

# Comparison of insulin lispro protamine suspension versus insulin glargine once daily added to oral antihyperglycaemic medications and exenatide in type 2 diabetes: a prospective randomized open-label trial<sup>†</sup>

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**Aims:** To compare efficacy and safety of two, once-daily basal insulin formulations [insulin lispro protamine suspension (ILPS) vs. insulin glargine (glargine)] added to oral antihyperglycaemic medications (OAMs) and exenatide BID in suboptimally controlled type 2 diabetes (T2D) patients.

**Methods:** This 24-week, open-label, multicentre trial randomized patients to bedtime ILPS ( $n = 171$ ) or glargine ( $n = 168$ ). Non-inferiority of ILPS versus glargine was assessed by comparing the upper limit of 95% confidence intervals (CIs) for change in haemoglobin A1c (HbA1c) from baseline to week 24 (adjusted for baseline HbA1c) with non-inferiority margin 0.4%.

**Results:** Non-inferiority of ILPS versus glargine was demonstrated: least-squares mean between-treatment difference (ILPS minus glargine) (95% CI) was 0.22% (0.06, 0.38). Mean HbA1c reduction was less for ILPS- versus glargine-treated patients ( $-1.16 \pm 0.84$  vs.  $-1.40 \pm 0.97\%$ ,  $p = 0.008$ ). Endpoint HbA1c  $< 7.0\%$  was achieved by 53.7% (ILPS) and 61.7% (glargine) ( $p = \text{NS}$ ). Overall hypoglycaemia rates ( $p = \text{NS}$ ) and severe hypoglycaemia incidence ( $p = \text{NS}$ ) were similar. Nocturnal hypoglycaemia rate was higher in patients treated with ILPS versus glargine ( $p = 0.004$ ). Weight gain was similar between groups (ILPS:  $0.27 \pm 3.38$  kg; glargine:  $0.66 \pm 3.93$  kg,  $p = \text{NS}$ ). Endpoint total insulin doses were lower in patients treated with ILPS versus glargine ( $0.30 \pm 0.17$  vs.  $0.37 \pm 0.17$  IU/kg/day,  $p < 0.001$ ).

**Conclusions:** ILPS was non-inferior to glargine for HbA1c change over 24 weeks, but was associated with less HbA1c reduction and more nocturnal hypoglycaemia. Treat-to-target basal insulin therapy improves glycaemic control and is associated with minimal weight gain when added to OAMs and exenatide BID for suboptimally controlled T2D.

**Keywords:** exenatide, glucagon-like peptide-1 receptor agonist therapy, glycaemic control, HbA1c, hypoglycaemia, insulin glargine, insulin lispro protamine suspension, type 2 diabetes

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## Introduction

Many therapies are available for treatment of type 2 diabetes (T2D), and various clinical algorithms have been proposed to aid clinicians in the management of patients with T2D. Treatment usually starts with patient education, lifestyle-directed interventions to promote weight loss and

increase physical activity, and with initiation of metformin (MET) [1, 2]. As metabolic deterioration occurs over time, additional glucose-lowering agents are usually required to achieve and maintain targeted haemoglobin A1c (HbA1c) goals [1, 2]. Initiation of insulin therapy is necessary for most T2D patients as  $\beta$ -cell function declines [1–3].

In addition to glycaemic efficacy, glucagon-like peptide-1 receptor agonist (GLP-1 RA) therapy has potential for weight loss with low risk of hypoglycaemia [4–14]. In the comprehensive diabetes management algorithm for T2D by the American Association of Clinical Endocrinologists (AACE), GLP-1 RA therapy in combination with MET is a recommended option for treatment of patients with HbA1c values  $\geq 7.5\%$  or in combination with two oral antihyperglycaemic medications (OAMs) for asymptomatic patients with HbA1c  $> 9.0\%$  [2]. Exenatide twice daily (BID)

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monotherapy or in combination with OAMs suppresses post-breakfast and post-dinner glycaemic excursions, but has limited impact on fasting plasma glucose (FPG) levels [5, 11–14]. The combination of basal insulin with short-acting GLP-1 RA offers the advantage of complementary pharmacologic effects to control both fasting and postprandial plasma glucose (PPG) levels, respectively [1, 2, 4, 6–14].

