Exenatide improves β-cell function up to 3 years of treatment in patients with type 2 diabetes: a randomised controlled trial

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Abstract

Objective: Glucagon-like peptide (GLP)-1 receptor agonist treatment improves β-cell function. In this study, we investigated whether the improvements are sustained during a 3-year treatment period.

Research design and methods: Sixty-nine metformin-treated type 2 diabetes patients were randomised to the GLP1 receptor agonist, exenatide (EXE) twice daily (BID) or to insulin glargine (GLAR). β-cell function parameters were derived using the Mari model from standardised breakfast and lunch meals that were administered before treatment, and after 1 and 3 years of treatment. EXE was administered before breakfast.

Results: Fifty-nine (EXE: n = 30; GLAR: n = 29) and thirty-six (EXE: n = 16; GLAR: n = 20) patients completed the meal at 1- and 3-year treatment respectively. After 3 years, groups had comparable glycaemic control (HbA1c: EXE 6.6 ± 0.2% and GLAR 6.9 ± 0.2%; P = 0.216). Compared with GLAR, at 1 and 3 years, EXE induced a stronger reduction in post-breakfast glucose concentrations (P < 0.001), with lower C-peptide levels (P < 0.001). Compared with GLAR, EXE increased insulin secretion at 8 mmol/L glucose throughout the study period (P < 0.01). Both treatments improved β-cell glucose sensitivity after 1-year treatment. However, only EXE treatment sustained this improvement for 3 years. No consistent changes in other β-cell parameters including rate sensitivity and potentiation were observed.

Conclusions: Compared with GLAR, EXE improved the parameters of β-cell function, especially insulin secretion at 8 mmol/L glucose and β-cell glucose sensitivity, which was sustained during the 3-year treatment period.

Introduction

Type 2 diabetes (T2D) is characterised by defects in both insulin sensitivity and insulin secretion (1). The progressive loss of β-cell function over time results in a need for glucose-lowering agents, eventually resulting in the need for insulin replacement therapy in many patients (2, 3, 4). Therapies that can preserve β-cell function in T2D are required.

In the last decade, glucagon-like peptide-1 (GLP1) receptor agonists have been introduced for the treatment of T2D. GLP1 receptor agonists mainly lower blood glucose...
levels by inhibiting gastric emptying (postprandial), increasing insulin secretion and decreasing glucagon secretion, in a glucose-dependent manner (5, 6). Although in a number of rodent models, GLP1 receptor agonist treatment durably improved β-cell function, and also increased β-cell mass (7), there is no evidence for increased functional β-cell mass following GLP1 receptor agonist treatment in humans (8, 9). The extent to which the improvement in β-cell function by GLP1 receptor agonists is sustained over time (i.e. during treatment) is unclear due to the scarcity of long-term studies using dynamic tests of β-cell function. In trials of duration longer than 1 year, β-cell function was estimated in the fasting state using surrogate indices (10, 11), which provides only a limited reflection of β-cell function.

Earlier we reported that 1 month following cessation of therapy, 3-year treatment with the GLP1 receptor agonist exenatide (EXE), compared with insulin glargine (GLAR), induced a small improvement in the disposition index, which was calculated by multiplying 1st phase C-peptide secretion (derived from hyperglycaemic clamp) and insulin sensitivity (obtained by hyperinsulinaemic–euglycaemic clamp) (8). The improved disposition index was driven by an increment in insulin sensitivity, while C-peptide secretion was unchanged as compared with baseline after treatment cessation. This modest improvement in β-cell defect, however, did not result in better glycaemic control.

In this study, we report the effects of EXE twice daily (BID), as compared with GLAR, on meal-stimulated β-cell function parameters during 1–3 years of treatment. The meal-related response provides different aspects of β-cell function, including β-cell glucose sensitivity, which are generated under more physiological conditions, i.e. in the postprandial state. In this state, the GLP1 receptor agonist EXE also induces effects beyond the β-cell, including inhibition of gastric emptying, reduction of glucagon levels and endogenous glucose production (EGP) (12). In this study, in contrast to the previous publication, the patients were undergoing treatment during the β-cell function analyses.

**Research design and methods**

Details on the study design were reported previously (5, 8). Briefly, 69 patients were randomised (using a permuted block randomisation scheme stratified by site and baseline HbA1c stratum (≤8.5% or >8.5%)) at the three study sites in Finland, Sweden and the Netherlands.

