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CLINICAL CARE AND TECHNOLOGY

The rate of hyperglycemia and ketosis with insulin degludec-based treatment compared with insulin detemir in pediatric patients with type 1 diabetes: An analysis of data from two randomized trials

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Background: Historically, data on the rate of hyperglycemia and ketosis have not been collected in clinical trials. However, it is clinically important to assess the rate of these events in children with type 1 diabetes (T1D). This question was addressed in two pediatric trials using insulin degludec (degludec).

Objective: To assess the rate of hyperglycemia and ketosis in two-phase 3b trials investigating degludec (Study 1) and degludec with insulin aspart (IDegAsp [Study 2]) vs insulin detemir (IDet).

Subjects: Patients (aged 1-17 years inclusive) with T1D treated with insulin for ≥3 months.

Methods: Study 1: patients were randomized to degludec once daily (OD) or IDet OD/twice daily (BID) for 26 weeks, followed by a 26-week extension phase. Study 2: patients were randomized to IDegAsp OD or IDet OD/BID for 16 weeks. Bolus mealtime IAsp was included in both studies. In Study 1, hyperglycemia was recorded if plasma glucose (PG) was >11.1 mmol/L, with ketone measurement required with significant hyperglycemia (>14.0 mmol/L). In Study 2, hyperglycemia was recorded with PG >14.0 mmol/L where the subject looked/felt ill, with ketone measurement also required in these hyperglycemic patients. In this post hoc analysis, the hyperglycemia threshold was 14.0 mmol/L for uniformity.

Results: Despite similar rates of hyperglycemia with degludec/IDegAsp compared with IDet, the rates of ketosis were lower with degludec/IDegAsp.

Conclusions: These trials, the first to systematically collect data on ketosis in pediatric patients with T1D, demonstrate the potential of degludec/IDegAsp to reduce rates of metabolic decompensation, compared with IDet.

KEYWORDS

hyperglycemia, insulin degludec/insulin aspart, insulin detemir, ketosis, type 1 diabetes

1 | INTRODUCTION

Control of hyperglycemia is a key focus of diabetes management and insulin is the mainstay of treatment for type 1 diabetes (T1D). Insulin deficiency leads to hyperglycemia and elevated ketones (ketosis) and, if not managed correctly, progresses to diabetic ketoacidosis (DKA). The

ABBREVIATIONS: AE, adverse event; BID, twice daily; CI, confidence interval; DKA, diabetic ketoacidosis; FAS, full analysis set; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; IAsp, insulin aspart; IDeg, insulin degludec; IDegAsp, insulin degludec/insulin aspart; IDet, insulin detemir; ISPAD, International Society for Pediatric and Adolescent Diabetes; OD, once daily; PG, plasma glucose; PYE, patient-years of exposure; SAE, serious adverse event; SAS, safety analysis set; T1D, type 1 diabetes.

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International Society for Pediatric and Adolescent Diabetes (ISPAD) has developed specific guidelines for the assessment and monitoring of glycemic control in children and adolescents with diabetes.[1] While ketone levels ≤0.6 mmol/L are considered normal, elevated levels >0.6 mmol/L indicate mild ketosis, >1.5 mmol/L represents the level at which there is a high risk of progression to ketoacidosis, and ketoacidosis is imminent with ketone levels >3.0 mmol/L.[1] DKA is a major health concern in children with T1D and is associated with significant morbidity and mortality.[2,3] Despite this concern, there is a lack of systematic collection of the rate of ketosis in pediatric populations with T1D. Unchecked, ketosis will progress to DKA. In children with established diabetes, 4.9% to 7.1% of children and adolescents experienced at least one episode of DKA in the previous year.[4,5]

DKA in established diabetes is a preventable condition, and education on "sick-day rules" is routinely provided to all patients and their families. This emphasizes the importance of frequent checking for ketones and glucose, and administering additional insulin as required. Nonetheless, the relatively high rates of DKA, particularly in adolescents, remain a significant public health challenge, and DKA remains the commonest cause of death in pediatric T1D.[6]

Glycemic control can be affected by the pharmacokinetic and pharmacodynamic properties of insulins, with variable time-action profiles leading to variability in plasma glucose (PG). The aim of insulin treatment is to emulate physiological insulin secretion as closely as possible. Insulin degludec (degludec) is a new-generation basal insulin with a flat pharmacokinetic profile and a long duration of action. Degludec has been co-formulated with insulin aspart (IAsp) in a novel co-formulation of 70% degludec and 30% IAsp (IDegAsp) in a single injection.[7] When dosed once daily (OD) with the main meal, this co-formulation provides insulin coverage for the meal via the IAsp component, and sustained basal insulin coverage for over 24 hours via the degludec component.[7] This treatment potentially allows delivery of basal-bolus therapy with fewer insulin injections, and may be of particular utility in patients with needle phobia, or who are poorly adherent to insulin therapy.

