Once weekly exenatide compared with insulin glargine titrated to target in patients with type 2 diabetes (DURATION-3): an open-label randomised trial

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Summary

Background Diabetes treatments are needed that are convenient, provide effective glycaemic control, and do not cause weight gain. We aimed to test the hypothesis that improvement in haemoglobin A1c (HbA1c) achieved with once weekly exenatide was superior to that achieved with insulin glargine titrated to glucose targets.

Methods In this 26-week, open-label, randomised, parallel study, we compared exenatide with insulin glargine in adults with type 2 diabetes who had suboptimum glycaemic control despite use of maximum tolerated doses of blood-glucose-lowering drugs for 3 months or longer. Patients were randomly assigned to add exenatide (2 mg, once-a-week injection) or insulin glargine (once-daily injection, starting dose 10 IU, target glucose range 4.0–5.5 mmol/L) to their blood-glucose-lowering regimens. Randomisation was with a one-to-one allocation and block size four, stratified according to country and concomitant treatment (70% metformin only; 30% metformin plus sulphonylurea). Participants and clinical investigators were not masked to assignment, but investigators analysing data were. The primary endpoint was change in HbA1c, from baseline, and analysis of this outcome was by modified intention to treat for all patients who received at least one dose of study drug. This trial is registered at ClinicalTrials.gov, number NCT00641056.

Findings 456 patients were randomly allocated to treatment and were included in the modified intention-to-treat analysis (233 exenatide, 223 insulin glargine). Participants who received at least one dose of study drug and for whom baseline and at least one postbaseline measurement of HbA1c were available were included in the primary efficacy analysis. Change in HbA1c, at 26 weeks was greater in patients taking exenatide (n=228; −1.5%, SE 0.05) than in those taking insulin glargine (n=220; −1.3%, 0.06; treatment difference −0.16%, 0.07, 95% CI −0.29 to −0.03). 12 (5%) of 233 patients allocated to exenatide and two (1%) of 223 taking insulin glargine discontinued participation because of adverse events (p=0.012). A planned extension period (up to 2.5 years’ duration) is in progress.

Interpretation Once weekly exenatide is an important therapeutic option for patients for whom risk of hypoglycaemia, weight loss, and convenience are particular concerns.

Funding Amylin Pharmaceuticals; Eli Lilly and Company.

Introduction Management of diabetes has developed from a symptomatic glucocentric approach to include strategies targeting pathophysiological principles and, in addition to durable blood-glucose lowering, reduce bodyweight.1 Treatments are needed that are convenient, address both fasting and postprandial glucose control, reduce risk of hypoglycaemia, and avoid counterproductive side-effects (eg, weight gain).2 A class of agents introduced within the past 5 years, the glucagon-like peptide-1 (GLP-1) receptor agonists, has the potential to address fasting and postprandial glucose control with weight loss and a low risk of hypoglycaemia.3 Exenatide twice a day, the first approved GLP-1 receptor agonist, has several glucoregulatory actions, including stimulation of glucagon-dependent insulin secretion, reduction of glucagon secretion, decrease of food intake, and slowing of gastric emptying.4 In clinical trials, exenatide twice a day lowered fasting and postprandial glucose concentrations and was associated with improved glycaemic control and reduced bodyweight in a substantial percentage of patients.5–8 A once weekly formulation of exenatide has been developed, with the goal of sustained glycaemic control alongside increased convenience of standard once-a-week dosing. This formulation has been associated with haemoglobin A1c (HbA1c) reduction, weight loss, and low hypoglycaemic risk in randomised clinical trials.9 We aimed to test the hypothesis that improvement in HbA1c concentration achieved with once-weekly exenatide is better than that achieved with the existing standard second-line treatment for patients not responding to oral blood-glucose-lowering agents, insulin glargine titrated to glucose targets.

Methods

Patients This phase 3, open-label, randomised, parallel study was undertaken during 26 weeks between May 13, 2008, and May 19, 2009, at 72 sites across the USA (and Puerto Rico), the European Union, Russia, Australia, Korea, Taiwan, and Mexico. Patients were identified, under direction from the site principal investigators, from patient populations at all
Potential participants were subsequently recruited according to standard local practices. Written informed consent and patient screening were completed at visit 1, per protocol.

