

Research: Treatment

Safety and efficacy of insulin degludec/insulin aspart with bolus mealtime insulin aspart compared with standard basal–bolus treatment in people with Type 1 diabetes: 1–year results from a randomized clinical trial (BOOST[®] T1)

I. B. Hirsch¹, E. Franek², H. Mersebach³, L. Bardtrum⁴ and K. Hermansen⁵

¹School of Medicine, University of Washington, Seattle, WA, USA, ²Mossakowski Medical Research Centre, Polish Academy of Sciences and Department of Internal Diseases, Endocrinology and Diabetology, Central Clinical Hospital MSW, Warsaw, Poland, ³Novo Nordisk Inc., Princeton, NJ, USA, ⁴Novo Nordisk A/S, Søborg, Denmark and ⁵Aarhus University Hospital, Aarhus, Denmark

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Abstract

Aims To evaluate the long-term safety and efficacy of a simplified basal–bolus regimen of once-daily insulin degludec/insulin aspart (IDegAsp) with additional IAsp vs. a standard basal–bolus insulin regimen of insulin detemir (IDet) with IAsp in adults with Type 1 diabetes.

Methods This was an open-label trial comprising a 26-week core phase followed by a 26-week extension phase. Participants were randomized to IDegAsp once daily at the main meal and IAsp at remaining meals (IDegAsp+IAsp), or IDet (once or twice daily) and IAsp at all meals (IDet+IAsp). Insulins were titrated to target plasma glucose of < 5 mmol/l (< 90 mg/dl) at pre-breakfast (IDegAsp and IDet) and at pre-meal (IAsp).

Results After 52 weeks, the overall confirmed hypoglycaemia rate was 31.8 episodes/patient-years of exposure (PYE) with IDegAsp+Asp and 36.7 episodes/PYE with IDet+IAsp, and the rate of nocturnal confirmed hypoglycaemia was significantly lower with IDegAsp+Asp than with IDet+IAsp (3.1 vs. 5.4 episodes/PYE, respectively; $P < 0.05$). Adverse event rates were comparable between groups. Mean HbA_{1c} decreased from baseline by 0.7% (IDegAsp+IAsp) and 0.6% (IDet+IAsp), achieving 60 or 61 mmol/mol (7.6% or 7.7%, respectively), at Week 52. The mean total daily insulin dose was lower with IDegAsp+IAsp than with IDet+IAsp (ratio: 0.87; 95% CI 0.79–0.95; $P = 0.0026$).

Conclusions Once-daily treatment with IDegAsp and IAsp as bolus insulin for remaining meals was associated with significantly lower risk of nocturnal confirmed hypoglycaemia, improved glycaemic control and showed non-inferiority compared with IDet+IAsp, the standard of care in Type 1 diabetes.

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Introduction

Individuals with Type 1 diabetes are dependent on insulin treatment, typically requiring four or more injections per day to cover basal and prandial needs [1]. The risk of hypoglycaemia continues to be a concern with intensive basal–bolus insulin regimens [1], with recent observational data indicat-

ing that the risk of severe hypoglycaemia strongly correlates with the duration of Type 1 diabetes [2]. In parallel, the requirement for multiple daily injections can constrain day-to-day activities, with increasing injections leading to a higher treatment burden and the potential for skipped injections [3,4]. Insulin treatment combinations that provide efficacious and well-tolerated basal and prandial glycaemic coverage, with fewer daily injections, would be beneficial to reduce treatment burden and improve treatment adherence in people with Type 1 diabetes.

The combination of a basal and a prandial insulin has historically proven elusive, as the basal insulin analogues such as insulin detemir (IDet) and insulin glargine (IGlar)

Correspondence to: Irl B. Hirsch. E-mail: ihirsch@u.washington.edu
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What's new?

- For people with Type 1 diabetes, modern-day basal-bolus regimens requiring separate daily injections of basal and prandial insulin are the standard of care.
- To date, it has not been possible to combine basal and bolus insulin in a single injection (thereby reducing the injection number) without adversely affecting the glucose-lowering properties of both components.
- Insulin degludec/insulin aspart (IDegAsp) is a combination of the basal insulin analogue, insulin degludec, and the rapid-acting insulin analogue, insulin aspart.
- This Phase 3 trial presents the first long-term safety and efficacy data comparing IDegAsp with mealtime bolus with a standard basal-bolus regimen in Type 1 diabetes.

could not be formulated with rapid-acting insulin analogues without adversely affecting the pharmacodynamic properties of the rapid-acting component [5]. The development of insulin degludec (IDeg), a basal insulin that forms stable dihexamers in solution at physiological pH [6], has allowed for the possibility of co-formulation with another insulin analogue [7].