It was of clinical importance to assess the rate of hyperglycemia and ketosis in the pediatric clinical trials investigating degludec and IDegAsp, both compared with insulin detemir (IDet). The long duration of action resulting from the degludec component would be expected to reduce ketosis. In this analysis, we assess the rates of hyperglycemia and ketosis in the two-phase 3b pediatric trials investigating degludec plus mealtime IAsp (NN1250-3561 [Study 1]) and IDegAsp plus mealtime IAsp (at the meals where IDegAsp was not given; NN5401-3816 [Study 2]). The comparator for both studies was IDet plus mealtime IAsp. To the best of our knowledge, these are the first trials to systematically collect epidemiological data on the rate of hyperglycemia and ketosis in a pediatric population.

2 | METHODS

2.1 | Trial design and participants

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 trials were conducted according to the Declaration of Helsinki and International Conference on Harmonization Consolidated Guidelines on 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. These open-label trials are registered at www.clinicaltrials.gov: NCT01513473 and NCT01835431.

Patients with T1D aged 1 to 17 years (inclusive), previously treated with any insulin regimen for at least 3 months at a total daily insulin dose of ≤2 U/kg, and with glycated hemoglobin (HbA1c) levels ≤11% (96.7 mmol/mol), were eligible for inclusion. Patients were randomized to degludec OD or IDet OD or twice daily (BID) for 26 weeks, followed by a 26-week extension phase in Study 1, and IDegAsp OD or IDet OD or BID for 16 weeks in Study 2. Mealtime IAsp was included as the bolus insulin in both studies (Figure S1).

2.2 | Assessments

In both Studies 1 and 2, self-measured blood glucose (SMBG) measurements were performed with capillary blood automatically calibrated to plasma-equivalent glucose values, using centrally supplied glucose monitors able to capture both blood glucose and blood ketones. In Study 1, hyperglycemia was recorded if PG was >11.1 mmol/L (200 mg/dL) or in Study 2 with PG >14.0 mmol/L (252 mg/dL) where the patient also looked/felt ill. In both studies, PG was to be measured when there was the suspicion of a hyperglycemic episode. In this post hoc analysis, the threshold for hyperglycemia was set as 14.0 mmol/L (252 mg/dL) for uniformity. In both studies, capillary blood ketones were to be measured with hyperglycemia and PG >14.0 mmol/L (252 mg/dL). Significant ketosis was regarded as a meter-determined blood beta-hydroxybutyrate level above the protocol-defined threshold of 1.5 mmol/L (27 mg/dL), the level at which there is a high risk of ketoacidosis, in accordance with ISPAD guidelines.

In addition to the protocol-defined level of 1.5 mmol/L (27 mg/dL), mildly elevated ketones (>0.6 mmol/L [10.8 mg/dL]) and markedly elevated ketones (>3.0 mmol/L [54 mg/dL]) were considered of clinical interest and so were included in this post hoc analysis.

Change from baseline in HbA1c level after 26 and 52 weeks of treatment was measured as previously reported for Study 1[8] and at 16 weeks for Study 2.[9]

2.3 | Safety assessments

All patients receiving at least one dose of trial product were included in the safety analysis set.

Safety measures included all adverse events (AEs) and serious adverse events (SAEs).

2.4 | Statistical analysis

Analyses of efficacy endpoints were based on the full analysis set. Estimated mean treatment differences (or rate ratios) were presented together with two-sided 95% confidence intervals.

Change from baseline in HbA1c was analyzed as previously described.[8,9]

The number of hyperglycemic episodes (>14 mmol/L; 252 mg/dL) and episodes of ketosis are presented using descriptive statistics. The number of events (hyperglycemic episodes and episodes of ketosis) was analyzed using negative binomial regression using a log link and the logarithm of the exposure time (100 years) as offset. The model included treatment, sex, region, and age group as fixed effects.