Eligible patients with type 2 diabetes were aged 18 years or older (no upper limit specified) with suboptimum glycaemic control despite maximum tolerated doses of metformin or combined metformin and sulphonylurea treatment for 3 months or longer. Inclusion criteria were: at screening: HbA1c concentration between 7·1% and 11·0%, inclusive; body-mass index (BMI) between 25 kg/m² and 45 kg/m²; and a stable bodyweight for 3 months or more. Participants had to have been treated with a stable dose of metformin of 1500 mg or more per day for 8 or more weeks before screening. Exclusion criteria were: more than three episodes of major hypoglycaemia within 6 months of screening; treatment within 4 weeks of screening with systemic glucocorticoids; and treatment for longer than 2 weeks with insulin, thiazolidinediones, α-glucosidase inhibitors, meglitinides, exenatide twice-a-day formulation, dipeptidyl peptidase-4 inhibitors, or pramlintide acetate within 3 months of screening. Prescription and non-prescription weight-loss drugs were excluded within 3 months of screening and during the entire 26-week study.

The study was done in accordance with ethics principles stated in the Declaration of Helsinki, as revised in 2000. An ethics review board at every study site approved the protocol, and all participants gave written informed consent. The study included a continuing extension period (planned up to 2.5 years’ duration) within which participants will continue on randomised open-label treatment.

### Randomisation and masking

After a 2-week screening period, patients were assigned to add once weekly exenatide or once daily insulin glargine to their blood-glucose-lowering regimens, with a one-to-one allocation and block (size four) randomisation, stratified according to country and oral blood-glucose-lowering treatment (70% metformin only; 30% metformin plus sulphonylurea). Random assignment was achieved with a computer-generated randomisation sequence that was administered by the sponsor via an automated voice-response system. Study participants and clinical investigators were not masked to treatment assignment, but investigators analysing data were.

### Procedures

In the group allocated to receive exenatide, a 2 mg dose was injected into abdominal subcutaneous tissue at randomisation and once a week (within 2 days of date of first injection) thereafter. The 26-week treatment duration allowed for implementation of the INITIATE (Initiate Insulin by Aggressive Titration and Education) dosing algorithm for insulin glargine. Patients started insulin glargine treatment with 10 IU per day, measured fasting blood glucose concentrations every morning, and were instructed to adjust insulin doses to achieve a target glucose of 4.0–5.5 mmol/L. Patients and investigators were asked to adhere to titration targets; however, there was no central supervision to enforce titration. Insulin glargine was injected at the same time every day, preferably at bedtime. Patients continued their stable metformin dosing until week 26. If a patient taking metformin and sulphonylurea...
had confirmed hypoglycaemia, we recommended reduction of the sulphonylurea dose. Specific instructions for eight-point self-monitored blood-glucose profiles (measured before and 2 h after morning, midday, and evening meals, at bedtime, and at 0300 h) were given to both treatment groups.

The primary endpoint was change in HbA1c at week 26 compared with baseline. Secondary endpoints were proportions of patients achieving HbA1c targets (<7.0% and <6.5%), fasting serum glucose concentrations, self-monitored blood-glucose concentrations, bodyweight, fasting serum lipid concentrations, urinary albumin-to-creatinine ratio, high-sensitivity C-reactive protein, homoeostasis model assessment of β-cell function and insulin sensitivity, alanine aminotransaminase, and creatinine ratio, high-sensitivity C-reactive protein, fasting serum lipid concentrations, urinary albumin-to-glucose concentrations, bodyweight, and <6.5%), fasting serum glucose concentrations, self-proportions of patients achieving HbA1c targets (<7.0% and ≥8%).

Statistical analyses

SAS (version 9.1) was used for all analyses. For the primary analysis, we tested the hypothesis that change in HbA1c at week 26 was greater in patients allocated to exenatide than in those assigned to insulin glargine titrated to target. A sample size of 205 patients per treatment was needed to achieve 92% power to detect a difference of 0.4% in change in HbA1c from baseline (two-sided t test, significance level 0.05, common SD 1 -2%). Analysis of HbA1c was for the modified intention-to-treat analysis set, which we defined as patients randomly allocated to treatment who were exposed to one or more doses of study drug and had both a baseline and at least one postbaseline measurement of HbA1c. We used a maximum likelihood-based mixed-model repeated measures analysis of covariance, with treatment, baseline HbA1c, <8% and ≥8%, and ≥8% for <8%, and at least one postbaseline measurement of HbA1c for the modified intention-to-treat analysis set, which we defined as patients randomly allocated to treatment who were exposed to one or more doses of study drug and had both a baseline and at least one postbaseline measurement of HbA1c.
3·0 mmol/L necessitating the assistance of another person because of severe impairment in consciousness or behaviour. Symptoms of hypoglycaemia were defined as any sign or symptom reported by the patient, but not confirmed with a blood glucose measurement.