Once-daily ‘treat-to-target’ basal insulin regimens, which are focused on titration of doses to achieve an FPG target, have become the standard for initiation of insulin in T2D patients [1–3, 15]. For patients with persistently elevated FPG and HbA1c values despite treatment with a GLP-1 RA and OAMs, clinicians are faced with the choice of initiating basal insulin therapy with discontinuation of the GLP-1 RA [6, 7] or addition of insulin to the GLP-1 RA/OAM regimen [7–14]. A recent nationwide audit by the Association of British Clinical Diabetologists (ABCD) in UK reported nearly 40% of exenatide patients were also taking concomitant insulin therapy, along with continued use of OAMs [7]. The order of addition of exenatide and insulin was not assessed in this study [7]. Two other observational cohort studies found that 25–30% of patients who received exenatide and basal insulin were started on basal insulin after exenatide. Patients in these studies experienced 0.4–1.2% HbA1c reduction irrespective of treatment order [8, 9]. Additional studies have shown improvement in glycaemic control in subjects who have insulin added to GLP-1 RA therapy [10–14, 16].

The aim of this study was to evaluate and compare the efficacy and safety of two basal insulin analogues in T2D patients who have suboptimal glycaemic control while receiving stable doses of exenatide and one or two OAMs. The insulins used, insulin lispro protamine suspension (ILPS), a protamine-based basal insulin analogue (available in some European countries, Israel and Japan [17, 18]) and insulin glargine (glargine), have similar duration of glucose-lowering activity when administered once daily (at 0.8 IU/kg) [19].

## Materials and Methods

### Study Design and Objectives

This study was an open-label, randomized, active-control, parallel, 24-week clinical trial conducted between November 2007 and December 2009 at 49 study centres in the USA and Puerto Rico (NCT00560417, F3Z-US-IOPB). The primary objective was to determine whether ILPS was non-inferior to glargine as measured by change in HbA1c from baseline to 24-week endpoint [last observation carried forward (LOCF)] in T2D patients treated with exenatide BID plus MET with or without sulphonylurea (SU) or pioglitazone (PIO). Secondary measures included: percentage of patients with HbA1c < 7.0% and ≤6.5% at endpoint; seven-point self-monitored plasma glucose (SMPG) profiles; rate and incidence of patient-reported hypoglycaemia (overall, nocturnal, non-nocturnal and severe); weight change; insulin dose; adverse events (AEs) and treatment-emergent adverse events (TEAEs). The study was conducted in accordance with the International Conference on Harmonisation Guidelines for Good Clinical Practice and the

Declaration of Helsinki. All patients provided written informed consent.

Patients were 18–74 years of age with T2D, taking exenatide 10 µg twice-daily plus MET (1500–2500 mg/day) with or without either SU (at least one-half maximal dose) or PIO (30–45 mg/day) for at least 3 months, with HbA1c ≥ 7.0% and ≤10% and body mass index (BMI) ≤45 kg/m<sup>2</sup>. Doses of OAMs at study entry were maintained throughout the trial, except that reduction or discontinuation of SU was allowed at investigator discretion if patients experienced hypoglycaemia not attributed to other common occurrences such as missed meals, short-term changes in diet or exercise or excess insulin treatment.

Patients were excluded from the study if they had a history of insulin therapy (outside of pregnancy or acute short-term use) in the prior 2 years, clinically significant haematologic, oncologic, renal, cardiac, hepatic or gastrointestinal disease, more than one episode of severe hypoglycaemia in the prior 6 months, or were receiving other antihyperglycaemic or weight loss drugs or chronic systemic glucocorticoids.

After an initial 2-week screening period, patients were randomly assigned to receive either ILPS or glargine once-daily at bedtime while continuing their pre-study OAM(s) and exenatide (Figure 1). Randomization was stratified by SU use and baseline HbA1c (≤8.5% or >8.5%). Insulin was started with 6 IU daily, and titrated using dosing algorithms to achieve FPG targets of 4.4–5.5 mmol/l for ILPS and 4.1–5.5 mmol/l for insulin glargine.

ILPS and glargine have different pharmacokinetic/pharmacodynamic (PK/PD) profiles [19, 20]. Therefore, different dose adjustments based on FPG levels were used for these two insulins in order to optimize treatment for patients in both groups. The dose algorithm for ILPS (increments +6 to –4 units every week) was adapted from Fogelfeld et al. 2010 [21] and Strojek et al. 2010 [22]. The dose algorithm for glargine (increments from +8 to –4 units every week) was adapted from Riddle et al. 2003 [3] (Table 1).

During the first 8 weeks of the study, insulin dose was adjusted at least weekly to achieve an optimized dose for each patient. Thereafter, dose adjustments were performed if clinically needed according to the appropriate titration algorithm. HbA1c levels were measured by a central laboratory using high-pressure liquid chromatography (Bio-Rad Variant Turbo/Variant II; Bio-Rad Laboratories, Hercules, CA, USA and Dundee, Scotland). SMPG was measured by patients and recorded twice-daily before breakfast and dinner, and seven-point SMPG profiles [three pre-meal (including fasting before breakfast), three 2-h post-meal and one nocturnal (03:00 hours)] were performed on three separate days in the 2 weeks prior to visits at baseline and at weeks 4, 8, 12, 18 and 24.