Patients randomised to EXE initiated treatment at a dose of 5μg twice daily (BID) for a period of 4 weeks, followed by a dose increase to 10μg BID. EXE was titrated to a maximum dose of three times (TID) 20μg, or the maximum tolerated dose, when HbA1c value at two consecutive visits ranged between 7.1 and 7.5%, or when HbA1c was >7.6% at any given visit. Patients randomised to GLAR started with an initial dosage of 10IU once daily (QD) at bedtime, followed by self-adjustment of the daily dose according to a fixed-dose treat-to-target (fasting plasma glucose (FPG) <5.6mmol/L) algorithm, as described previously (13). Loss of glucose control was defined by fasting blood glucose concentrations greater than or equal to 12.2mmol/L for 4 or more days out of 7 days during the study, with the increase in glucose concentrations not secondary to a readily identified inter-current illness or pharmacological treatment. The study protocol was approved by each site’s ethics review committee and was conducted in accordance with the principles described in the Declaration of Helsinki. Patients were recruited at the local sites through advertising. All participating patients gave their written informed consent before screening. This study is registered with ClinicalTrials.gov under number NCT00097500.

**Standardised mixed-meal test**

Patients arrived at the study centre after an overnight fast. We placed a cannula into the non-dominant dorsal hand or wrist vein and maintained in a heated box at 50°C for blood collections. Two sequential mixed-meal tests were performed before randomisation, and after 1 and 3 years of treatment. At each meal visit, subjects received two standardised high-fat mixed meals: one at breakfast (08:30h) and one at lunchtime (12:30h). Each meal consisted of 50g fat, 75g carbohydrates and 35g protein to provide a strong secretory stimulus for the β-cell. The breakfast consisted of an Egg McMuffin (McDonald’s), croissant with butter, 200mL semi-skimmed milk, combined with 20mL cream. The lunch consisted of Quarter Pounder (McDonald’s), croissant with butter and 200mL semi-skimmed milk. Subjects were instructed to consume each meal within 15 min. Blood samples for determination of glucose, insulin and C-peptide were collected at times minus 15, 0, 10, 15, 20, 30, 45, 60, 90, 120, 150, 180, 210, 240, 250, 255, 260, 270, 285, 300, 330, 360, 420 and 480 min. During the meal tests at year 1 and 3, patients received their study medication at the protocol-specified time, which was chosen according to the current prescription guidelines. Patients randomised to EXE were given the study drug 15 min before breakfast.
Laboratory analyses

Plasma glucose concentrations were measured at bedside using an YSI 2300 STAT PLUS (Yellow Springs Instruments, Yellow Springs, OH, USA) in Sweden and the Netherlands, and using a Beckman Coulter Glucose Analyzer II (Beckman Coulter, Fullerton, CA, USA) in Finland. Serum was separated by centrifugation (1300–1500 g) and stored at −80°C until analysis. Insulin and C-peptide samples were analysed at the VU University Medical Center using an immunoradiometric assay (Centaur; Bayer Diagnostics, Mijdrecht, The Netherlands). Intra-assay and inter-assay coefficient of variation for insulin were 4 and 7% and for C-peptide 5 and 8% respectively. HbA1C (normal range: 4.3–6.1%, DCCT standardised Bio-Rad assay), FPG and serum safety parameters were measured by a central laboratory (Quintiles International, Livingston, UK).

Calculations

Incremental area under the 4-h postprandial curves (iAUCs) for glucose, insulin and C-peptide curves was determined by using the trapezoidal rule. iAUCs for breakfast and lunch were calculated separately. Insulin sensitivity was estimated using the OGIS index (14).

β-cell function model

β-cell function was assessed from the meal test using a model describing the relationship between insulin secretion (ISR, expressed in pmol min⁻¹ m⁻²) and glucose concentration as the sum of two components (15, 16).

The first component represents the dependence of ISR on glucose concentration through a dose–response function relating the two variables. From the dose–response, β-cell glucose sensitivity (the slope) and ISR at a fixed glucose concentration of 8 mmol/L (approximately the mean fasting glucose concentration in the groups before treatment) were calculated. The dose–response was modulated by a potentiation factor accounting for various mechanisms (prolonged hyperglycaemia, non-glucose substrates, gastro-intestinal hormones, neural modulation and drug effects) (17). The potentiation factor averaged one during the test and expressed relative potentiation or inhibition of ISR; its excursion was quantified by the ratio between the 3-h and the baseline value (potentiation ratio). The second ISR component represents the dependence of ISR on the rate of change of glucose concentration and is determined by a single parameter (rate sensitivity) related to early insulin release (17).