3 | RESULTS

Participant disposition and baseline characteristics for Studies 1 and 2 are shown in the Supporting Information (Figure S2, Tables S1 and S2). Studies 1 and 2 showed non-inferiority in terms of HbA1c reduction for degludec or IDegAsp compared with IDet, respectively (Study 1 change in HbA1c: −0.20% vs −0.31%, respectively, estimated treatment difference (ETD) 0.15% [−0.03;0.32]; Study 2 change in HbA1c: −0.30% vs −0.30%, ETD −0.04% [−0.23;0.15]). Table 1 shows the episodes of hyperglycemia and ketosis for Study 1 (PG levels >14.1 mmol/L [252 mg/dL]) and Study 2 (hyperglycemia was recorded if PG >14 mmol/L where the patient looked/felt ill). In Study 1, 125 events were experienced by 39 patients in the degludec arm vs 195 events in 60 patients in the IDet arm. In Study 2, eight events were experienced by six patients in the IDegAsp arm vs 17 events in 11 patients in the IDet arm.

3.1 | Hyperglycemia with and without symptoms

The hyperglycemic episodes with and without symptoms for patients with PG levels >14 mmol/L (252 mg/dL) are shown in Table 2. Similar rates of hyperglycemia were reported in the degludec arm compared with the IDet arm for Study 1 and in the IDegAsp arm compared with the IDet arm for Study 2.

Similar numbers of patients reported hyperglycemia episodes with symptoms in Study 1; however, the number of events and rate/100 patient-years were lower in the degludec arm vs the IDet arm in both the core (13.98 vs 23.84 events per patient-year of exposure [PYE], degludec vs IDet) and the extension phase (23.55 vs 28.53 events/PYE, degludec vs IDet).

In Study 1, 62.3% of patients in the IDet treatment arm were using IDet BID at the end of the core phase and 64.0% were using IDet BID at the end of the extension phase; in Study 2, 54.2% of patients in the IDet treatment arm were using IDet BID. All patients in the IDegAsp treatment arms received IDegAsp OD.

3.2 | Episodes of ketosis

Ketone levels were measured for a similar number of hyperglycemic episodes in the degludec and IDet arms of Study 1. Compliance with ketone testing was 98.9% vs 99.4% in the degludec and IDet arms, respectively. Although the protocol for Study 2 required measurement of ketones if patients had PG levels >14 mmol/L (252 mg/dL) and looked or felt ill, many patients did not measure ketone bodies at these times, particularly those on IDet; ketones were measured in approximately 74% of hyperglycemic episodes in the IDegAsp treatment arm but only on 67% of occasions in the IDet treatment arm. Despite this imbalance, fewer ketosis episodes (ketones levels >1.5 mmol/L) were recorded in the IDegAsp arm (Table 1).

In Study 1, recurrent ketosis (defined here as more than one episode during the 26-week core or extension phases of the study) occurred in 10.3% (n = 18) of patients in the degludec arm vs 15.4% (n = 27) of patients in the IDet arm. In Study 2, recurrent ketosis occurred in 1.1% (n = 2) patients in both the degludec and IDet arms.

TABLE 1 Episodes of hyperglycemia and ketosis

		Number of episodes per patient-year of exposure			
	Trial arm (n)	Hyperglycemia[a]	Episodes of ketones > 0.6 mmol/L (10.8 mg/dL)	Episodes of ketones > 1.5 mmol/L (27 mg/dL)	Episodes of ketones > 3.0 mmol/L (54 mg/dL)
Study 1 (26 weeks core phase)	IDeg + IAsp (n = 174)	95	3.46	0.51	0.02
	IDet + IAsp (n = 175)	97	6.90	1.02	0.19
Rate ratio [95% CI] for IDeg vs IDet (FAS)		0.99 [0.84; 1.15]	0.39 [0.25; 0.63]*	0.36 [0.17; 0.76]*	0.12 [0.02; 0.63]*
Study 1 (26 weeks core phase + 26 weeks extension)	IDeg + IAsp (n = 174)	173	3.62	0.68	0.10
	IDet + IAsp (n = 175)	174	6.14	1.09	0.23
Rate ratio [95% CI] for IDeg vs IDet (FAS)		0.97 [0.84; 1.13]	0.44 [0.28; 0.68]*	0.41 [0.22; 0.78]*	0.28 [0.10; 0.77]*
Study 2 (16 weeks)	IDegAsp + IAsp (n = 181)	10.94	0.37	0.11	0.04
	IDet + IAsp (n = 179)	8.33	0.76	0.24	0.07
Rate ratio [95% CI] for IDegAsp vs IDet (FAS)		1.08 [0.64; 1.81]	0.41 [0.17; 1.04]	0.44 [0.11; 1.74]	NA