Safety was monitored throughout the study, and the occurrence and nature of AEs were recorded. Serious AEs were defined as events resulting in death, life-threatening experience, hospitalization or significant disability. Hypoglycaemia was defined as one or more signs or symptoms typically associated with hypoglycaemia, or plasma glucose (PG) ≤ 3.9 mmol/l [23]. Severe hypoglycaemia was defined as any occurrence of neuroglycopenic symptoms requiring assistance from another person with either a PG < 2.8 mmol/l or prompt

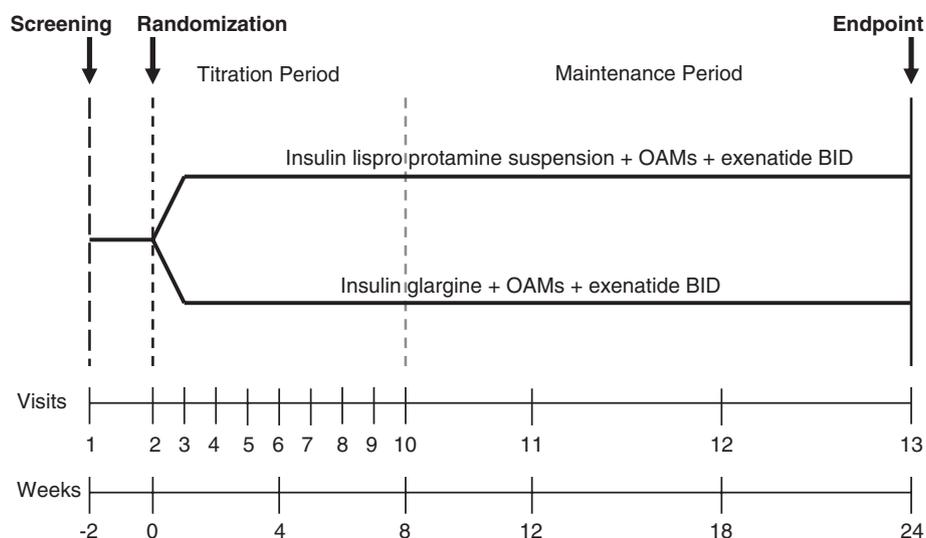


Figure 1. Study diagram.

Table 1. Insulin dosing algorithms.

Insulin lispro protamine suspension*		Insulin glargine†	
Fasting plasma glucose values (mmol/l)	Dose change (U)	Fasting plasma glucose values (mmol/l)	Dose change (U)
<3.1‡	-4	<3.1‡	-4
3.1–4.4‡	-2	3.1–4.0‡	-2
4.4–5.5§	0	4.1–5.5§	0
5.5–7.7§	+2	5.5–6.6§	+2
7.8–10.0§	+4	6.7–7.7§	+4
>10.0§	+6	7.8–9.9§	+6
		≥10.0§	+8

\*Adapted from Refs. [21] and [22].

†Adapted from Ref. [3].

‡At least one fasting plasma glucose since the last assessment.

§During the dose titration period (first 8 weeks), dose adjustments were made at least weekly based on daily fasting plasma glucose levels until target level was reached or nocturnal/fasting hypoglycaemia occurred; during dose maintenance period, titrations were continued per respective algorithm as clinically needed.

recovery after oral carbohydrate, glucagon or intravenous glucose [23, 24]. Nocturnal hypoglycaemia was defined as any hypoglycaemic event between bedtime and waking. Non-nocturnal hypoglycaemia was defined as any event between waking and bedtime.

### Statistical Methods

Power calculation indicated that 168 patients per treatment arm would provide 80% power to determine if ILPS is non-inferior to glargine when added to OAMs and exenatide BID, with a pre-specified margin of 0.4% difference in least-squares (LS) mean HbA1c change, assuming no true difference, 15% dropout rate and a standard deviation (s.d.) of 1.2 at a significance level of 0.05. This non-inferiority margin has been used in other

