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ORIGINAL ARTICLE

Once-daily initiation of basal insulin as add-on to metformin: a 26-week, randomized, treat-to-target trial comparing insulin detemir with insulin glargine in patients with type 2 diabetes

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Aims: This study assessed the efficacy and safety of once-daily insulin initiation using insulin detemir (detemir) or insulin glargine (glargine) added to existing metformin in type 2 diabetes (T2D).

Methods: This 26-week, multinational, randomized, treat-to-target trial involved 457 insulin-naïve adults with T2D (HbA1c 7–9%). Detemir or glargine was added to current metformin therapy [any second oral antidiabetic drug (OAD) discontinued] and titrated to a target fasting plasma glucose (FPG) ≤90 mg/dl (≤5.0 mmol/l). Primary efficacy endpoint was change in HbA1c.

Results: Mean (s.d.) HbA1c decreased with detemir and glargine by 0.48 and 0.74%-points, respectively, to 7.48% (0.91%) and 7.13% (0.72%) [estimated between-treatment difference, 0.30 (95% CI: 0.14–0.46)]. Non-inferiority for detemir at the *a priori* level of 0.4%-points was not established. The proportions of patients reaching HbA1c ≤ 7% at 26 weeks were 38% and 53% (p = 0.026) with detemir and glargine, respectively. FPG decreased ~43.2 mg/dl (~2.4 mmol/l) in both groups [non-significant (NS)]. Treatment satisfaction was good for both insulins. Hypoglycaemia, which occurred infrequently, was observed less with detemir than glargine [rate ratio 0.73 (95% CI 0.54–0.98)]. The proportions of patients reaching HbA1c ≤ 7% without hypoglycaemia in the detemir and glargine groups were 32% and 38% (NS), respectively. Weight decreased with detemir [−0.49 (3.3) kg] and increased with glargine [+1.0 (3.1) kg] (95% CI for difference: −2.17 to −0.89 kg).

Conclusion: While both detemir and glargine, when added to metformin therapy, improved glycaemic control, glargine resulted in greater reductions in HbA1c, while detemir demonstrated less weight gain and hypoglycaemia.

Keywords: insulin detemir, insulin glargine, insulin initiation, metformin, oral antidiabetic drug

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Introduction

Initiating insulin therapy with a once-daily basal insulin therapy in patients with type 2 diabetes (T2D) is a simple and well-tolerated strategy that builds patient confidence and can be intensified to keep pace with disease progression [1,2]. Previous treat-to-target clinical trials have demonstrated that the basal insulin analogues, insulin detemir (detemir, Levemir®, Novo Nordisk A/S, Bagsvaerd, Denmark) [3,4] and insulin glargine (glargine, Lantus®, Sanofi, Paris, France) [5], improve glycated haemoglobin (HbA1c) to a similar extent to protaminated basal insulin (NPH), while exposing patients to significantly lower risks of hypoglycaemia; furthermore, detemir has been associated with less weight gain [3,4]. Additionally, patients can successfully and safely self-titrate these basal insulins towards appropriate fasting plasma glucose (FPG) targets [6–10].

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The relatively long duration of action of detemir and glargine allows them to be used once daily (OD) in the majority of patients with T2D [4,5,7–9]. The majority of glycaemic clamp studies have shown that these insulin analogues have similar time-action profiles at therapeutically relevant doses in T2D, although some studies have suggested otherwise [11–13]. A recent Cochrane analysis demonstrated no differences between insulin detemir and insulin glargine in terms of efficacy or safety, although in some studies there was a difference in injection frequency between the two insulins [14].

Another issue in patients initiating insulin therapy is the ongoing role of oral antidiabetic drugs (OADs). Many studies discontinue thiazolidinediones (TZDs) due to local licence restrictions over combination with insulin, while sulphonylureas (SUs) are often discontinued due to concerns about the risk of hypoglycaemia [15]. Metformin, barring specific contraindications, is usually continued in patients with T2D starting insulin.

This study was designed to compare the efficacy and tolerability of detemir and glargine using equal OD dosing

regimens, as recommended in the product licensing for insulin initiation in T2D. The study protocol included a target FPG of 90 mg/dl (5.0 mmol/l, normal physiological level), set in the expectation that this would not compromise tolerability as demonstrated in earlier trials using different titration algorithms [7,9]. Insulin secretagogues (primarily SUs) and TZDs were discontinued and the metformin dose left unchanged to reflect usual clinical practice.

Materials and Methods

This was a 26-week, multinational, randomized, open-label, treat-to-target trial comparing the efficacy and safety of adding OD detemir or glargine to metformin treatment in insulin-naïve patients with sub-optimally controlled T2D. Participants were ≥18 years old, diagnosed with T2D ≥6 months prior to inclusion, and taking metformin monotherapy (MM) at a stable daily dose ≥1500 mg, or with a second OAD (dual oral therapy maximum) at the maximum tolerated dose (minimum 1000 mg) for ≥3 months. Subjects were required to have HbA1c of 7–9%, the upper limit chosen to exclude subjects likely to require more intensive insulin regimens. Body mass index (BMI) was limited to ≤35 kg/m^2 to exclude potentially very insulin-resistant subjects likely to require very large insulin doses, who might therefore have had difficulty attaining target control within the trial duration.