Abbreviations: CI, confidence interval; FAS, full analysis set; IAsp, insulin aspart; IDeg, insulin degludec; IDegAsp, insulin degludec/insulin aspart; IDet, insulin detemir; n, number of patients; NA, not analyzed because of insufficient data; PG, plasma glucose.

*$P < 0.05$.

[a] Hyperglycemia: episodes with PG >14.1 mmol/L (252 mg/dL) (Study 1); PG >14.0 mmol/L (252 mg/dL) where patient looked/felt ill (Study 2).

TABLE 2 Episodes of hyperglycemia with plasma glucose >14 mmol/L

	IDeg or IDegAsp			IDet		
	N	Events	Rate/100 pt-yrs	N	Events	Rate/100 pt-yrs
Study 1 core phase						
All episodes[a]	95	11 284	13 149.2	97	12 231	14 451.9
With symptoms	68	1200	1398.4	70	2018	2384.4
Study 1 core phase + extension phase						
All episodes	173	33 217	20 573.7	174	29 102	19 742.8
With symptoms	128	3799	2353.0	114	4206	2853.3
Study 2						
All episodes[b]	72	599	1094	73	449	833

Abbreviations: IDeg, insulin degludec; IDet, insulin detemir; N, number of patients; PG, plasma glucose; pt-yrs, patient-years.
[a] Includes all episodes with PG >14.0 mmol/L (252 mg/dL) irrespective of symptoms.
[b] Patients in study 2 only recorded hyperglycemic episodes with symptoms.

Rates of elevated ketones or ketosis were significantly lower with degludec vs IDet during the core phase and extension phase of Study 1 (ketones >0.6, >1.5, and > 3.0 mmol/L). Rates of elevated ketones or ketosis were numerically lower with IDegAsp vs IDet in Study 2 (ketones >0.6, >1.5, and > 3.0 mmol/L) (Table 1 and Figure 1). The beneficial effect of degludec/IDegAsp was more marked at higher levels of ketosis.

Analysis of the rate of episodes of ketosis by age group (1-5, 6-11, and 12-17 years) showed that episodes of ketosis (>1.5 mmol/L) were highest in children aged 1-5 years in both studies (Table 3). Rates of ketosis were consistently lower with degludec/IDegAsp vs IDet across age groups. The rates of ketosis with symptoms were numerically lower with degludec and IDegAsp compared with IDet in both trials (Table 4).

3.3 | Adverse events

The majority of reported AEs for both groups in Studies 1 and 2 were mild or moderate in severity and considered unlikely to be related to trial product. AEs are reported in detail in Thalange et al.[8] and Battelino et al.[9]

4 | DISCUSSION

Management of T1D in children is complex. Tight glycemic control is extremely important but challenging to achieve, particularly during illness. DKA may result from mismanagement of insulin during illness or non-adherence with insulin therapy. Specific ISPAD guidelines exist for the assessment and monitoring of glycemic control[1] and sick-day management in children and adolescents with diabetes.[10] The sick-day guidelines emphasize the importance of educating patients and their families on how to manage their diabetes during illness, with the aim of avoiding or minimizing DKA by measuring their blood glucose and ketone levels more frequently.[10]

Insulin therapy is the mainstay of treatment in T1D and may be intensified in an attempt to achieve tighter glycemic control. However, intensification of insulin therapy is associated with an increased risk of hypoglycemia. In contrast, degludec, with its flat pharmacokinetic profile and long duration of action, offers the potential to improve glycemic control by providing sustained basal insulin coverage for over 24 hours.