Insulin degludec/insulin aspart (IDegAsp) is a soluble co-formulation of IDeg and insulin aspart (IAsp) in a 70:30 ratio [7]. The distinct basal and prandial pharmacodynamic characteristics of IDeg and IAsp remain unaffected when combined in IDegAsp [8]. IDegAsp is associated with a reduced risk of hypoglycaemia and improved fasting plasma glucose control compared with premixed insulins [9–11]. In Type 2 diabetes, IDegAsp can be administered once or twice daily with the main meal(s) whilst allowing the participant to change the time of administration, if dosed with the largest meal when taken daily [7]. Furthermore, IDegAsp does not require resuspension [12,13], which coupled with its mealtime-related flexibility, makes it distinctly different from premixed insulins.

BOOST[®] T1 was a 52-week study consisting of a core and an extension phase, each 26 weeks long. In the core phase of the BOOST T1 study (26 weeks), IDegAsp with bolus IAsp at additional mealtimes (IDegAsp+IAsp) improved glycaemic control and was non-inferior to standard basal (IDet) and bolus (IAsp) regimen (IDet+IAsp) in participants with Type 1 diabetes [14]. IDegAsp+IAsp treatment was also associated with a lower risk of nocturnal hypoglycaemia and fewer daily injections, indicating that IDegAsp+IAsp offers the potential for a simpler alternative compared with basal-bolus treatment in Type 1 diabetes [14].

Here, we present the results after 52 weeks of treatment (BOOST T1 study), to assess the long-term safety and efficacy of IDegAsp+IAsp vs. IDet+IAsp in Type 1 diabetes.

Subjects and methods

This was a 52-week multinational, multicentre, open-labelled, two-arm, parallel, randomized, treat-to-target trial; results from the 26-week core have been reported in detail previously [14]. Briefly, eligible participants were randomized 2:1 to receive IDegAsp once daily (at main meal) with additional IAsp (at remaining meals) or IDet once daily (evening meal) with IAsp (at mealtimes). Dosing of IDegAsp could be rescheduled to another main meal during the trial according to participant and physician preference. In cases of inadequate glycaemic control after 8 weeks of treatment, participants randomized to IDet+IAsp received a second morning dose (i.e. twice daily). Insulins were titrated to target plasma glucose values of 4–5 mmol/l (72–90 mg/dl) before breakfast (IDegAsp and IDet) and before meals (IAsp) [14]. For participants requiring an additional IDet dose, the second dose (at breakfast) was titrated to the same target based on the mean of the pre-dinner plasma glucose levels from the preceding 3 days. The core phase was followed by a 1-week washout period during which participants were treated with neutral protamine Hagedorn (NPH) to enable assessment of antibodies against trial insulin analogues. At Week 26, eligible participants entered the 26-week extension phase, continuing treatment as per original randomization, preferably at the same dose levels as reported at the end of the core phase.

The core and extension studies were conducted in accordance with the Declaration of Helsinki and International Conference on Harmonisation (ICH) Good Clinical Practice Guidelines.

Primary endpoints (safety) included adverse events, hypoglycaemic episodes, insulin dose, body weight, clinical laboratory values and vital signs. Confirmed hypoglycaemia was defined as severe hypoglycaemia requiring assistance or episodes of a plasma glucose level of < 3.1 mmol/l (< 56 mg/dl). Hypoglycaemia occurring between 00.01 and 05.59 h (inclusive) was classified as nocturnal. Key secondary endpoints (efficacy) included change from baseline in HbA_{1c}, fasting plasma glucose levels and nine-point self-measured plasma glucose levels.