This trial is registered at ClinicalTrials.gov, number NCT00641056.

Role of the funding source
Sponsors were involved in the study design, protocol development, collection, review, and analysis of the data, and writing of the report. MD, LVG, and SS had full access to the primary data. MD had final responsibility for the decision to submit for publication.

Results
Table 1 shows baseline characteristics. 456 patients received one or more doses of study drug and were included in the primary efficacy analysis (233 exenatide, 223 insulin glargine; figure 1). The number of patients who discontinued participation did not differ between treatment groups (p=0·130). Mean doses of insulin glargine increased from a baseline 10 IU per day to 31 IU per day at endpoint (last measurement brought forward). Mean doses of metformin were roughly 2000 mg throughout the study; nearly one in four patients had a reduction in sulphonylurea dose. At endpoint, 46 (21%) of 223 patients taking insulin glargine had self-monitoring fasting glucose concentrations within the range of 4·0–5·5 mmol/L specified by the titration algorithm.

Mean endpoint HbA1c concentrations for both groups were near the 7·0% target (exenatide, n=228, 6·8%, SE 0·05; insulin glargine, n=220, 7·0%, 0·06). At week 8, mean reduction in HbA1c was significantly greater with exenatide treatment than with insulin glargine (p=0·0003), and this finding persisted until study end (figure 2). Change in HbA1c at 26 weeks was –1·5% (0·05) for patients allocated to exenatide and –1·3% (0·06) for those receiving insulin glargine (treatment difference –0·16%, SE 0·07, 95% CI –0·29 to –0·03; p=0·017).

More patients treated with exenatide than with insulin glargine achieved HbA1c targets of lower than 7·0% (129 [60%] of 216 exenatide patients vs 101 [48%] of 212 patients taking insulin glargine; p=0·010). 80 (35%) of 227 patients taking exenatide and 50 (23%) of 218 of those allocated to insulin glargine achieved HbA1c concentrations lower than 6·5% (p=0·004). These analyses included only patients who had not reached the HbA1c target before baseline. Figure 2 shows HbA1c reductions in patients with baseline HbA1c concentrations higher or lower than 8%. In patients taking exenatide plus metformin only (n=159), HbA1c was reduced by 1·5% (0·06), and in those taking insulin glargine plus metformin only (n=154) by 1·4% (0·07) (treatment difference –0·18%, SE 0·08, 95% CI –0·34 to –0·02; p=0·031).

Exenatide was associated with a progressive decrease in bodyweight, but insulin glargine with a progressive increase (figure 3). Mean change in bodyweight at week 26 compared with baseline was −2·6 kg (SE 0·2) for patients allocated to exenatide (n=233), and 1·4 kg (0·2) for those taking insulin glargine (n=223; p=0·001). The treatment difference was –4·0 kg (95% CI –4·6 to –3·5; p<0·0001). Bodyweight findings in the subgroup taking study drug plus metformin only did not differ from those of the overall treatment groups (figure 3). In patients taking exenatide, reductions in bodyweight were noted for both those who reported nausea (n=30; −3·5 kg, SE 0·7; and those who did not (n=203; −2·2 kg, 0·3; p=0·077).

181 (79%) of 228 patients allocated to receive exenatide had both a reduction in HbA1c and bodyweight, whereas 138 (63%) of 220 patients taking insulin glargine had a reduction in HbA1c paired with weight gain (figure 4). Regression plots show that baseline bodyweight was not
associated with change in bodyweight or treatment-related change in HbA1c. Baseline HbA1c was, however, correlated with change in HbA1c. Changes in waist circumference were associated with changes in bodyweight in both the exenatide (n=223, \( r^2=0.21 \), \( p<0.0001 \)) and insulin glargine groups (n=217, \( r^2=0.15 \), \( p<0.0001 \)); a bodyweight reduction of 1 kg predicted a reduction of 0.6–0.7 cm in waist circumference in the exenatide group.