Exclusion criteria included use of glucagon-like peptide-1 (GLP-1) analogues in the preceding 3 months, anticipated change in any systemic treatment that might affect glucose metabolism, medical conditions likely to interfere with participation, pregnancy or its intention and breast-feeding.

After a 2-week screening period, subjects were randomized to detemir + metformin or glargine + metformin, with any second OAD discontinued at this time (no wash-out period). Both insulins were administered OD anytime in the evening from 1 h before the last main meal until bedtime, with a starting dose of 10 U. Metformin doses remained unchanged during the trial to avoid any confounding effects of different dose changes. Subjects were stratified by pre-trial treatment: MM, metformin and TZD (−TZD), or metformin + OAD other than TZD (−OAD).

Insulin doses were titrated weekly (under investigator's direction) to an FPG target ≤90 mg/dl (≤5.0 mmol/l). Dose adjustment was based on the average of three consecutive pre-breakfast self-monitored plasma glucose (SMPG) measurements. Subjects were issued a blood glucose meter [Precision®, Abbott Diabetes Care, Illinois, USA with test strips calibrated for plasma glucose (PG) value] and instructed on its use and data recording. If mean FPG was 92–144 mg/dl (5.1–8.0 mmol/l), insulin dose was to be increased by 2 U. For each 18 mg/dl (1.0 mmol/l) above that range [but ≤180 mg/dl (≤10 mmol/l)], an additional 2 U was to be added, with a maximum of 8 U added if mean FPG was >180 mg/dl (>10 mmol/l). No dose adjustment was made if mean FPG was >71 to ≤90 mg/dl (>3.9 to ≤5.0 mmol/l), with no value ≤71 mg/dl (≤3.9 mmol/l) without an obvious explanation. The dose was to be reduced by 2 U if one or more fasting SMPG readings were 56–71 mg/dl (3.1–3.9 mmol/l), and by 4 U if <56 mg/dl (<3.1 mmol/l).

The study was conducted in accordance with the Declaration of Helsinki. Approval was obtained from the relevant ethics committees. All participants gave written informed consent. Clinical trials registration number: NCT00909480

Efficacy Endpoints

The primary efficacy endpoint was changed in HbA1c from baseline. HbA1c was assessed using a National Glycohaemoglobin Standardisation Program-certified assay from blood samples collected at baseline, an interim visit (week 12) and study end. Laboratory-measured FPG was also assessed from these samples.

Secondary endpoints included the proportion of subjects achieving HbA1c levels ≤7 or ≤6.5% at 26 weeks, and the proportions achieving this without symptomatic hypoglycaemia during the last month of treatment. Change in FPG, nine-point SMPG profile, within-subject variation of fasting SMPG and patient-reported outcomes captured by the validated Diabetes Medication Satisfaction (DiabMedSat) and Diabetes Productivity Measure (DPM) questionnaires [16] were assessed.

Safety Endpoints

Safety endpoints included change in weight and BMI from baseline, and the incidence of hypoglycaemic episodes and adverse events (AEs) during the trial. Hypoglycaemic episodes were defined as 'major' if the subject was unable to self-treat, 'minor' if the subject could self-treat and PG was confirmed <56 mg/dl (<3.1 mmol/l) with or without symptoms, or 'symptomatic' if the subject experienced hypoglycaemic symptoms, but PG was recorded as >56 mg/dl (>3.1 mmol/l) or no measurement was taken. Nocturnal hypoglycaemic episodes (23:00–05:59 hours) were similarly categorized.

Statistical Methods

In order to assess non-inferiority with respect to HbA1c, we analysed HbA1c change from baseline to study end in a normal linear regression model with treatment, previous treatment (stratification) and country as factors, and baseline HbA1c as a covariate. A 95% CI was calculated for the estimated difference between detemir and glargine and the upper level of the CI compared with the FDA-recommended non-inferiority margin of 0.4%. The analysis was made on the full analysis set (FAS; all randomized subjects exposed to at least one dose of treatment) and the per-protocol (PP) analysis set (all subjects exposed for ≥18 weeks who did not significantly breach the protocol). The last observation carried forward (LOCF) approach was applied for missing values at study end.

The proportion of subjects reaching HbA1c ≤7 or ≤6.5% (with or without symptomatic hypoglycaemia) at 26 weeks was analysed using a logistic regression model including treatment, previous OAD treatment (stratification) and country as factors, and baseline HbA1c as a covariate. Odds ratios for detemir versus glargine were estimated from the model and presented with 95% CI and p-value based on FAS.