Statistical analysis

Baseline characteristics and end-point measurements are presented as mean ± s.e.m. Linear mixed models were used to assess within- and between-group treatment effects. The dependent variable used in the model was the outcome of interest (i.e. β-cell function parameters and fasting glucose/insulin). For within-group effects, time was included as fixed factor, and analyses were performed separately for the EXE and GLAR groups. For between-group effects, treatment and time were included as the fixed factors. The effect of interest was the intervention–time interaction, which displays the effect of intervention at each time point (year 1 and 3), corrected for pretreatment values. The statistical models included factors for study site (the Netherlands/Sweden/Finland), baseline HbA1c stratum (≤8.5%/>8.5%) and body weight. Models were checked for meeting test assumptions, and where necessary, adjustments were made. Correlations between β-cell parameters and HbA1c were performed using Pearson’s test. All analyses were performed using SPSS 22.0 (IBM SPSS). All inferential statistical tests were conducted at a significance level of 0.05 (two-sided).

Results

Clinical characteristics

Patients’ characteristics are given in Table 1, which have been published previously (5, 8). No differences were observed between the groups at baseline. Fifty-nine patients (EXE: n = 30; GLAR: n = 29) completed both the pre-treatment and 1-year meal test. Thirty-six patients (EXE: n = 16; GLAR: n = 20) participated in the 3-year meal test (Supplementary Fig. 1, see section on supplementary data given at the end of this article).
Table 1  Anthropometrics and metabolic variables. Data are presented as mean±s.e.m.

<table>
<thead>
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<th></th>
<th>Baseline</th>
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<th>P value 1</th>
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<td>n</td>
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<td>16</td>
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<tr>
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<td>29</td>
<td>20</td>
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<tr>
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<td>–</td>
<td>–</td>
<td>–</td>
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<tr>
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<td>73</td>
<td>70</td>
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<td>85.9±2.8</td>
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<tr>
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<td>94.8±3.3</td>
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<td>BMI (kg/m²)</td>
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<td>Diabetes duration (years)</td>
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<td>Medication dosage</td>
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<td>EXE (µg/day)</td>
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<tr>
<td>GLAR (µ/day)</td>
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<td>HbA1c (%)</td>
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<td>GLAR</td>
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<tr>
<td>Fasting glucose (mM)</td>
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<td>&lt;0.001</td>
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<td>7.2±0.3</td>
<td>7.0±0.3</td>
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<tr>
<td>GLAR</td>
<td>8.9±0.4</td>
<td>5.4±0.2</td>
<td>5.7±0.2</td>
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<tr>
<td>Fasting insulin (pm)</td>
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<td>&lt;0.001</td>
<td>&lt;0.001</td>
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<td>87±12</td>
<td>79±8</td>
<td>76±8</td>
<td></td>
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<tr>
<td>GLAR</td>
<td>76±12</td>
<td>151±13</td>
<td>187±26</td>
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<tr>
<td>Fasting C-peptide (nM)</td>
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<td>&lt;0.001</td>
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<td>EXE</td>
<td>0.9±0.1</td>
<td>0.8±0.1</td>
<td>0.8±0.1</td>
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<tr>
<td>GLAR</td>
<td>0.8±0.1</td>
<td>0.6±0.1</td>
<td>0.6±0.1</td>
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<tr>
<td>OGIS (mL/min m²)</td>
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<td></td>
<td>0.775</td>
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<tr>
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<td>337±15</td>
<td>351±20</td>
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<tr>
<td>GLAR</td>
<td>249±7</td>
<td>352±11</td>
<td>362±15</td>
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</table>

OGIS, oral glucose insulin sensitivity. P value 1 denotes EXE vs GLAR year-1 data; P value 2 denotes EXE vs GLAR year-3 data.

The majority (69%) of patients treated with EXE was treated with a dose of 10µg BID (average dosage provided in Table 1). At 1 and 3 years of treatment, the mean ±s.e.m. GLAR dosages used were 33.6±3.5 and 33.7±4.0 units per day respectively. The reduction in HbA1c was similar between the groups at both year 1 and year 3, while fasting glucose levels were lower in the GLAR group (Table 1) (8). EXE significantly reduced body weight compared with GLAR, with the mean weight difference 7.4±1.4 kg at 3 years (P<0.001) (8). The data of the participants who completed the entire study protocol are provided Supplementary Table 1.