Mean fasting serum glucose concentrations were reduced in both groups (exenatide, n=214, –2.1 mmol/L, SE 0.2; insulin glargine, n=207, –2.8 mmol/L, 0.2); however, reduction was greatest with insulin glargine (treatment difference 0.6 mmol/L, 95% CI 0.2–1.0; \( p=0.001 \)). Figure 5 shows self-monitoring blood-glucose profiles for baseline and week 26. At baseline, mean daily glucose concentrations were 10.8 mmol/L (SE 0.2) for patients taking exenatide (n=203) and 10.6 mmol/L (0.2) for those allocated to insulin glargine (n=201), with suboptimum postprandial glucose control reported after meals. Both treatments reduced fasting and postprandial glucose at all eight timepoints (all

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**Figure 4:** Individual associations between assessments of HbA1c and bodyweight with exenatide once weekly versus insulin glargine titrated to target

(A) Individual associations between changes in haemoglobin A1c (HbA1c) and bodyweight. (B) Individual associations between baseline bodyweight and bodyweight change. (C) Individual associations between baseline bodyweight and HbA1c change. (D) Individual associations between baseline HbA1c and HbA1c change. Sample sizes were 228 for exenatide and 220 for insulin glargine for (A), (C), and (D). Sample sizes for (B) were 233 exenatide and 222 insulin glargine.
Patients receiving insulin glargine had lower glucose concentrations at 0300 h (p=0·022) and before breakfast (p<0·0001) than did those taking exenatide, whereas those treated with exenatide had lower glucose concentrations after dinner (p=0·004) than did the insulin glargine group. Exenatide caused greater reduction in postprandial glucose excursions than did insulin glargine after morning (p=0·001) and evening meals (p=0·033). Accordingly, a beneficial increase in the hyperglycaemia marker 1,5-anhydroglucitol was recorded in both the exenatide group (6·0 μg/mL, SE 0·3) and the insulin glargine group (4·2 μg/mL, 0·3; treatment difference 1·8 μg/mL, 0·4; 95% CI 1·0–2·6; p<0·0001).
Patients in both treatment groups had improvements between baseline and endpoint in IWQOL-Lite, BES, and DTSQs total scores; only patients taking exenatide had significant improvements on the EQ-5D index (data not shown). Between-treatment differences in total scores were not recorded for any of the five instruments; however, significant improvements for the exenatide compared with the insulin glargine group were reported for one of the IWQOL-Lite domains (self-esteem) and one EQ-5D dimension (usual activities) (data not shown). No other domains differed between treatments.

113 (48%) of 233 patients allocated to exenatide and 114 (51%) of 223 insulin glargine patients received lipid-lowering treatments. Antihypertensive drugs were used by 165 (71%) and 163 (73%) patients, and drugs affecting heart rate by 87 (37%) and 88 (40%). Table 2 and table 3 show changes in metabolic and cardiovascular measures in both treatment groups. Mean heart rate at 26 weeks was raised compared with baseline in the exenatide but not the insulin glargine group (p<0.0001); no other cardiovascular measures differed between groups. Changes in fasting lipid concentrations, blood pressure, and heart rate were not a result of modifications in concomitant lipid-lowering or antihypertensive drugs or drugs affecting heart rate (data not shown). We noted no associations between changes in heart rate and changes in blood pressure (data not shown).

Table 4 shows data for adverse events and withdrawals. Gastrointestinal events including nausea and diarrhoea were among the most frequently reported adverse effects for patients taking exenatide; nasopharyngitis and headache were most common with insulin glargine. Gastrointestinal events were all mild or moderate in intensity. No serious adverse event was reported by more than one patient, with the exception of chest pain (n=2; webappendix). No deaths occurred in either group.

Variability in pancreatic enzyme concentrations was noted throughout the trial, and a few patients had either amylase or lipase concentrations raised to more than three times the upper limit of normal at both baseline (two exenatide; three insulin glargine) and at endpoint (five exenatide; no insulin glargine). These changes were generally asymptomatic, with the exception of one patient taking exenatide who was diagnosed with oedematous pancreatitis (peak amylase and lipase concentrations less than three times the upper limit of normal). The patient was not admitted to hospital and abdominal pain resolved a day after onset, at which time exenatide was expected to have been present at therapeutic concentrations. At a follow-up visit about 2 months later, the patient was fully recovered. Most patients had completed their baseline visit and many patients had finished the week 26 visit when a study amendment to include calcitonin measurement was made. Calcitonin concentrations were within normal limits in all patients (exenatide, n=15; insulin glargine, n=24) for whom data were available for analysis at endpoint (webappendix).

70 (71%) of 98 patients who tested negative for anti-exenatide antibodies and 87 (68%) of 127 who tested positive reported one or more adverse event. Mean HbA1c–0·5 to –0·1; p=0·010). Assessment of individual patients confirmed that the presence of antibodies to exenatide was not predictive of treatment response (data not shown).