Nine-point SMPG profiles at week 26 were analysed using a linear mixed model, with treatment, time, previous treatment

(stratification), country and treatment-by-time interaction as fixed factors and subject as a random effect. Summary statistics were tabulated for within-subject variation in pre-breakfast SMPG. FPG, weight and BMI were analysed using a normal linear regression model with the same factors as for HbA1c and the relevant baseline value as a covariate. The DiabMedSat and DPM questionnaires were summarized descriptively based on numerical values of 0–100.

Hypoglycaemia was analysed using a negative-binomial regression model, adjusting for treatment, country and previous treatment (stratification), and using the log-transformed exposure time as an offset variable. Treatment differences were presented as an estimate of the rate ratio (detemir vs. glargine) with a two-sided 95% CI and corresponding p-value. Hypoglycaemia and AE information was recorded in patient diaries and collected throughout the trial. AEs were summarized descriptively.

Results

Demographics, Baseline Characteristics and Patient Disposition

Patients were recruited in Argentina (n = 21), India (n = 51), Republic of Korea (n = 26), Thailand (n = 33) and the USA (n = 322). Patient disposition is summarized in figure 1. Of 457 subjects randomized, 453 were exposed to either detemir (n = 226) or glargine (n = 227), with 378 (82.7%) completing the trial. Demographic and baseline characteristics were similar between treatment groups (Table 1).

Efficacy

At study end, the observed mean (s.d.) HbA1c reductions with detemir and glargine from baseline were 0.48% (0.94%) and 0.74% (0.76%) (without LOCF) to end-of-study values of 7.48% (0.91%) and 7.13% (0.72%), respectively, in the FAS (figure 2A). The estimated between-treatment difference (detemir–glargine) was 0.30% (95% CI: 0.14–0.46%) in the FAS and 0.35% (95% CI: 0.19–0.51%) in the PP analysis set. As the upper 95% CI values exceeded 0.4%, non-inferiority for detemir could not be confirmed. HbA1c reduction for the three groups stratified according to OAD use at baseline is shown in figure 2B.

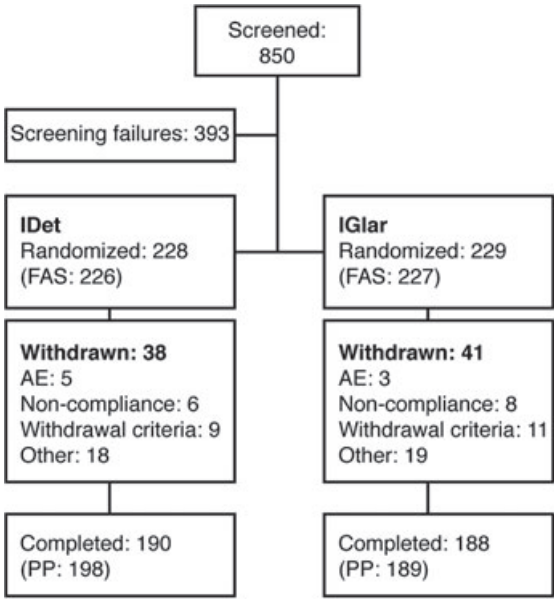

Figure 1. Patient disposition. AE, adverse event; FAS, full analysis set; IDet, insulin detemir; IGlar, insulin glargine; PP, per-protocol.

Table 1. Demographic and baseline characteristics (full analysis set).

	Detemir	Glargine
Number of subjects	226	227
Age, years, mean (s.d.)	57.3 (10.2)	57.3 (10.3)
Gender, % female/male	43/57	44/56
Body weight, kg, mean (s.d.)	82.8 (17.2)	81.7 (16.2)
BMI, kg/m^2, mean (s.d.)	28.9 (4.0)	29.1 (3.9)
HbA1c, %, mean (s.d.)	7.96 (0.62)	7.86 (0.58)
FPG, mg/dl, mean (s.d.) [mmol/l, mean (s.d.)]	156.0 (40.7) [8.66 (2.26)]	152.4 (39.8) [8.46 (2.21)]
Diabetes duration, years, mean (s.d.)	8.0 (5.6)	8.4 (6.6)
Previous OAD treatment, n (%)		
Metformin monotherapy	62 (27.4)	62 (27.3)
Metformin + TZD	15 (6.6)	15 (6.6)
Metformin + OAD other than TZD	149 (65.9)	150 (66.1)

BMI, body mass index; Detemir, insulin detemir; FPG, fasting plasma glucose; Glargine, insulin glargine; HbA1c, glycated haemoglobin; OAD, oral antidiabetic drug; s.d., standard deviation; TZD, thiazolidinedione.

The proportions of patients reaching HbA1c ≤ 7% at 26 weeks were 38% (80/209) and 53% (107/204) (p = 0.026) in the detemir and glargine groups, respectively; whereas for patients reaching HbA1c ≤ 7% without hypoglycaemia in the last 4 weeks, there was no significant difference between the treatments [32% (67/209) and 38% (78/204), respectively, non-significant (NS); p = 0.438]. HbA1c ≤ 6.5% was attained by 11% (22/209) and 21% (42/209) in the detemir and glargine groups, respectively (p = 0.011), 8.6% (18/209) and 15.2% (31/204) without hypoglycaemia (p = 0.073).