Postprandial profiles

After 1 and 3 years of treatment, EXE induced a strong reduction in postprandial glucose levels following breakfast (P<0.001) compared with baseline (Figs 1A and 2A). By contrast, GLAR treatment had no effect on post-breakfast incremental glucose after 1 year, while glucose excursions increased after 3 years (P<0.001; Figs 1B and 2A). EXE was associated with lower post-breakfast glucose levels than GLAR after 1 and 3 years of treatment (both P<0.001; Fig. 2A). No differences were seen after the lunch meal between the groups, where the glucose excursions were higher following treatment with either EXE or GLAR (Figs 1A, B and 2B) than that after breakfast. During the 8-hour meal test, EXE reduced postprandial glucose levels significantly, both compared with GLAR and baseline (P<0.001) (Fig. 2C). EXE reduced the glucose concentrations after breakfast, in addition to reducing insulin and C-peptide levels (Figs 1C, E and 2D, G). GLAR did
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Exenatide and β-cell function

β-cell function measures

EXE improved the insulin secretion at 8 mmol/L glucose compared with GLAR during the 3-year treatment period ($P<0.001$) (Fig. 3A). Compared with baseline values, EXE increased glucose sensitivity, which was sustained throughout the 3-year period (year 1 vs baseline: $15.0\pm 6.7$ pmol/min.m$^2$. mM; $P<0.05$; year 3 vs baseline: $21.6\pm 8.4$ pmol/min.m$^2$. mM; $P<0.01$). Meanwhile the initial increase seen with GLAR (year 1 vs baseline: $21.4\pm 6.9$ pmol/min.m$^2$. mM; $P<0.01$) was not present after 3 years of treatment (year 3 vs baseline: $2.1\pm 7.8$ pmol/min. m$^2$. mM; $P=0.794$). At 3 years of treatment, the between-group difference in β-cell glucose sensitivity showed a trend towards significance in favour of EXE (difference $17.9\pm 3.5$ pmol/min.m$^2$. mM; $P=0.06$) (Fig. 3B). At year 1, rate sensitivity increased more with GLAR compared with EXE, an effect that disappeared at 3 years of treatment (Fig. 3C). No differences were seen with regard to potentiation between the groups (Fig. 3D). At year 3, the insulin secretion at 8 mmol/L glucose ($r=-0.649$; $P=0.007$) and glucose sensitivity ($r=-0.678$; $P=0.004$) were inversely correlated with HbA1c in the EXE-treated individuals, but not in the GLAR-treated group ($r=0.292$ and $r=-0.045$ respectively; $P=ns$ for both).

Safety and tolerability

The safety data of this study have been discussed in detail previously (8). In general, the study medication...
was well tolerated. The most common adverse events of EXE included gastrointestinal complaints (42.9%), mostly mild-to-moderate nausea. Most commonly reported adverse event associated with GLAR treatment was minor hypoglycaemia. No major hypoglycaemia was observed in this study.

**Discussion**

In this study, we show that EXE, a short-acting GLP1 receptor agonist, compared with GLARG, improves β-cell glucose sensitivity and insulin secretion at 8mmol/L glucose, for up to 3 years of treatment in similarly well-controlled metformin-treated type 2 diabetes patients, statistically independent of changes in body weight. The effects of EXE are thus sustained, concern multiple parameters derived during the postprandial state, and occur in face of an expected improvement in insulin sensitivity. This is a novel finding, as the prior 3-year study on this cohort assessed insulin secretion with the hyperglycaemic clamp 1 month after cessation of therapy and did not observe a sustained improvement of insulin secretion by EXE treatment (8).

At year 1, GLAR treatment also improved the standardised insulin secretion rate at 8mmol/L glucose, glucose sensitivity and rate sensitivity compared with baseline. This probably occurred because of lowering glucotoxicity and/or by inducing β-cell rest. Compared with EXE, the improvement in rate sensitivity reached borderline significance. However, none of these effects was sustained at year 3, while glycaemic control remained similar. At year 1, EXE improved insulin secretion at 8mmol/L glucose, glucose sensitivity and potentiation compared with baseline, confirming data from previous short-term studies using GLP1 receptor agonists (18, 19). The difference in insulin secretion at 8mmol/L glucose was significantly different compared with GLAR. In contrast to GLAR, the improvement in insulin secretion at 8mmol/L glucose and glucose sensitivity with EXE was sustained at year 3, indicating preserved β-cell responsiveness. Between-group changes at year 3 were significant for insulin secretion at 8mmol/L glucose and reached borderline significance for glucose sensitivity. The significant inverse correlations of insulin secretion at 8mmol/L glucose and glucose sensitivity after 3 years of EXE treatment with HbA1c demonstrate the importance of β-cell function in glycaemic control with GLP1 receptor agonist treatment.
GLP1 receptor agonists have previously been shown to improve β-cell function in type 2 diabetic patients using both static and dynamic tests; the latter includes hyperglycaemic clamps (5, 20) and oral glucose or meal tolerance tests (9, 18, 19). However, these studies were limited by the relatively short treatment duration (i.e. 1 year maximum). The importance of studies of longer duration is stressed by landmark trials such as the United Kingdom Prospective Diabetes Study (UKPDS) and A Diabetes Outcome Progression Trial (ADOPT), where initial treatment success was followed by rapid loss of glycaemic control due to β-cell failure associated with a number of drugs (3, 4).