Minor hypoglycaemia was reported in 19 (8%) of 233 exenatide patients (46 events) compared with 58 (26%) of 223 insulin glargine patients (135 events). Symptoms of hypoglycaemia not confirmed by blood-glucose measurement were also reported less often in patients taking exenatide (28 [13%] of 233 patients, 73 events) than in those receiving insulin glargine.
(70 [31%] of 223 patients, 298 events). Hypoglycaemia was reported most frequently in patients receiving concomitant sulphonylurea; however, incidence was consistently lower with exenatide than with insulin glargine, irrespective of background treatment (figure 6). Three patients (one taking exenatide with metformin, one taking insulin glargine with metformin, and one taking insulin glargine with metformin and a sulphonylurea) had an episode of hypoglycaemia that necessitated the assistance of another person, but did not involve loss or severe impairment of consciousness. All three episodes resolved with oral carbohydrate administration and did not lead to study discontinuation.

Discussion

Exenatide once weekly resulted in greater HbA1c reduction after 26 weeks of treatment than did insulin glargine titrated to target, and was associated with progressive bodyweight reduction. However, the clinical importance of this improvement in glycaemic control is uncertain. Insulin glargine produced significantly greater reductions in fasting glucose than did exenatide; however, significantly greater reductions in postprandial glucose excursions were recorded for exenatide than for insulin glargine, as additionally shown by the raised circulating concentrations of 1,5-anhydroglucitol.12 Hypoglycaemic events were reported most frequently in patients receiving concomitant sulphonylurea in both treatment groups, but hypoglycaemia incidence was consistently lowest with exenatide, irrespective of background treatment. The clinical importance of the small but significant increase in mean heart rate with exenatide treatment is unclear. In this study, increased heart rate was not associated with adverse outcomes.

In DURATION-3, we compared a once-weekly GLP-1 receptor agonist with basal insulin treatment in a study designed to test superiority of one treatment compared with another. A notable strength of the study was use of the standard next step in treatment for patients not responding to oral blood-glucose-lowering treatment as an active comparator. In a previously reported open-label non-inferiority trial of exenatide once weekly versus twice a day, exenatide given once weekly resulted in greater improvement in glycaemic control than did the drug given twice daily, with no increased hypoglycaemia and similar weight loss.13 Robust treatment responses reported with exenatide given once weekly compared with two mealtime doses per day might be due in part to increased suppression of fasting glucagon associated with continuous exposure to the drug and increased reduction of fasting glucose.1

The twice-a-day formulation of exenatide has also been compared with insulin glargine in four trials varying in duration and design.14–17 In a previous 6-month study with similar design and baseline characteristics to those of DURATION-3, exenatide twice a day and insulin glargine achieved equivalent improvements in overall glycaemic control (ie, an HbA1c reduction of 1.1%, endpoint 7.1%).18 A modified GLP-1 analogue for daily use, liraglutide, has also been compared with insulin glargine in a 6-month study.19 In that trial, the mean insulin glargine dose was slightly lower than in DURATION-3 (24 IU per day vs 31 IU per day), and endpoint HbA1c for the insulin glargine-treated group was slightly higher than we report (7.2% vs 7.0%). A similar difference in HbA1c treatment effect was described in favour of liraglutide (roughly 0.2%), despite the reduced insulin dose and high endpoint HbA1c attained. Similar treatment differences in bodyweight were reported.

Study limitations dictate that caution should be exercised during interpretation and generalisation of these results. Our study was in a predominantly white population, and would be strengthened by replication in other ethnic groups. Additionally, the completion rates for the two treatments were not equal in part because more patients receiving exenatide discontinued participation because of adverse events, including injection-site reactions, than did those receiving insulin glargine. A notable limitation of DURATION-3 was its open-label nature, since a potential bias towards the novelty of a new promising treatment could not be excluded. Masking was not feasible in this study, mainly because patients injected a fixed dose of exenatide once weekly or titrated insulin glargine daily. Furthermore, information about patient adherence or expectations of the study drug was not systematically captured, therefore the effect of bias toward one treatment or the
other was not fully characterised. Finally, although the study was 26 weeks in duration, an extension period (planned up to 2.5 years’ duration) is in progress, within which participants are continuing on randomised open-label treatment.

A key clinical concern about initiation of insulin treatment is finding of an appropriate balance between improvement of glycaemic control and management of the risks of hypoglycaemia and weight gain. Insulin doses and titration schemes are affected by severity of diabetes and existing treatment (eg, sulphonylurea).