The pre-specified stratification by previous OAD therapy showed the highest proportion achieving target was among those receiving MM: 62% of patients [55% (32/58) detemir, 70% (39/56) glargine] receiving pre-trial MM achieved HbA1c ≤ 7%, 50% [48% (28/58) detemir, 52% (29/56) glargine] without hypoglycaemia. In contrast, 39% [31% (42/136) detemir, 47% (62/133) glargine] of the –OAD subgroup achieved HbA1c ≤7%, 29% [25% (34/136) detemir, 33% (44/133) glargine] without hypoglycaemia. Among the small number of patients in the –TZD subgroup, 40% (12/30) achieved HbA1c ≤ 7%, 33% (10/30) without hypoglycaemia, with no differences between insulin arms.

Laboratory FPG values for both treatment arms decreased at study end (figure 2C, D). Mean (s.d.) FPG decreased by −44.8 (46.3) mg/dl [−2.49 (2.57) mmol/l] for detemir and −43.4 (52.7) mg/dl [−2.41 (2.93) mmol/l] for glargine. Mean (s.d.) FPG values at study end for detemir were 112.0 (33.8) mg/dl [6.22 (1.88) mmol/l] and for glargine were 109.6 (42.8) mg/dl [6.09 (2.38) mmol/l]. There was no significant difference in