treat-to-target basal insulin studies [21, 22, 25–29]. All analyses were performed on the intention-to-treat population who had at least one post-baseline assessment by the LOCF method. The primary outcome (change in HbA1c from baseline to endpoint) was analysed using the analysis of covariance (ANCOVA) model with treatment, baseline HbA1c and stratification variables [SU use and baseline HbA1c strata ( $\leq 8.5\%$  and  $> 8.5\%$ )]. Non-inferiority of ILPS versus glargine in HbA1c change from baseline would be claimed if the upper limit of 95% confidence interval (CI) for treatment difference (ILPS minus glargine) was less than 0.4%. The endpoint SMPG profiles (average over 3-day values) were analysed with an ANCOVA model with factors of treatment, stratification variables and baseline. No adjustments were made for multiple comparisons. Other continuous variables (weight and insulin dose) were analysed similarly using an ANCOVA model with factors of treatment, stratification variables and baseline (if applicable). Hypoglycaemia rate was analysed with a negative binomial model. A logistic regression model was used to analyse the proportion of subjects achieving HbA1c targets of  $< 7.0\%$  and  $\leq 6.5\%$ . Other categorical variables were analysed using Fisher’s exact test to compare treatments.

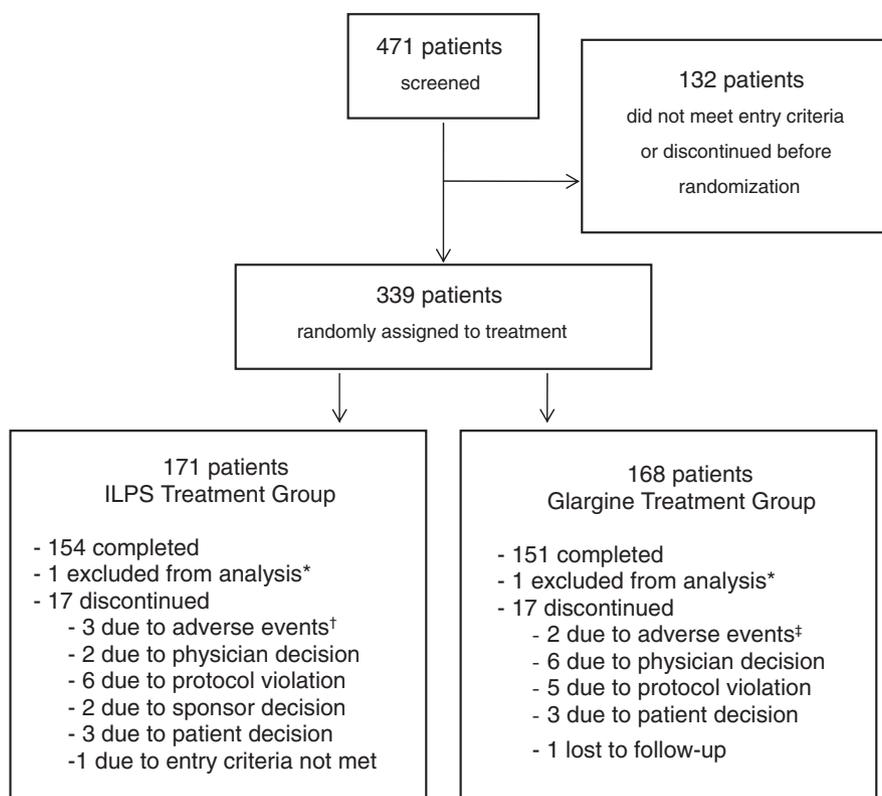
## Results

### Patient Disposition

Three hundred and thirty-nine patients were randomized, and 171 were assigned to ILPS and 168 to glargine (Figure 2). Approximately 90% of ILPS- and glargine-treated patients completed the study. Reasons for discontinuation from the study were similar for the two insulin treatment groups.

### Patient Demographics and Baseline Characteristics

Baseline demographics and disease characteristics of the cohort are presented in Table 2. Overall, the mean age was 56.4 years with 50.1% women. Mean BMI was 34.9 kg/m<sup>2</sup>.



\*All patients (n=2) from one site were excluded from analyses due to compliance issues at the site.

†adverse events leading to discontinuation: one case of colon cancer (serious adverse event), one case of nausea, and one case of impaired gastric emptying (both moderate)

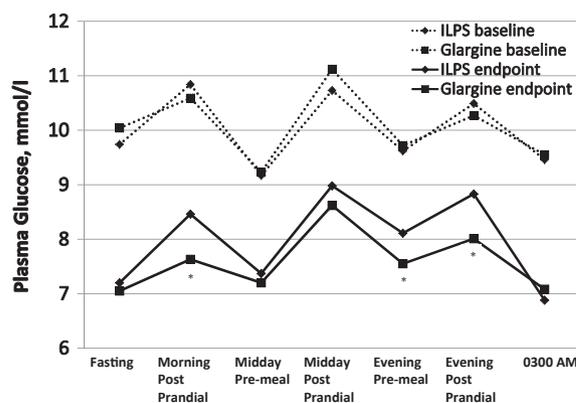
‡adverse events leading to discontinuation: one pregnancy and once case of cholelithiasis (both serious adverse events)

**Figure 2.** Patient disposition diagram.

Mean duration of diabetes was 9.9 years. Mean baseline HbA1c was  $8.2 \pm 0.8\%$ . The two treatment groups were largely comparable, although more ILPS-treated patients were women ( $p = 0.051$ ) and more received concomitant treatment with MET/PIO ( $p = 0.0289$ ), and more glargine-treated patients received MET only ( $p = 0.033$ ). Distribution by ethnicity was similar between the two treatment groups.