Safety endpoints were analysed in all participants who were exposed to IDegAsp, IDet or IAsp [safety analysis set (SAS)]. A treatment-emergent adverse event was defined as an event that had a date of onset on, or after, the first day of exposure to randomized treatment in the main trial, and no later than 7 days after the last day of randomized treatment. The number of hypoglycaemic episodes was analysed in the full analysis set (consisting of all participants randomized at the start of the core phase) using a negative binomial regression model – with a log-link function and the logarithm to the period when a hypoglycaemic episode was considered treatment-emergent as offset. Other adverse events were summarized using descriptive statistics. Treatment differences from baseline to Week 52 were performed on the full

analysis set with treatment, antidiabetic therapy at screening, sex and region as fixed factors, and age and baseline values as covariates. Statistical analysis of primary and secondary endpoints was conducted as previously reported [14]. Insulin doses (log transformed) were compared at the end of the treatment period by *post hoc* analysis. Based on a one-tailed *t*-test size of 2.5% and assuming a standard deviation (SD) of 1.1% for HbA_{1c}, a minimum sample size of 447 was calculated to provide $\geq 95\%$ power to demonstrate the non-inferiority of IDegAsp over IGlAr during the core phase. The sample size for the extension trial was determined by the number of participants continuing from the main trial. Missing values (including intermittent missing values) were imputed using the last observation carried forward method.

Results

Participant disposition and baseline characteristics

The proportion of participants entering and completing the extension phase was 91.7% ($n = 233/254$) for IDegAsp+IAsp and 92.6% ($n = 113/122$) for IDet+IAsp (Fig. 1).

The proportion of participants who withdrew during the extension phase was 8.0% ($n = 21/254$) for IDegAsp+IAsp and 7.0% ($n = 9/122$) for IDet+IAsp, with no differences in the reasons and the time for withdrawals (Fig. 1).

The baseline characteristics of participants in the extension phase compared with the core phase are summarized in Table S1.

Adverse events

A similar percentage of participants with IDegAsp+IAsp (73.8%; $n = 267/362$) and IDet+IAsp (70.6%; $n = 127/180$) reported treatment-emergent adverse events, the majority of which were mild or moderate in severity. Injection-site reactions (none of them serious) were reported by 1.9% ($n = 7/362$) of participants on IDegAsp+IAsp vs. 6.7% ($n = 12/180$) on IDet+IAsp. One participant on IDet+IAsp experienced the majority ($n = 28$) of non-serious injection-site events.

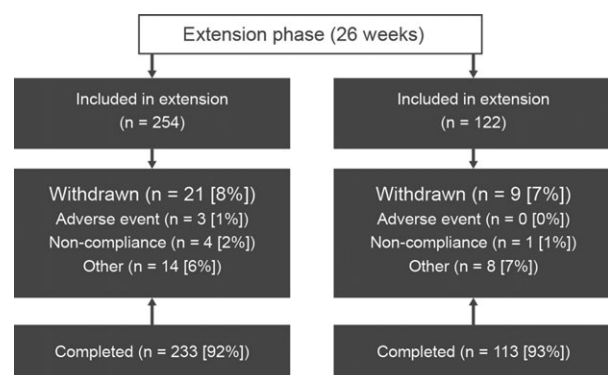


FIGURE 1 Participant disposition BOOST[®] T1 study. *n*, number of participants.

The rate of serious adverse events over the course of 52 weeks was similar between the IDegAsp+IAsp [0.24 events/patient-years of exposure (PYE)] and IDet+IAsp groups (0.19 events/PYE). The most frequently reported serious adverse event possibly or probably considered to be related to treatment was hypoglycaemia [4.1% participants (0.08 events/PYE) with IDegAsp+IAsp vs. 5.0% participants (0.06 events/PYE) with IDet+IAsp] followed by hypoglycaemic unconsciousness [1.9% participants (0.02 events/PYE) with IDegAsp+IAsp vs. 2.2% participants (0.03 events/PYE) with IDet+IAsp]. No deaths or major adverse cardiovascular events were reported. Serious adverse events are shown in Table S2 (SAS).