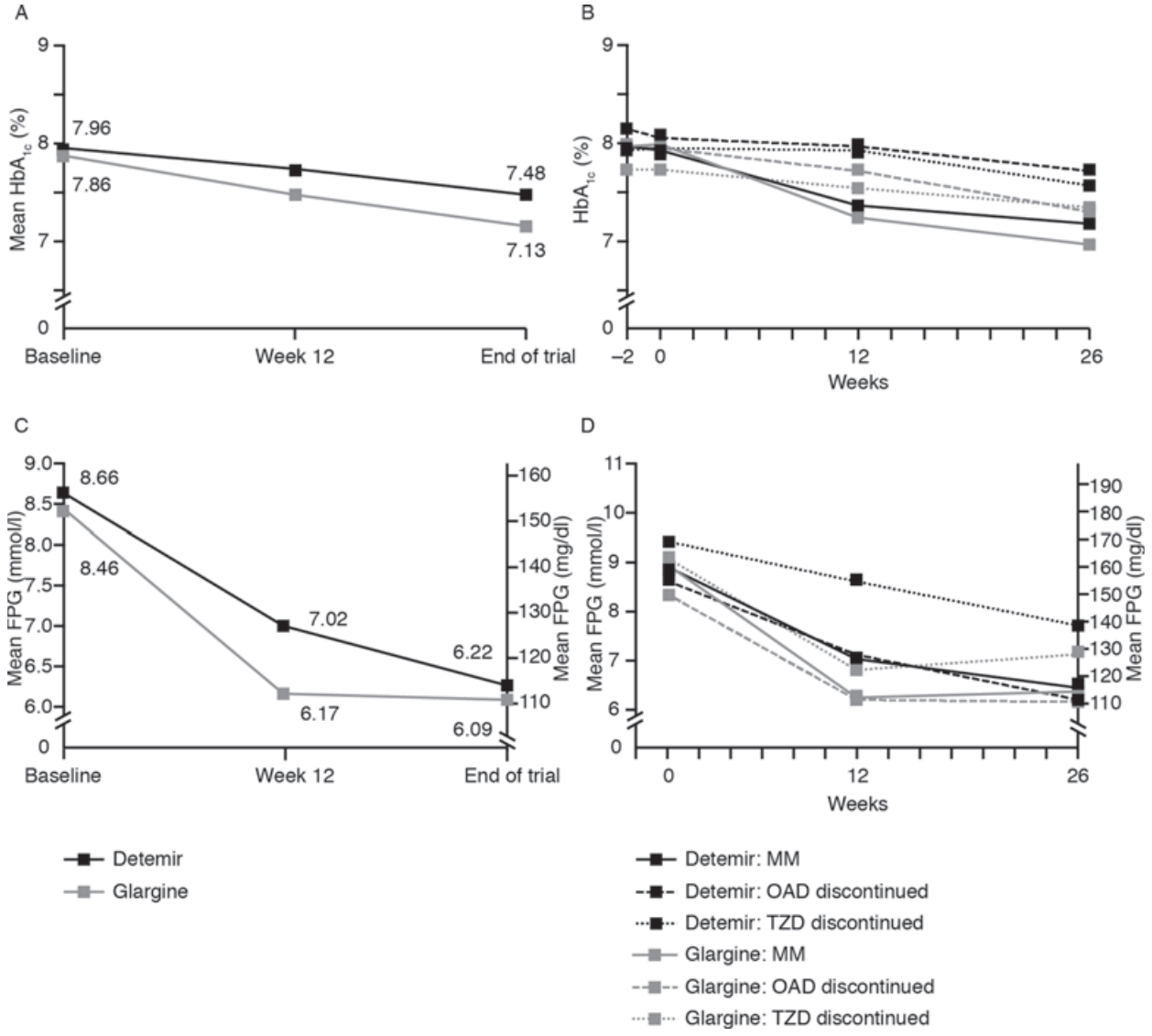

Figure 2. Glycaemic control over 26 weeks in FAS. (A) Observed mean HbA1c over time by insulin arm (data adjusted for baseline HbA1c, previous OAD and country). (B) Observed mean HbA1c over time stratified by insulin arm and OAD subgroup. (C) Observed mean FPG over time by insulin arm. (D) Observed mean FPG over time stratified by insulin arm and OAD subgroup. Detemir, insulin detemir; FAS, full analysis set; FPG, fasting plasma glucose; Glargine, insulin glargine; HbA1c, glycated haemoglobin; MM, metformin monotherapy; OAD, oral antidiabetic drug; TZD, thiazolidinedione.

FPG between insulins at study end: estimated difference (FAS), detemir−glargine: 1.62 (95% CI: −5.22 to 8.64) mg/dl [0.09 (95% CI: −0.30 to 0.48) mmol/l].

SMPG decreased at all time points during the trial for both insulins (figure 3). SMPG values were comparable overnight, but significantly lower values in favour of glargine at 26 weeks were observed before and after lunch: detemir−glargine: 12.06 (95% CI: 2.70−21.24) and 15.66 (95% CI: 6.30−24.84) mg/dl [0.67 (95% CI: 0.15−1.18) and 0.87 (95% CI: 0.35−1.38) mmol/l], and before and after dinner: 13.32 (95% CI: 3.96−22.68) mg/dl and 10.80 (95% CI 1.44−19.98) mg/dl [0.74 (95% CI: 0.22−1.25) and 0.60 (95% CI: 0.08−1.11) mmol/l], respectively.

Within-subject variation of fasting SMPG decreased in both treatment arms over 26 weeks and was significantly lower for detemir versus glargine at study end, as measured by a *post-hoc* analysis of estimated standard deviation of SMPG (1.13 vs. 1.25, respectively, $p = 0.036$).

Patient-reported outcomes indicated overall satisfaction with treatment in both insulin arms, with similar improvements in efficacy and productivity scores following initiation of either insulin. Median DiabMedSat scores for efficacy increased from 53 to 72 for both insulins, and scores increased very little for burden (82 to 85) and symptoms (72 to 76) for both insulins. DPM scores increased for life productivity (75 to 83) and work productivity (85 to 90) for both insulins.

The mean (s.d.) insulin doses at study end were 57 (30) U with detemir and 51 (26) U with glargine, corresponding to mean (s.d.) total insulin doses per kg body weight of 0.70 (0.34) U/kg and 0.61 (0.28) U/kg, respectively; the modest difference

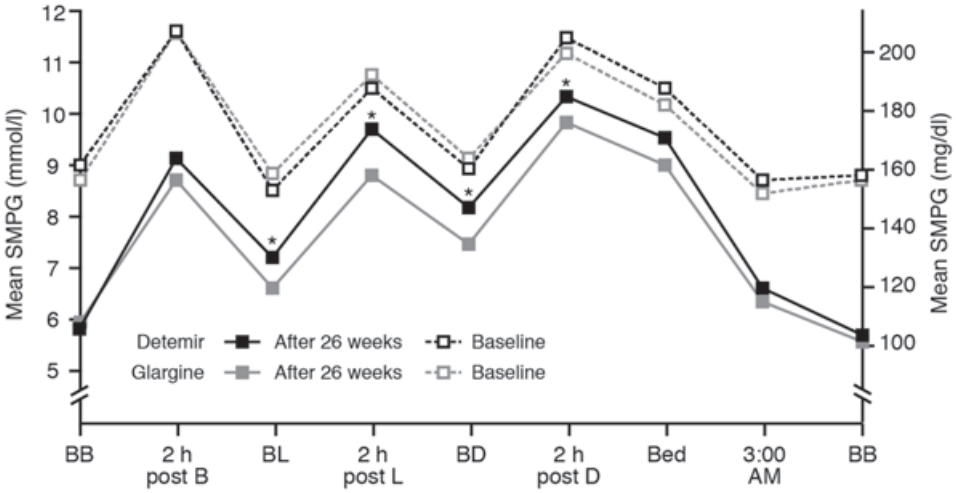

Figure 3. Observed nine-point SMPG profiles (FAS) at baseline and after 26 weeks by basal insulin arm ($p < 0.05$). B, breakfast; BB, before breakfast; BD, before dinner; BL, before lunch; D, dinner; Detemir, insulin detemir; FAS, full analysis set, Glargine, insulin glargine; L, lunch; OAD, oral antidiabetic drug; PG, plasma glucose; SMPG, self-monitored plasma glucose.

Table 2. Summary of treatment-emergent hypoglycaemic episodes – safety analysis set.