### Glycaemic Control

At 24-week endpoint, LS mean difference in HbA1c change from baseline between treatment groups (ILPS minus glargine) was 0.22% (95% CI: 0.06–0.38), demonstrating non-inferiority of ILPS to glargine. Mean reduction in HbA1c was less for ILPS-treated patients than glargine-treated patients (Table 3). There was no significant difference in the percentage of patients from both treatment groups who achieved HbA1c  $<7.0\%$  or  $\leq 6.5\%$ . Endpoint FPG levels were similar between treatment groups; however, mean endpoint postprandial PG values were higher in patients treated with ILPS versus glargine (Table 3; Figure 3). SMPG values post-morning meal, and before and after the evening meal were significantly higher for ILPS- versus glargine-treated patients (Figure 3).



**Figure 3.** Self-monitored plasma glucose profiles. The asterisk indicates time periods when insulin lispro protamine suspension (ILPS) and glargine were significantly different ( $p < 0.05$ ).

### Hypoglycaemia and Safety Parameters

Overall hypoglycaemia rate and severe hypoglycaemia incidence in the ILPS and glargine treatment groups were similar (Table 3). Although a higher nocturnal hypoglycaemia rate was observed in patients treated with ILPS compared with patients

**Table 2.** Baseline demographics and characteristics of randomized patients.\*

	ILPS (n = 171)	Glargine (n = 168)	p Value	Overall (n = 339)
Age, years	56.5 ± 9.7	56.2 ± 9.3	0.797	56.4 ± 9.5
Sex, n (%)				
Men	76 (44.4)	93 (55.4)	0.051	169 (49.9)
Women	95 (55.6)	75 (44.6)		170 (50.1)
Ethnicity, n (%)				
African American	13 (7.6)	14 (8.3)	0.756	27 (8.0)
Asian	7 (4.1)	6 (3.6)		13 (3.8)
Hispanic	21 (12.3)	17 (10.1)		38 (11.2)
Native American	-	1 (0.6)		1 (0.3)
White	130 (76.0)	130 (77.4)		260 (76.7)
Duration of diabetes, years	9.5 ± 6.0	10.3 ± 6.6	0.245	9.9 ± 6.3
Baseline HbA1c, %	8.21 ± 0.79	8.22 ± 0.80	0.888	8.22 ± 0.79
Baseline weight, kg	101.6 ± 18.7	102.3 ± 19.7	0.718	102.0 ± 19.2
Baseline body mass index, kg/m <sup>2</sup>	34.9 ± 5.2	34.8 ± 5.2	0.800	34.9 ± 5.2
Concomitant OAMs, n (%)				
Metformin only	40 (23.4)	47 (28.0)	0.033	87 (25.7)
Metformin/sulphonylurea	105 (61.4)	104 (61.9)	0.949	209 (61.7)
Metformin/pioglitazone	22 (12.9)	10 (6.0)	0.029	32 (9.4)

HbA1c, haemoglobin A1c; ILPS, insulin lispro protamine suspension; OAMs, oral antihyperglycaemic medications; s.d., standard deviation.

\*Values are presented as mean ± s.d. unless otherwise noted. p Values compare ILPS and glargine treatment groups.

treated with glargine, ILPS treatment was associated with a lower rate of non-nocturnal hypoglycaemia. The total daily insulin dose was significantly lower in patients treated with ILPS versus glargine. Mean weight gain was similar between groups.

Serious AEs during this trial and AEs leading to study discontinuation were infrequent, and the rates were similar in both treatment groups (Table 3 and Figure 2). Three patients treated with ILPS discontinued the study; reasons for discontinuation included one case of colon cancer, one case of nausea and one case of impaired gastric emptying (both moderate). Two patients treated with glargine discontinued the study; reasons for discontinuation were one pregnancy and one case of cholelithiasis. For TEAEs, 86 ILPS-treated patients (50.3%) experienced at least one TEAE versus 110 patients (65.5%) in the glargine treatment group ( $p = 0.006$ ). The only individual TEAE that was significantly different between treatment groups was viral gastroenteritis [ILPS: 2 patients (1.2%), glargine: 12 patients (7.2%);  $p = 0.006$ ]. No deaths occurred in this study.