Hypoglycaemic episodes

Cumulative analyses over the entire treatment period showed observed rates of overall confirmed hypoglycaemia of 31.8 episodes/PYE with IDegAsp+IAsp and 36.7 episodes/PYE with IDet+IAsp at Week 52 (SAS), with an estimated rate ratio (ERR) (IDegAsp+IAsp/IDet+IAsp) of 0.95 (95% CI 0.79–1.14; $P = 0.5892$) (Fig. 2a). At Week 52, the rate of nocturnal confirmed hypoglycaemia was significantly lower with IDegAsp+IAsp than with IDet+IAsp [observed rates: 3.1 vs. 5.4 episodes/PYE, respectively (ERR 0.62; 95% CI 0.48–0.79; $P < 0.05$)] (Fig. 2b). The rate of severe hypoglycaemia was similar with IDegAsp+IAsp (0.3 episodes/PYE) and IDet+IAsp (0.5 episodes/PYE; ERR 0.98; 95% CI 0.54–1.79).

Body weight

The observed mean weight gain was moderate after 52 weeks in both groups (1.8 kg with IDegAsp+IAsp vs. 1.2 kg with IDet+IAsp; $P < 0.05$).

Laboratory measurements

There were no clinically relevant differences from baseline to Week 52, or between treatment groups, in clinical laboratory measurements, lipids, physical examination, vital signs, electrocardiograms or funduscopy. The mean level of insulin antibodies cross-reactive to IDegAsp+IAsp, IDet+IAsp and human insulin was low at baseline and remained low throughout the 52 weeks with IDegAsp+IAsp, although increasing slightly with IDet+IAsp. Mean levels of IDeg-, IDet- and IAsp-specific antibodies remained low throughout the 52-week period.

Insulin dose

At Week 52, the mean total insulin dose ratio in units (IDegAsp+IAsp/IDet+IAsp) was 0.87 (95% CI 0.79–0.95; $P = 0.0026$), indicating that the mean total daily insulin dose (basal + bolus insulin) at the end of the extension phase was 13% lower with IDegAsp+IAsp than with IDet+IAsp (Fig. 2c). Although the total daily bolus insulin

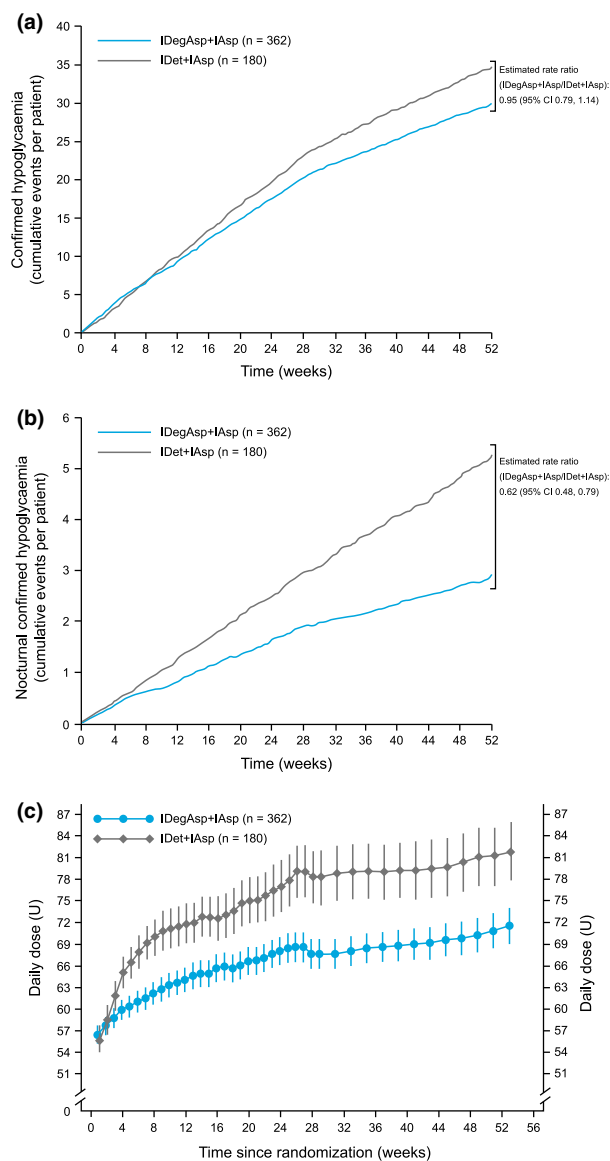


FIGURE 2 One-year safety and efficacy of IDegAsp+IAsp compared with basal-bolus therapy with IDet+IAsp in participants with Type 1 diabetes. Data shown are: (a) cumulative number of hypoglycaemia episodes during treatment (safety analysis set), (b) cumulative number of nocturnal confirmed hypoglycaemic episodes during treatment (safety analysis set), and (c) mean total daily insulin dose over time (full analysis set). Error bars represent standard errors of mean total daily insulin doses.