	Detemir (n = 226)			Glargine (n = 227)			
	103.3			103.5			Rate ratio (95% CI)
Exposure (years)	N (%)	E	R	N (%)	E	R	p = detemir vs. glargine
All events	104 (46)	329	3.19	123 (54)	457	4.41	0.73 (0.54; 0.98) p = 0.034
Major	0	0	0	2 (1)	2	0.02	—
Minor	54 (24)	119	1.15	72 (32)	156	1.51	0.71 (0.48; 1.05) p = 0.084
Symptoms only	78 (35)	210	2.03	88 (39)	299	2.89	0.72 (0.50; 1.05) p = 0.085
All nocturnal events	58 (26)	115	1.11	45 (20)	91	0.88	1.24 (0.80; 1.91) p = 0.333
Nocturnal major	0	0	0	0	0	0	0
Nocturnal minor	29 (13)	39	0.38	19 (8)	30	0.29	1.24 (0.66; 2.30) p = 0.503
Nocturnal symptoms only	39 (17)	76	0.74	36 (16)	61	0.59	1.23 (0.74; 2.06) p = 0.427

CI, confidence interval; Detemir, insulin detemir; E, number of episodes; Glargine, insulin glargine; Nocturnal, 23:00–05:59 hours; R, episodes/year.

was statistically significant as confirmed in a *post-hoc* analysis ($p = 0.0208$ for U and $p = 0.0119$ for U/kg).

Safety Endpoints

The overall rate of hypoglycaemia was low, with fewer than five episodes/subject-year in either treatment arm (Table 2); the only two major events reported occurred with glargine. There was a significantly lower (27%) rate of all hypoglycaemic episodes with detemir versus glargine, with no difference in the rate of nocturnal hypoglycaemia (Table 2).

Weight decreased slightly with detemir and increased slightly with glargine (figure 4A). Observed mean (s.d.) weight change was −0.49 (3.3) kg with detemir and +1.0 (3.1) kg with glargine, with a statistically significant estimated treatment difference of −1.5 kg (95% CI: −2.17 to −0.89 kg) in favour of detemir. Observed mean change in BMI was −0.19 (1.13) kg/m^2 with detemir and +0.36 (1.09) kg/m^2 with glargine; estimated treatment difference was −0.58 (95% CI: −0.80 to −0.36). When weight change was divided into baseline BMI groups (figure 4B) and previous treatment (figure 4C), the weight advantage of detemir seemed to be preserved within all categories.

A total of 64.2% (145/226) of subjects receiving detemir reported 509 AEs versus 61.7% (140/227) of subjects receiving glargine reporting 448 AEs. Injection-site reactions were reported in 14 subjects treated with detemir and 8 subjects treated with glargine. A *post-hoc* analysis showed no significant differences between the two insulins in terms of injection-site reactions ($p = 0.43$). Most AEs were mild or moderate, with 8 and 15 serious AEs (SAEs) reported with detemir and glargine,