### Oral Antihyperglycaemia Medications

Concomitant OAM treatment was associated with clinical response in both treatment arms (Table 4). The MET/PIO subgroups showed 0.35–0.36% greater HbA1c reductions compared with MET/SU subgroups, but the difference was statistically significant only for the ILPS arm. In addition, the MET/PIO subgroup had lower endpoint insulin dose in both arms, but the differences were not statistically significant. Patients on MET-only lost weight, while patients on other OAM combinations gained weight. For both ILPS and glargine, overall hypoglycaemia rates were significantly lower for the MET-only subgroup versus the MET/SU subgroup. Among ILPS-treated patients, overall hypoglycaemia rates

were also lower in the MET/PIO subgroup than in the MET/SU subgroup. Nocturnal hypoglycaemia was significantly lower for the MET-only subgroup versus MET/SU subgroup for ILPS-treated patients. For non-nocturnal hypoglycaemia, the MET-only subgroup had significantly lower rate versus MET/SU subgroup for both glargine- and ILPS-treated patients. The non-nocturnal hypoglycaemia rate was significantly lower for the MET/PIO subgroup versus MET/SU subgroup for ILPS-treated patients. Among patients treated with ILPS, there were two episodes of severe hypoglycaemia in the MET/SU subgroup, none in the MET-only subgroup, and one in the MET/PIO subgroup ( $p = 0.248$  across all subgroups). No episodes of severe hypoglycaemia occurred in any of the glargine-treated subgroups. Despite comparable numbers of patients receiving SU (Table 2), only 13 ILPS-treated patients (12.0%) had their SU dose reduced or discontinued as compared with 28 glargine-treated patients (25.7%;  $p = 0.015$ ).

### Discussion

This study is the first randomized controlled trial to compare addition of once-daily basal insulins, ILPS or glargine, in T2D patients who are not at optimal glycaemic control with combined exenatide BID/OAM therapy. ILPS was found to be non-inferior to glargine in change in HbA1c from baseline to the 24-week endpoint based on a pre-specified margin of 0.4%, although glargine was associated with greater HbA1c change and lower endpoint HbA1c. The SMPG profiles with either basal insulin treatment group showed marked improvement in FPG and preprandial values from baseline (Figure 3). For both insulin treatment groups, postprandial excursions were similar at baseline and endpoint, indicating continued efficacy of exenatide BID. In studies where basal insulin was added to OAMs (without exenatide BID), T2D patients showed distinctly

**Table 3.** Endpoint and change at endpoint values for efficacy and safety assessments.\*

	ILPS (n = 171)	Glargine (n = 168)	p Value
Endpoint HbA1c, %	7.04 ± 0.81	6.83 ± 0.78	0.008
Mean HbA1c change, %	-1.16 ± 0.84	-1.40 ± 0.97	0.008
Patients achieving HbA1c < 7.0%, n (%)	87 (53.7)	100 (61.7)	0.177
Patients achieving HbA1c < 7.0% with no hypoglycaemia, n (%)	17 (10.0)	19 (11.4)	0.727
Patients achieving HbA1c ≤ 6.5%, n (%)	46 (28.4)	63 (38.9)	0.060
Patients achieving HbA1c ≤ 6.5% with no hypoglycaemia, n (%)	12 (7.1)	12 (7.2)	1.000
Endpoint fasting plasma glucose, mmol/l	7.20 ± 1.75	7.05 ± 1.61	0.179
Endpoint postprandial plasma glucose, mmol/l	8.78 ± 2.04	8.11 ± 1.69	<0.001
Overall hypoglycaemia incidence, n (%)	120 (70.6)	125 (74.9)	0.394
Overall number of hypoglycaemia episodes	1248	1371	0.394
Overall hypoglycaemia rate, episodes/patient/year	16.27 ± 23.19	18.05 ± 24.59	0.570
Nocturnal hypoglycaemia rate, episodes/patient/year	4.88 ± 8.43	3.01 ± 7.21	0.004
Non-nocturnal hypoglycaemia rate, episodes/patient/year	11.36 ± 19.16	14.83 ± 21.00	0.044
Severe hypoglycaemia incidence, n (%)	3 (1.8)	0	0.249
Insulin dose, IU	31.1 ± 18.9	37.9 ± 18.5	<0.001
Insulin dose, IU/kg/day	0.30 ± 0.17	0.37 ± 0.17	<0.001
Weight gain, kg	0.27 ± 3.38	0.66 ± 3.93	0.343
Patients with ≥1 serious adverse event, n (%)	9 (5.3)	5 (3.0)	0.414

HbA1c, haemoglobin A1c; ILPS, insulin lispro protamine suspension; s.d., standard deviation.