dose was not significantly different between treatment groups [1.01 U (95% CI 0.91, 1.12); $P = 0.8438$], the daily basal insulin dose was 19% lower in the IDegAsp+IAsp group compared with the IDet+IAsp group [IDegAsp+IAsp/IDet+IAsp was 0.81 U (95% CI 0.73–0.89; $P < 0.0001$)]. For IDegAsp+IAsp, the mean total daily insulin dose increased gradually over 52 weeks, whereas with IDet+IAsp the increase was steepest over the first 8 weeks of treatment (Fig. 2c). After 52 weeks, the basal/bolus split of total insulin dose was 42%/58% with IDegAsp+IAsp vs. 47%/53% with IDet+IAsp.

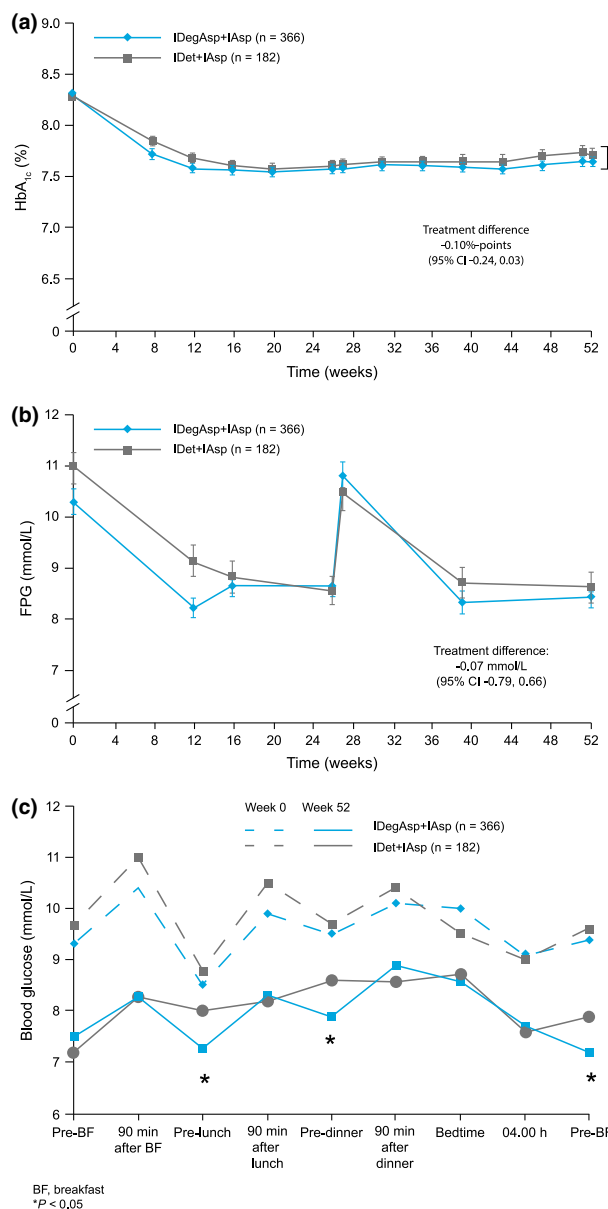


FIGURE 3 One-year (52-week) efficacy of IDegAsp+IAsp compared with basal-bolus therapy with IDet+IAsp in participants with Type 1 diabetes. Data shown are: (a) mean HbA_{1c} over time, (b) mean fasting plasma glucose levels over time, and (c) mean nine-point self-measured plasma glucose profile at baseline (Week 0) and Week 52 (full analysis set).

Glycaemic control

After 52 weeks of treatment, the observed mean HbA_{1c} decreased by 0.7% with IDegAsp+IAsp and 0.6% with IDet+IAsp, achieving 60 mmol/mol (7.6%) or 61 mmol/mol (7.7%), respectively, with an estimated non-significant mean treatment difference between groups of -0.10% (Fig. 3a).