Our long-term data are in line with the results from the open-label 3-year extension study of the EXE phase III programme. In the extension phase, EXE continued to improve homeostatic model assessment of β-cell function (HOMA-B), a static measure for β-cell function (11). However, this parameter provides very limited information regarding β-cell function compared with dynamic tests. Also, this parameter is more difficult to interpret when concomitant changes in insulin sensitivity occur, as is the case for EXE which increases insulin sensitivity, likely secondary to weight reduction (8).

Some studies in rodents have suggested that GLP1 may increase β-cell functional mass, resulting in improved glycaemic control even after cessation of therapy (7). However in humans, for EXE (8), liraglutide (9) and the dipeptidyl peptidase (DPP)-4 inhibitor vildagliptin (21), no such effects were observed. In fact, loss of glycaemic control occurred quickly after treatment discontinuation, despite a small improvement in disposition index by EXE treatment (8).

In this study, we show that the beneficial effects of EXE on β-cell function, along with HbA1c values, are sustained during treatment. Importantly, EXE was administered just before breakfast, as is usual for patients in the real-life setting. Therefore the effects observed during the breakfast meal tests are likely to be acute in nature, and show that there is no loss of efficacy over the 3-year period. The marked differences in postprandial glucose, insulin and C-peptide curves between the first and second meal further demonstrate the short-term effects of EXE.

The meal tests performed in this study confirm the postprandial profile of short-acting GLP1 receptor agonists. The profile is characterised by low postprandial glucose concentrations with concomitantly reduced insulin or C-peptide levels. The reduction in postprandial glucose levels, as was only seen in the breakfast meal in this study, in addition to improvement in β-cell function, is caused by reduced gastric emptying (22), glucagon secretion (6) and EGP (12). Due to the short duration of action of EXE, none of its effects was observed following the second meal. Similar observations have been shown for the other short-acting GLP1 receptor agonist lixisenatide and differ from long-acting GLP1 receptor agonists such as liraglutide (23).

A limitation of this study is the small number of patients who completed the entire protocol (44 and 61% for EXE and GLAR respectively). It should be noted that this study was very demanding for patients with a total of 30 visits, including three euglycaemic–hyperglycaemic clamp procedures and three consecutive meal tests. This led to withdrawal of consent after the initial 1-year study. In both the EXE and GLAR arms, we found no statistical difference between the subjects who continued in the extension study compared with the patients who stopped after 1-year treatment, including treatment-induced effects on weight, β-cell function and HbA1c. Nevertheless, we cannot exclude a certain selection bias. In addition, a number of patients were excluded due to loss of glycaemic control, which occurred primarily during the obligatory off-drug period that was part of the protocol (8).

To conclude, EXE, compared with GLAR, improves meal-related β-cell function that is sustained during 3-year treatment period.

Supplementary data
This is linked to the online version of the paper at http://dx.doi.org/10.1530/EJE-16-0286.

Declaration of interest
The study was collectively initiated and designed by the investigators from the study sites. The investigators had full access to the trial data and had control over the statistical analysis and interpretation of the study results. M C B and R J H are employees and stockholders of Eli Lilly and Co. During the study, M C B and R J H were employed at the VU University Medical Center. Before she passed away, M D was a consultant and speaker for Eli Lilly and Co. Through M D, the VU University Medical Center has received research grants from Amylin Pharmaceuticals, Inc., and Eli Lilly and Co. Through U S, the Sahlgrenska University Hospital has received research grants from Amylin Pharmaceuticals, Inc., and Eli Lilly and Co. H Y.-J serves as a consultant for Amylin Pharmaceuticals, Inc. Through H Y.-J, the Helsinki University Central Hospital has received research grants from Amylin Pharmaceuticals, Inc., and Eli Lilly and Co. B E is a consultant and speaker for Eli Lilly and Co. M-R T serves as a consultant for Novo Nordisk A/S. No other potential conflicts of interest relevant to this article are reported.

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Author contribution statement
M C B, A C and B E conducted the study. R J H, M R T, U S, M D and H Y J designed the study. M M S, D V R and A M analysed the data and performed statistical analyses. All authors contributed to the discussion. D V R and A M wrote the manuscript. D H van Raalte is the guarantor of this work.

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The study was collectively initiated and designed by the investigators from the study sites. The investigators had full access to the trial data and had control over the statistical analyses and interpretation of the study results.

References

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