\*Values presented as mean ± s.d. unless otherwise indicated.

**Table 4.** Safety and efficacy endpoints by OAM subgroup.

Subgroup	Change in HbA1c (%)		Endpoint insulin dose (IU/kg/day)		Weight change (kg)		Hypo rate (episodes/patient/year)		Nocturnal hypo rate (episodes/patient/year)		Non-nocturnal hypo rate (episodes/patient/year)		
	Mean	p Value*	Mean	p Value*	Mean	p Value*	Mean	p Value*	Mean	p Value*	Mean	p Value*	
ILPS-treated patients	MET/SU (n = 105)	-1.11	—	0.31	—	0.66	—	21.47	—	5.52	—	15.89	—
	MET (n = 40)	-1.14	0.642	0.34	0.290	-1.07	0.013	1.66	<0.001	0.41	0.001	1.03	<0.001
	MET/PIO (n = 22)	-1.47	0.005	0.22	0.099	0.72	0.980	6.57	0.009	3.93	0.627	2.64	0.003
Glargine-treated patients	MET/SU (n = 104)	-1.35	—	0.36	—	1.08	—	20.52	—	2.22	—	17.72	—
	MET (n = 47)	-1.43	0.141	0.40	0.084	-0.24	0.201	2.70	<0.001	0.48	0.061	2.22	<0.001
	MET/PIO (n = 10)	-1.70	0.115	0.30	0.568	0.50	0.906	16.06	0.682	0.85	0.454	15.21	0.848

Hypo, hypoglycaemia; ILPS, insulin lispro protamine suspension; MET, metformin; OAM, oral anythyperglycaemic medication; PIO, pioglitazone; SU, sulphonylurea.

\*p Values compare other (OAM) subgroups to MET/SU subgroup within each insulin treatment group.

different SMPG profiles with greater post-breakfast and post-dinner glycaemic excursions [3, 15, 30–32]. Endpoint FPG values were substantially above target levels for both treatment group; however, FPG values were within the range observed in previous treat-to-target studies (5.6–7.4 mmol/l) [3, 15, 30–32].

More than half of the patients in each treatment group achieved the target HbA1c of <7% (Table 3). Although there was no statistically significant difference between treatment groups, a greater percentage of glargine-treated patients achieved targets of HbA1c <7.0% and ≤6.5%. In both treatment groups, only a small proportion of patients who achieved these HbA1c targets did so without experiencing hypoglycaemia. This suggests that concerns about hypoglycaemia may be the reason mean endpoint FPG concentrations were above target levels, although higher incidence of hypoglycaemia in both groups was probably related to the high proportion of SU use among patients in this study (Table 4).

Addition of basal insulins to ongoing exenatide/OAM treatment was associated with a small increase in weight (weight gain of <0.7 kg in both treatment groups) in this study. This weight gain was generally smaller than that reported in treat-to-target glargine/OAM trials (1.9–3.0 kg) [3, 25–28] and less than what might have been expected for the change in HbA1c at endpoint (~2 kg for every 1% decrease in HbA1c) [33]. Data from head-to-head comparison studies of glargine and GLP-1 RAs (exenatide BID or QW or liraglutide) in patients with suboptimally controlled T2D indicated that ILPS treatment improved HbA1c and reduced weight as compared with glargine treatment [34]. Mean insulin requirements for both basal analogue groups in this study (0.30–0.37 IU/kg/day) were generally lower than in other studies adding basal insulins to previous OAM therapy (0.40–0.80 IU/kg/day) [3, 15, 30–32].

A recent head-to-head PK/PD study demonstrated longer duration of action for patients treated with glargine versus ILPS (at 0.6 IU/kg) [20]. This may account for the higher rate of non-nocturnal hypoglycaemia and greater need for

SU dose adjustments with glargine, and more nocturnal hypoglycaemia in patients treated with ILPS observed in this trial, although concomitant SU use may have impacted these observed hypoglycaemia rates as mentioned. Significantly greater insulin exposure (area under the baseline-corrected serum insulin concentration versus time curve from time 0 to 24 h) with ILPS versus glargine [20], as well as differences in SU dosage adjustments, may have also contributed to the lower dose requirements for ILPS. It is also possible that nocturnal hypoglycaemia may have curtailed dose uptitrations of ILPS. The differing titration algorithms used in this study, with slightly more aggressive glycaemic targets for glargine (Table 1), may also have contributed to the differences in HbA1c and PPG reductions in patients treated with glargine, who may have experienced greater nocturnal hypoglycaemia than otherwise would have been observed with titrations identical to those in patients treated with ILPS.

