, Dunger D, Klingensmith GJ. ISPAD Clinical Practice Consensus Guidelines 2009 Compendium. Assessment and management of hypoglycemia in children and adolescents with diabetes. Pediatr Diabetes. 2009;10(suppl. 12):134-144.
23. Food and Drug Administration. Guidance for Industry: diabetes mellitus: developing drugs and therapeutic biologics for treatment and prevention. Draft Guidance 2008. Rockville, MD: US Department of Health and Human Services, Food and Drug Administration (FDA), Center for Drug Evaluation and Research (CDER) [online]. https://www.fda.gov/downloads/Drugs/.../Guidances/ucm071624.pdf. Accessed December 2017.
24. Kobzová J, Vignérová J, Bláha P, et al. The 6th nationwide anthropological survey of children and adolescents in the Czech Republic in 2001. Cent Eur J Public Health. 2004;12:126-130.
25. Roelants M, Hausprie R, Hoppenbrouwers K. References for growth and pubertal development from birth to 21 years in Flanders, Belgium. Hum Biol. 2009;36:680-694.
26. Hernández et al. Curvas y Tablas de Crecimiento. Instituto de Investigación sobre Crecimiento y Desarrollo, Fundación F. Ortegozo. Madrid: Garsi; 1988.
27. Kuczmaryski RJ, Ogden CL, Guo SS, et al. 2000 CDC growth charts for the United States: methods and development. National Center for Health Statistics. Vital Health Stat 11. 2002;(246):1-190.
28. Thalange N, Deeb L, Iotova V, et al. Insulin degludec in combination with bolus insulin aspart is safe and effective in children and adolescents with type 1 diabetes. Pediatr Diabetes. 2015;16:164-176.
29. Davies M, Sasaki T, Gross JL, et al. Comparison of insulin degludec with insulin detemir in type 1 diabetes: a 1-year treat-to-target trial. Diabetes Obes Metab. 2016;18:96-99.
30. Lane W, Bailey TS, Gerety G, et al. Effect of insulin Degludec vs insulin glargine U100 on hypoglycemia in patients with type 1 diabetes: The SWITCH 1 Randomized Clinical Trial. JAMA. 2017;318:33-44.
31. Wallace JP, Wallace JL, McFarland MS. Comparing dosing of basal insulin analogues detemir and glargine: is it really unit-per-unit and dose-per-dose? Ann Pharmacother. 2014;48:361-368.
32. Thalange N, Bereket A, Larsen J, Hiort LC, Peterkova V. Insulin analogues in children with type 1 diabetes: a 52-week randomized clinical trial. Diabet Med. 2013;30:216-225.
33. Robertson KJ, Schoenle E, Gucev Z, Mordhorst L, Gall M-A, Ludvigsson J. Insulin detemir compared with NPH insulin in children and adolescents with type 1 diabetes. Diabet Med. 2007;24:27-34.
34. Schwartz NS, Clutter WE, Shah SD, Creyer PE. Glycem thresholds for activation of glucose counterregulatory systems are higher than the threshold for symptoms. J Clin Invest. 1987;79:777-781.

SUPPORTING INFORMATION
Additional supporting information may be found online in the Supporting Information section at the end of the article.

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