In DURATION-3, patients were instructed to titrate their insulin dosage to achieve a target fasting glucose of 4.0–5.5 mmol/L, in accordance with Yki-Jarvinen and colleagues. Patients and investigators were asked to adhere to titration targets, but forced titration was not used. The low proportion (21%) of patients achieving the fasting glucose target could be attributable in part to fear of hypoglycaemia and weight gain, especially in the absence of forced titration.

In three insulin glargine trials with forced titration, patients (ie, with slightly raised baseline HbA₁c, but similar BMI) received two to four times more phone calls from the study centre than did participants in DURATION-3, encouraging them to self-adjust their insulin doses. The percentage of participants achieving target fasting glucose in these trials ranged from 20% to 66%. Despite widely varying insulin doses (40–62 IU per day), endpoint HbA₁c, and percentage of patients reaching HbA₁c targets did not differ from the results of our study. Insulin doses of 25–34 IU per day were used in trials comparing exenatide twice a day with insulin glargine, none of which used forced titration. In these trials, non-inferior changes in HbA₁c were reported between exenatide and insulin glargine. Overall, the titration results in DURATION-3 largely do not differ from those reported previously, suggesting that despite the limitations of our study, participants received appropriate insulin treatment as established by the investigators.

The American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) recommend the addition of new treatment regimens, including early use of insulin as a tier 1 approach, when glycaemic goals are not achieved with lifestyle intervention and metformin. UK National Institute for Health and Clinical Excellence guidelines suggest a GLP-1 receptor agonist as an alternative to insulin (combined with metformin and a sulphonylurea) when obesity is an issue. Conversely, the American Association of Clinical Endocrinologists recommends early use of GLP-1 receptor agonists, before insulin treatment, while the insulin-secretory capacity of β cells remains viable. The ADA/EASD consensus panel additionally supports use of GLP-1 receptor agonists as a tier 2 approach, when weight loss and risk of hypoglycaemia are of concern and HbA₁c is lower than 8.0%.

In DURATION-3, HbA₁c-lowering effects were generally greatest when baseline HbA₁c was high, irrespective of type of blood-glucose-lowering treatment—a finding that is lent support by results of a meta-analysis of 61 studies of blood glucose-lowering agents. In type 2 diabetes, progressive loss of β-cell function (or mass) is widely regarded as a main factor underlying the gradual worsening of glycaemic control with time, and might predict reduced effectiveness in patients without functional β cells at treatment initiation.

Diabetes treatments that lower HbA₁c substantially, promote weight loss, and provide convenient dosing without the need for dose titration could improve adherence to treatment and lessen the burden of hyperglycaemia. Especially important in our study was the finding that baseline bodyweight was not predictive of glycaemic response. Furthermore, weight loss was not strongly associated with nausea and vomiting—a finding that is supported by results of previous clinical trials. Taken together, these findings showed that once-weekly exenatide resulted in greater reduction in HbA₁c than did insulin glargine titrated to target, and is an important therapeutic consideration for patients for whom convenience, weight loss, and risk of hypoglycaemia are particular concerns.

Contributors
MD, LVG, and SS were clinical site investigators for this study, and had full access to the primary data. MD led decisions about content and submission. All authors contributed to data analysis and interpretation, and writing and editing of the report. All authors gave approval of the final version of the report.

Conflicts of interest
MD is a consultant and speaker for Eli Lilly and Company, Novo Nordisk, and Merck, Sharp and Dohme, and a consultant for Sanofi-Aventis. Through MD the VU University Medical Centre in Amsterdam has received research grants from Amylin Pharmaceuticals Inc, Eli Lilly and Company, Novo Nordisk, Merck, Sharp and Dohme, Novartis, and Takeda. LVG has served on advisory panels for Abbott Laboratories, AstraZeneca, Bristol-Myers Squibb, Eli Lilly and Company, Novo Nordisk, and Sanofi-Aventis, and has received honoraria as member of the speaker’s bureau for Abbott Laboratories, AstraZeneca, Bristol-Myers Squibb, and Eli Lilly and Company. SS has served on an advisory panel for Eli Lilly and Company, has received travel grants from Novo Nordisk, Eli Lilly and Company, Merck, Sharp and Dohme, and Servier, and has received research funding support from Sanofi-Aventis. JN, DC, and MT are employees of Eli Lilly and Company. KT is an employee of Amylin Pharmaceuticals Inc.

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