Two trials of ILPS versus glargine as starter insulins in patients with T2D treated with OAMs (but not exenatide) have been reported. Esposito et al. [30] did not demonstrate any between-group differences in hypoglycaemia rates with once-daily ILPS versus glargine, possibly due to protocol-specified holding of evening SU doses; endpoint total daily dose was lower for patients treated with ILPS versus glargine ( $0.61 \pm 0.15$  and  $0.67 \pm 0.14$  IU/kg/day; mean difference  $0.06$  IU/kg/day, CI  $-0.115$  to  $-0.004$ ) [30] as was observed in this study. Strojek et al. [22] found higher nocturnal hypoglycaemia rates (and more severe hypoglycaemia as well) in ILPS-treated patients. However, in that study, twice-daily ILPS therapy was allowed, with 55% of ILPS-treated patients requiring split therapy to bring pre-dinner PG levels to specified targets, and no SU dose adjustments were allowed per protocol [22]. For patients receiving once-daily ILPS, total daily dose was significantly lower in patients treated with ILPS versus glargine ( $0.26 \pm 0.14$  vs.  $0.35 \pm 0.20$  IU/kg;  $p < 0.001$ ), and nocturnal hypoglycaemia rates did not differ [22].

Subgroup analyses for this study showed that, for both basal insulin groups, overall hypoglycaemia rate was higher with MET/SU and MET/PIO groups compared with MET-only group. Interestingly, hypoglycaemia rates in the MET/SU group were similar in the ILPS and glargine arms despite the fact that twice as many glargine-treated patients had their SU dose reduced or discontinued. Reduction by one-half or discontinuation of SU with initiation of exenatide therapy is generally recommended [4, 12, 35]. This may be even more important if the clinician contemplates adding basal insulins to exenatide/SU therapy in order to reduce the risk of daytime hypoglycaemia with glargine and nocturnal hypoglycaemia with ILPS treatment, and possibly also to minimize weight gain with either insulin.

The number of serious adverse events (SAEs) reported did not differ significantly among patients treated with ILPS versus glargine and the majority of SAEs were considered consistent with T2D. No new safety risks were identified and the safety risk profile for ILPS remains unchanged.

Basal insulin added to exenatide plus OAMs is consistent with the joint position statement of the American Diabetes

Association and The European Association for the Study of Diabetes and the recent AACE comprehensive diabetes management algorithm on the management of hyperglycaemia in T2D [1, 2], which list combination of MET plus GLP-1 RA as a dual therapy option and MET plus GLP-1 RA plus insulin as a possible triple therapy combination option. Further, these guidelines state that when advancing from dual to triple therapy, the use of insulin as the third therapy often gives the most robust response [1]. Adding basal insulin to regimens containing GLP-1 RAs has been noted to be more logical than the converse order (GLP-1 RA added to basal insulin) when progressive antihyperglycaemic therapy in T2D is required [10].

Limitations of this study include the imbalance in concomitant OAM therapies that the patients in each treatment arm were taking at baseline and continued throughout the study, although importantly, randomization was stratified for SU use. Compared with ILPS-treated patients, significantly more glargine-treated patients received concomitant treatment with MET only and significantly fewer received treatment with MET/PIO. Reduction or discontinuation of SUs was allowed per protocol for hypoglycaemia; however, this was not balanced between comparator arms and might have resulted in differences in efficacy and safety outcomes between the two treatment groups. This study was not powered to allow for analyses of results by ethnic subgroups.

In conclusion, ILPS was non-inferior to glargine for HbA1c change over 24 weeks at the pre-specified non-inferiority margin of 0.4%. Compared with glargine, ILPS-treated patients achieved a smaller change in HbA1c with more nocturnal hypoglycaemia, but similar overall hypoglycaemia rate, and minimal weight gain. Clinicians must weigh the relative merits of differing therapies for their patients based on many factors (including efficacy, side effects, comorbidities and cost) and in relation to individualized glycaemic targets [1]. Once-daily basal insulin added to exenatide plus OAMs was well-tolerated in this study and appears to substantially improve HbA1c and to allow a significant number of patients with suboptimally controlled T2D treated with OAMs and exenatide to reach glycaemic targets while experiencing minimal weight gain.

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## Conflict of Interest

R. F. A., T. C. B., J. K. W. and D. R. L. were principal investigators for the study and contributed to the interpretation of data and the writing of the manuscript; H. H. J., S. A. M. and J. A. J.

contributed to the design and analysis of the study, the interpretation of data and writing of the manuscript. J. G. J. contributed to the interpretation of data and writing of the manuscript. All authors approved the final version of the manuscript.

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