After 52 weeks, the proportion of participants who achieved the HbA_{1c} target of < 53 mmol/mol (< 7.0%) was

22.4% (82/366) with IDegAsp+IAsp and 17.0% (31/182) with IDet+IAsp [estimated odds ratio (IDegAsp+IAsp/IDet+IAsp) 1.56; 95% CI 0.94–2.59; $P = 0.0868$].

Fasting plasma glucose

After 52 weeks, fasting plasma glucose was reduced to similar levels [8.5–8.6 mmol/l (153–155 mg/dl)] in both groups (Fig. 3b).

Nine-point self-measured blood glucose

At Week 52, the mean self-measured plasma glucose levels before meals (lunch, main evening meal and breakfast the following day) were significantly lower with IDegAsp+IAsp than with IDet+IAsp ($P < 0.05$ in all cases) (Fig. 3c). The estimated overall mean of the nine-point self-measured plasma glucose profiles was similar between groups [8.1 mmol/l (146 mg/dl) with IDegAsp+IAsp vs. 8.3 mmol/l (149 mg/dl) with IDet+IAsp]. However, a significantly greater increment in mean prandial plasma glucose was observed with IDegAsp+IAsp vs. IDet+IAsp over all meals [estimated treatment difference 0.64 mmol/l (12 mg/dl)], particularly after lunch [estimated treatment difference 0.98 mmol/l (18 mg/dl)] and at the main evening meal [estimated treatment difference 0.80 mmol/l (14 mg/dl)] ($P < 0.05$ in all cases).

Injections of IDegAsp were distributed among all meals, indicating the opportunity for physicians to provide individualized IDegAsp treatment at any meal of the day. As reported for the core study, the majority of participants administered IDegAsp once daily with their main evening meal, with the remainder evenly split between breakfast and lunch after 52 weeks of treatment. The proportion of participants administering IDegAsp at dinner was 67.1%, with 20.2% administering IDegAsp at lunch and 14.4% at breakfast during Week 1, vs. 71% at dinner, 16% at lunch and 13% at breakfast after 52 weeks (based on recorded doses in the safety analysis set excluding participants who withdrew during the 52-week period). Regardless of the dosing time, the IDegAsp dose was adjusted based on pre-breakfast glucose measurement. Approximately 20% of participants reported adding a morning dose of IDet to their evening dose at least once in the 3 days leading up to the final visit.

Discussion

This study demonstrated that a novel regimen of IDegAsp+IAsp was well tolerated and associated with a significantly lower risk of nocturnal confirmed hypoglycaemia, and a lower risk in overall confirmed and severe hypoglycaemic episodes compared with IDet+IAsp following 52 weeks of treatment in participants with Type 1 diabetes. IDegAsp+IAsp effectively improved glycaemic control, providing long-term reductions in

HbA_{1c} and fasting plasma glucose levels, as reported with conventional basal–bolus therapy, and a lower total daily insulin dose and fewer daily injections.

Notably, pre-meal glucose levels at all three main meals were lower with IDegAsp+IAsp, which indicates the longer-acting nature of IDeg (> 42 h) compared with current basal insulin analogues (≤ 24 h) [15]. The latter result is consistent with evidence showing that the glucose-lowering effect of the IDeg component is unaffected by co-formulation [8,16]. Moreover, the mean prandial plasma glucose levels with IDegAsp were significantly lower than with IDet, likely reflecting the decrease in plasma glucose at pre-meals with IDegAsp, whereas participants receiving IDet had consistently high plasma glucose levels at most self-measured time points. The long duration of action of IDeg has been further demonstrated in a randomized, controlled, treat-to-target trial comparing evening administration without flexibility of timing of IDeg+IAsp once daily vs. IDet+IAsp (once or twice daily), in participants with Type 1 diabetes, among whom treatment with IDeg+IAsp resulted in significantly greater reductions in fasting plasma glucose and in rates of nocturnal confirmed hypoglycaemia compared with IDet+IAsp [17]. In this study, protocol-defined mean fasting plasma glucose values did not differ between groups, although pre-meal self-measured plasma glucose values (before dinner, lunch and breakfast the day following injection) were significantly lower with IDegAsp+IAsp.