DKA is associated with significant morbidity and mortality in children with T1D.[2,3] Despite the major health concerns of DKA, there is a lack of systematic collection of data on ketosis in children with T1D

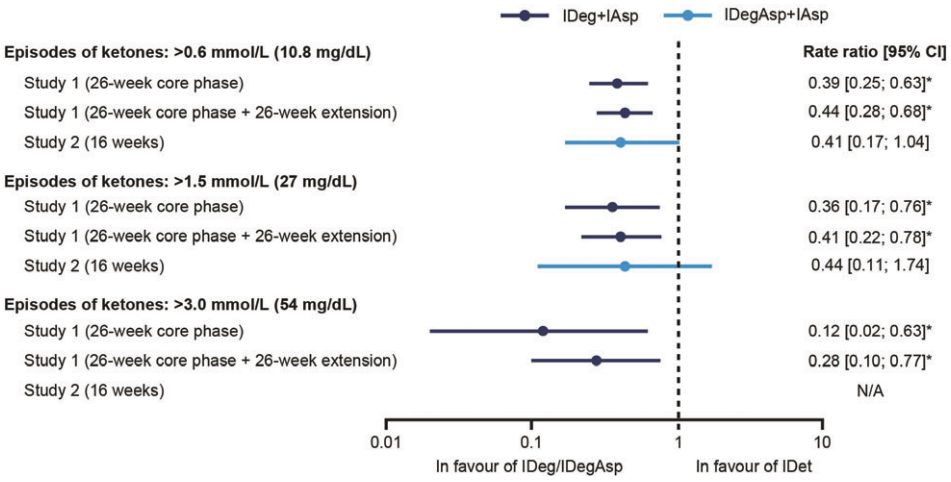

FIGURE 1 Forest plot showing rate of ketosis. *P < 0.05. Full analysis set. CI, confidence interval; IAsp, insulin aspart; IDeg, insulin degludec; IDegAsp, insulin degludec/insulin aspart; IDet, insulin detemir; NA, not analyzed due to insufficient data

TABLE 3 Hyperglycemic episodes and episodes of ketosis >1.5 mmol/L by age group

	IDeg or IDegAsp			IDet		
	N (%)	Events	Rate/100 pt-yrs	N (%)	Events	Rate/100 pt-yrs
Study 1 core phase						
1-5 years	43			41		
Episodes of ketosis	7 (16.3)	24	114	15 (36.6)	30	151
6-11 years	70			68		
Episodes of ketosis	5 (7.1)	12	34	10 (14.7)	25	75
12-17 years	61			66		
Episodes of ketosis	3 (4.9)	8	27	9 (13.6)	31	98
Study 1 core phase + extension phase						
1-5 years	43			41		
Episodes of ketosis	14 (32.6)	52	134	17 (41.5)	55	161
6-11 years	70			68		
Episodes of ketosis	9 (12.9)	33	50	17 (25.0)	54	92
12-17 years	61			66		
Episodes of ketosis	6 (9.8)	24	43	11 (16.7)	52	95
Study 2						
1-5 years	40			41		
Episodes of ketosis	2 (5.0)	3	25	2 (4.9)	4	33
6-11 years	61			61		
Episodes of ketosis	1 (1.6)	1	5	3 (4.9)	3	16
12-17 years	80			77		
Episodes of ketosis	1 (1.3)	2	8	3 (3.9)	5	21

Abbreviations: IDeg, insulin degludec; IDet, insulin detemir; N, number of patients; pt-yrs, patient-years; SMBG, self-measured blood glucose.
Safety analysis set.
Ketosis: self-monitored blood ketones >1.5 mmol/L (27 mg/dL; capillary blood ketone measurement performed if SMBG exceeded 14.0 mmol/L [252 mg/dL]).

TABLE 4 Episodes of ketosis with symptoms

	IDeg or IDegAsp			IDet		
	N	Events	Rate/100 pt-yrs	N	Events	Rate/100 pt-yrs
Study 1 core phase						
>0.6	21	37	43	40	147	174
>1.5	8	11	13	15	32	38
>3.0	0	—	—	5	9	4
Study 1 core phase + extension phase						
>0.6	33	75	46	44	250	170
>1.5	13	28	17	19	65	44
>3.0	3	7	4	7	21	14
Study 2						
>0.6	10	20	37	22	41	76
>1.5	4	6	11	8	13	24
>3.0	2	2	4	3	3	7

Abbreviations: IDeg, insulin degludec; IDet, insulin detemir; N, number of patients; pt-yrs, patient-years; SMBG, self-measured blood glucose.
Safety analysis set.
Ketosis: self-monitored blood ketones >1.5 mmol/L (37 mg/dL; capillary blood ketone measurement performed if SMBG exceeded 14.0 mmol/L [252 mg/dL]).

in randomized clinical trials. To the best of our knowledge, the two trials reported here are the first to collect data systematically on ketone levels in pediatric patients with T1D. Although the trials had different reporting criteria, the data from both trials demonstrate that degludec has a positive effect on controlling metabolic decompensation as indicated by the lower rate of ketosis with degludec/IDegAsp vs IDet. The results of the two studies are complementary to each other and reinforce the role of ketone measurement in helping to reduce the incidence of DKA in real-world practice.