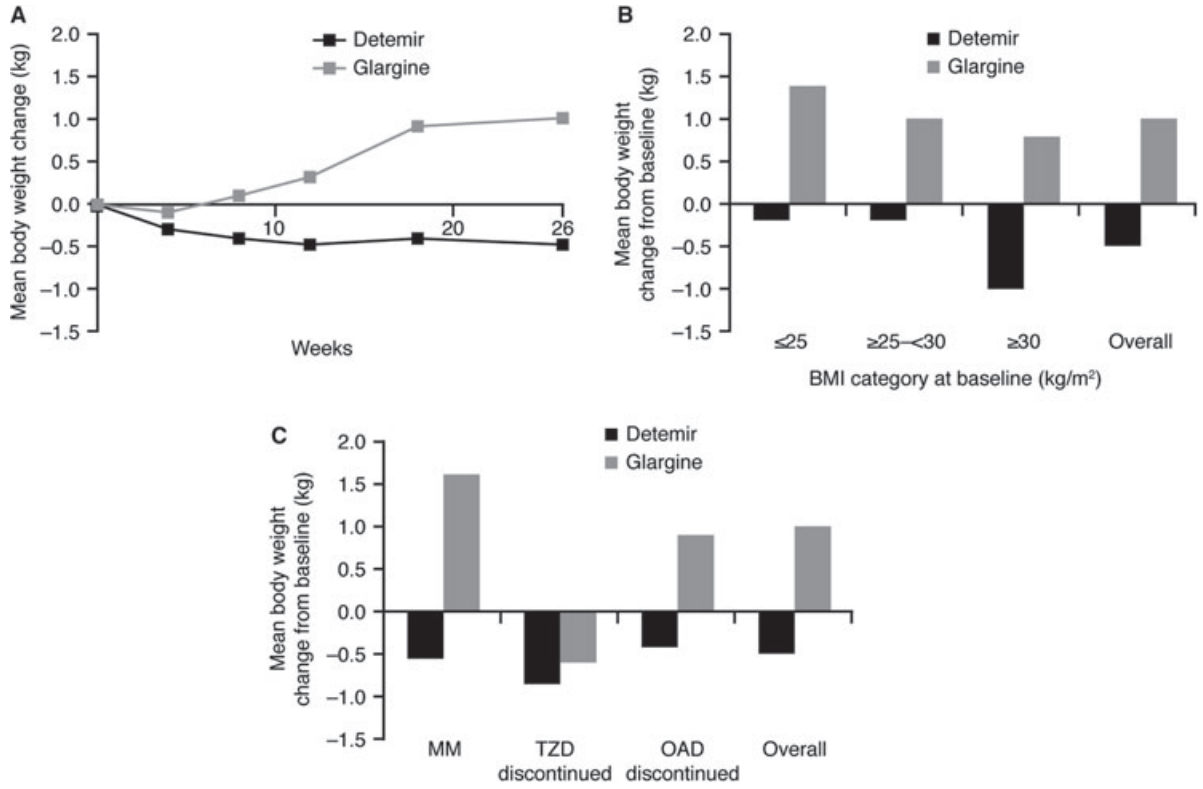

Figure 4. Change in body weight. (A) Observed trajectory for body weight change over 26 weeks by insulin arm. (B) Observed change in weight stratified by baseline BMI. (C) Observed change in weight over study stratified by OAD subgroup. BMI, body mass index; Detemir, insulin detemir; Glargine, insulin glargine; MM, metformin monotherapy; OAD, oral antidiabetic drug; TZD, thiazolidinedione.

respectively. The most frequently reported SAEs were cardiac disorders (detemir: 2; glargine: 5), gastrointestinal disorders (detemir: 2; glargine: 2), and infections and infestations (detemir: 2; glargine: 2). Two neoplasms were reported in subjects receiving glargine: one case of breast cancer and one of renal cell carcinoma. Few AEs – 52 events in 26 subjects for detemir and 30 events in 18 subjects for glargine – were considered probably or possibly related to study treatments. The difference was largely accounted for by AEs classified as general disorders and administration-site conditions. One SAE with glargine was recorded as possibly related to treatment. Few AEs led to withdrawal from the trial (figure 1).

Discussion

The primary endpoint of this study, non-inferiority of OD detemir versus glargine for HbA1c reduction based on an *a priori* magnitude for inferiority of 0.4% or worse, was not achieved. While non-inferiority of detemir versus glargine with a pre-defined margin was not confirmed, detemir cannot be concluded as inferior, as demonstrated by CONSORT criteria (Category G) (figure 5) [17]; from the 95% CIs, it can be inferred that HbA1c reduction with glargine was statistically greater than with detemir.

The FPG values achieved at 26 weeks with both detemir and glargine were similar, 110–112 mg/dl (6.1–6.2 mmol/l) (figure 2C), fulfilling the primary function of basal insulin

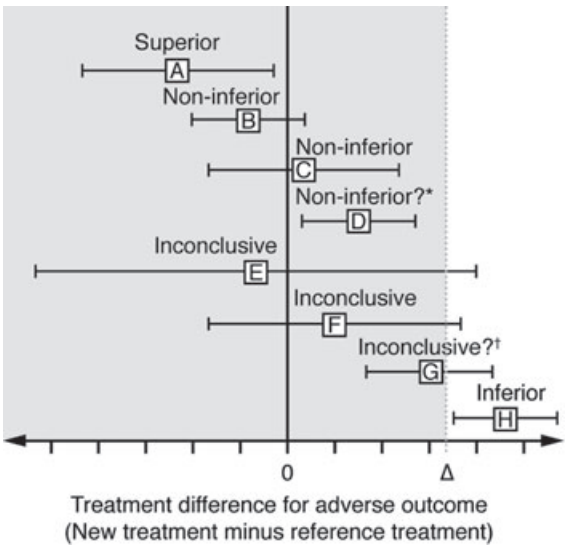

Figure 5. Possible scenarios of observed treatment differences for adverse outcomes (harms) in non-inferiority trials [17]. In our study, Δ is assumed to be 0.4% change in glycated haemoglobin. *This confidence interval (CI) indicates non-inferiority in the sense that it does not include Δ, but the new treatment is significantly worse than the standard. Such a result is unlikely because it would require a very large sample size. †This CI is inconclusive in that it is still plausible that the true treatment difference is less than Δ, but the new treatment is significantly worse than the standard.

to correct fasting hyperglycaemia; however, FPG levels were still decreasing with insulin detemir, but had already stabilized after 12 weeks in the insulin glargine group. This 'lag' in correction of FPG may have contributed to the difference in HbA1c observed between the two groups at 26 weeks. Indeed, looking at different substrata of patients across the trial, it seems those patients who discontinued TZDs, particularly in the insulin detemir arm, had higher fasting glucose compared with the other subgroups (figure 2D). In addition, glycaemic excursions were lower during the day with glargine than with detemir, also contributing to the difference in HbA1c.