The mean total daily insulin dose was lower for IDegAsp+IAsp compared with IDet+IAsp, indicating that a lower dose of IDeg was required to achieve similar levels of overall glycaemic control in the present population in line with previous evidence [17].

In this trial, participants administered IDegAsp once daily with any main meal, and with the option of altering the daily dose timing. The majority of participants chose to administer IDegAsp with their main evening meal. This flexibility in dose timing did not compromise safety as the overall rate of confirmed hypoglycaemia was lower with IDegAsp+IAsp and the rate of nocturnal hypoglycaemia over time was in favour of IDegAsp compared with standard basal–bolus insulin therapy. The effect of IDegAsp on hypoglycaemia rates, particularly in the context of shifting administration time, allowed some degree of flexibility in the timing of the basal dose without compromising fasting glucose control.

Of relevance is that, although severe hypoglycaemia was low with both study regimens, participants with recurrent hypoglycaemia and hypoglycaemia unawareness were excluded from participation, which might potentially contribute to the low frequency of severe hypoglycaemia and may be considered a limitation of this study. The results presented here are in line with recent studies demonstrating that IDeg+IAsp is associated with significantly lower rates of nocturnal hypoglycaemia compared with IGl+IAsp or IDet+IAsp in Type 1 diabetes [18,19]. This may be attributable to the lower day-to-day variability in glucose-

lowering properties of IDeg vs. earlier basal insulin analogues [20]. In a meta-analysis that included two trials of participants with Type 1 diabetes on basal–bolus therapy, compared with IGLar, IDeg treatment was associated with lower rates of nocturnal hypoglycaemia, lower levels of fasting plasma glucose and lower total daily insulin dose [21]. The reduction in nocturnal hypoglycaemia is particularly relevant, because such episodes have the potential to disrupt participants' day-to-day activities (such as work or travel), and lead to insulin dose reductions by participants [22].

The lesser weight gain observed with IDet+IAsp vs. IDegAsp+IAsp in the present study is consistent with previous findings, which have demonstrated a weight advantage with IDet compared with neutral protamine Hagedorn insulin and IGLar [23–26]. Moreover, no significant difference in weight gain has been observed between IDegAsp and IGLar in previous trials [27,28].

Considering the increase in perceived burden associated with each additional daily insulin injection and resultant implications for potential omission of injections [3,22], the results of the extension phase support results reported during the core phase [14], confirming that IDegAsp at any main meal, plus IAsp as bolus for any remaining meals, is as well tolerated and efficacious as standard IDet+IAsp basal–bolus therapy.

This is the first study to demonstrate that intensive insulin therapy with IDegAsp+IAsp can be achieved with three injections instead of a minimum of four in participants with Type 1 diabetes. The ability to provide effective glycaemic control over 52 weeks with one less injection compared with a conventional basal–bolus insulin regimen could be of real value to participants by alleviating the injection burden, and thereby potentially improving adherence and quality of life.

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Competing interests

IBH received research support from Sanofi-USA and Novo Nordisk, and served as consultant for Abbott Diabetes Care, Roche and Valeritas. EF served as adviser to Novartis and Novo Nordisk and was involved in speaker bureaux for AstraZeneca/Bristol-Myers Squibb, Bioton, Boehringer Ingelheim, Eli Lilly, Janssen Cilag, Merck, MSD, Novartis, Novo Nordisk, Sanofi, Servier and TEVA. KH served as adviser to AstraZeneca/Bristol-Myers Squibb, Boehringer Ingelheim, Janssen-Cilag, Merck and Novo Nordisk, was involved in speaker bureaux for AstraZeneca/Bristol-Myers Squibb, Boehringer Ingelheim, Janssen Cilag, Eli Lilly, Merck, Novo Nordisk, Sanofi and Takeda, and was a stockholder of Novo

Nordisk. HM was an employee and shareholder of Novo Nordisk. LB was an employee and shareholder of Novo Nordisk.

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Author contributions

IBH, EF, KH, HM and LB were involved in the conception and design or analysis and interpretation of data of this trial. All authors contributed to the writing of the manuscript, reviewing and editing critically for important intellectual content.

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Supporting Information

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

- Table S1.** Demographics and baseline disease characteristics
Table S2. Serious adverse events by system organ class – safety analysis set