A similar number of hyperglycemic episodes were reported for both trial arms in Studies 1 and 2; however, episodes of ketosis were numerically lower in the degludec/IDegAsp vs IDet arms, with results

reaching statistical significance in Study 1. The lower number of ketosis episodes observed in the degludec/IDegAsp arms may be attributed to the prolonged duration of action of degludec/IDegAsp and hence, in addition to more predictable glycemic control, the reduced risk of ketosis. This finding was despite over half of patients in both studies receiving IDet BID (Study 1: IDet BID 64%, Study 2: IDet BID 54%).

The rate ratios for episodes of ketosis between the treatment arms in Study 2 were not statistically significant; however, there were numerically fewer episodes of ketosis in the IDegAsp vs IDet arm, although this did not reach statistical significance and estimated rate ratios were consistent with those in Study 1. The duration of Study 2 (16 weeks) may have been insufficient to discern a statistically significant reduction in ketosis. Recurrent ketosis was experienced by 10.3% of patients in the degludec arm vs 15.4% of patients in the IDet arm in Study 1 and in 1.1% of patients in each arm of Study 2, demonstrating that even in a carefully controlled clinical trial context, some children appear prone to ketosis and experience recurrent events.

While data on compliance are not available for these studies, it can be assumed that the patients in these rigorously monitored clinical trials would be more likely to take their insulin as prescribed during the trial compared with treatment adherence in clinical practice. With the rates of hyperglycemia and ketosis reported here, this further indicates that degludec/IDegAsp may be useful in real-world practice where doses are more likely to be missed.

DKA in children with a known diagnosis of diabetes is an avoidable condition, and represents a major public health challenge. Strategies to reduce the rate of DKA include regular teaching on sick-day rules management, particularly the importance of ketone measurement, and avoidance of insulin omission. The analysis reported here, as reported previously for Study 1 (degludec + IAsp OD, vs IDet + IAsp BID),[8] shows that there was a numerical reduction in the rates of ketosis with degludec/IDegAsp when compared with IDet in two-phase 3b clinical trials in pediatric patients with diabetes. Thus, use of degludec or IDegAsp might also form a useful therapeutic strategy in children with T1D, particularly those with recurrent ketosis events.

These data demonstrate the potential of degludec/IDegAsp, compared with IDet, to reduce the rate of ketosis and metabolic decompensation in children with T1D. Furthermore, these data highlight the ongoing need for patients to understand the importance of avoiding ketosis, and consequently DKA— the commonest cause of death in children with T1D.

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DATA SHARING AND DATA ACCESSIBILITY

Access request proposal form and the access criteria can be found at novonordisk-trials.com. The data will be made available on a specialized SAS data platform.

CONFLICTS OF INTEREST

N.T. reports payments for speaking and advising in the field of diabetes and to attend conferences and industry-sponsored events from a number of companies, including Novo Nordisk. His former institution (Norfolk & Norwich University Hospital, UK) receives funding for the conduct of clinical trials. He was Signatory Investigator for two Novo Nordisk-sponsored international RCTs (including Study 1 in this paper) as well as Principal Investigator for several studies in the diabetes field. No relevant financial interests/shareholdings L.B. reports no relevant conflicts of interest. G.K. reports consultancy fees for Novo Nordisk, Boehringer-Ingelheim, Takeda, and AstraZeneca. D.R.F. reports grants in clinical trials and personal fees as speaker and advisory board from Abbott, BD, Janssen, Lilly, Novo Nordisk, Sanofi, Bayer, and Boehringer Ingelheim. L.B. and D. T. are employees and shareholders in Novo Nordisk A/S. T. D. reports grants from Boehringer Ingelheim, AstraZeneca, Roche, Insulet, Abbot, and DexCom.

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SUPPORTING INFORMATION

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

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