Nevertheless, while the FPG reduction observed in this study was clinically relevant, the magnitude of HbA1c reduction was smaller in both insulin groups than the range reported in the previously mentioned Cochrane review [14]. It is possible that postprandial glucose control was not optimized in this study following discontinuation of pre-existing OAD treatment (mostly SUs). Subjects who discontinued OADs showed a similar reduction in FPG, consistent with proper basal insulin titration, but a smaller reduction in HbA1c versus those continuing on MM. Previous trials of basal insulin initiation, in which greater HbA1c reductions were reported, mostly retained pre-existing OAD doses [3–5,9,18,19]. Nybäck-Nakell [20] showed that many patients with T2D receiving insulin but discontinuing SUs experienced a rapid decline in glycaemic control. In a randomized controlled trial in insulin-naïve patients comparing glargine and NPH insulin, there was no difference in SMBG profiles (or HbA1c), even though NPH is clearly a shorter acting insulin than glargine, but on the other hand the OADs were continued. It is possible that discontinuing SUs might actually highlight (or accentuate) differences in duration of biologic activity of different basal insulins. It could be speculated that the continued use of OADs when basal insulin is initiated and optimized is prudent, barring any specific contraindications to their use. Another explanation for the less than expected drop in HbA1c might be the low baseline HbA1c levels (<8%). In the TITRATE® study [9] however, which compared two different FPG targets for detemir insulin initiation with continued OAD use, there were substantially greater HbA1c reductions (with over 50% of subjects achieving an HbA1c of ≤7%) despite a similar baseline HbA1c to our study. Interestingly, the FPG levels achieved in our study were similar to those reported at study end in TITRATE [9].

An additional consequence of SU discontinuation was the relatively higher insulin doses needed by study end. This was also seen in the LANMET trial, where SUs were discontinued when initiating glargine or NPH insulin in 110 insulin-naïve patients with T2D; end-of-trial mean daily doses were 0.66 and 0.69 U/kg, respectively [21]. When the total insulin dose level reaches between 0.5 and 1.0 U/kg, the ADA/EASD guidelines state that additional prandial insulin is required as soon as is appropriate [2].

A major benefit of the basal insulin + OAD regimen is the simplicity and safety of the approach, with the option of subsequent step-wise intensification once patient acceptance of insulin injection therapy is achieved. Both insulins were well tolerated in this study with low rates of hypoglycaemia in both arms. Detemir was associated with less hypoglycaemia; however, this difference must be considered in the context of the more rapid FPG reduction and lower overall HbA1c attained in the glargine group. The difference in final weight outcome, favouring detemir, is consistent with many other studies demonstrating less weight gain with detemir compared with other basal insulins (including glargine), at comparable rates of glycaemic control [3,4]. While some weight gain is expected with insulin initiation [22], in our study initiation and titration of detemir was associated with modest weight reduction, in conjunction with improvement in glycaemic control. Although discontinuation of SUs and TZDs probably contributed to this observation, weight loss also occurred when detemir was added to MM, in contrast to weight gain observed with glargine. Weight reduction with detemir initiation has been reported in an observational study [23] and the TRANSITION study [24] in which SUs were also discontinued and a dipeptidyl peptidase-4 (DPP-4) inhibitor added. The weight advantage of detemir over glargine seemed to be preserved across all BMI categories (figure 4B). This is consistent with previous studies in which weight-change data were stratified by baseline BMI [3,23,25]. The mechanism for the relative weight-sparing effect of detemir remains unknown, although several hypotheses exist [22].

The decision to discontinue other OADs, and additionally not adjust metformin doses, could be considered a limitation of this study, as it might have contributed to the less-than-expected HbA1c reduction in both study groups. Similarly, a titration algorithm prescribing more frequent insulin dose adjustments, such as was done in several patient self-adjustment studies [6–10], and currently supported by the ADA/EASD guidelines, might have achieved greater HbA1c improvement within the study period [2].

Conclusions

HbA1c levels were statistically lower for glargine versus detemir in this study, and non-inferiority for the primary endpoint of HbA1c reduction could not be confirmed for OD detemir versus OD glargine. Both insulins effectively lowered FPG to clinically relevant targets and were well tolerated as add-on to metformin for previously insulin-naïve patients with T2D. Detemir was associated with less overall hypoglycaemia and favourable weight change.

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Conflict of Interest

L. M. has received research support from Novo Nordisk, MannKind, Boeringher Ingelheim and Pfizer, and is a

consultant to Novo Nordisk and Halozyme. J. K. has received honoraria and spokesperson/speaker's bureau fees from Novo Nordisk. M. D. is an employee and stock-holder of Novo Nordisk. A. N. is an employee of Novo Nordisk. P. H. is an advisory panel member for Merck, Novo Nordisk, Orexigen and Pfizer; a board member for Novo Nordisk; a consultant for BMS, Merck and Pfizer; and has received research support from Novo Nordisk and Pfizer.

L. M. contributed to the design, conduct and data collection, data analysis and writing/editing of the manuscript. J. K. contributed to analysis of data, drafting and revision of the article. M. D. contributed to the collection and analysis of the data, and in writing up the article. A. N. contributed to the design, data analysis and interpretation, and in writing up the article. P. H. contributed to analysis of data, assessing the results and writing up the article.

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