Diabetes, Obesity and Metabolism 13: 268–275, 2011.

ORIGINAL ARTICLE

Efficacy and safety of insulin detemir once daily in combination with sitagliptin and metformin: the TRANSITION randomized controlled trial

P. Hollander[1], K. Raslova[2], T. V. Skjøth[3], J. Råstam[3] & J. F. Liutkus[4]

[1]*Baylor Endocrine Center, Baylor University Medical Center, Dallas, TX, USA*
[2]*Metabolic Center Ltd. and Slovak Medical University, Bratislava, Slovak Republic*
[3]*Novo Nordisk, Soeborg, Denmark*
[4]*Medicine Professional Corporation, Vascular Risk Modification Clinic, Cambridge, Ontario, Canada*

Aim: The aim of this trial was to evaluate the efficacy and safety of the combination of once-daily insulin detemir (IDet) and sitagliptin (SITA) versus SITA ± sulphonylurea (SU), both in combination with metformin (MET) in insulin-naive subjects.

Methods: In a 26-week, open-label, randomized, parallel-group study in type 2 diabetes, insulin-naive subjects concomitantly treated with MET ± second oral antidiabetic drug (OAD) were randomized 1 : 1 to IDet + SITA + MET or SITA + MET ± SU. All continued with MET treatment, and those treated with SU continued if randomized to SITA + MET ± SU. Efficacy endpoints included glycosylated haemoglobin (HbA1c), fasting plasma glucose (FPG), 9-point self-measured plasma glucose (SMPG), weight, body mass index (BMI). Safety endpoints included adverse events (AEs) and hypoglycaemia.

Results: Significantly higher reductions in HbA1c, FPG and SMPG were achieved with IDet + SITA + MET compared with SITA + MET ± SU. Estimated HbA1c decreased by 1.44% in the IDet + SITA + MET group versus 0.89% in SITA + MET ± SU, $p < 0.001$. FPG decreased by 3.7 mmol/l (66.3 mg/dl) versus 1.2 mmol/l (22.2 mg/dl), $p < 0.001$, respectively. Small decreases in weight and BMI were observed in both arms, with no significant differences. AEs were mild or moderate and were more common in the SITA + MET ± SU arm than in the IDet + SITA + MET arm. There was no major hypoglycaemia. Observed rates of hypoglycaemia were very low (1.3/1.7 episodes/patient year) in both arms. The subgroup treated with MET and SUs prior to the trial achieved similar results.

Conclusions: The combination of once-daily IDet with SITA showed a clinically and significantly better improvement in glycaemic control than SITA in combination with or without SUs. Both regimens were associated with a low rate of hypoglycaemia and slight weight reduction.

Keywords: diabetes mellitus, efficacy, insulin detemir, metformin, once daily, safety, sitagliptin, sulphonylurea

Date submitted 8 October 2010; date of first decision 20 October 2010; date of final acceptance 18 November 2010

Introduction

The importance of good glycaemic control to avoid or delay late-stage diabetes complications has been documented in a series of long-term follow-up studies [1–4]. Early treatment strategies beyond lifestyle changes and metformin (MET) include adding other oral antidiabetic drugs (OADs), incretin therapies or basal insulin [5]. For patients who need more than one type of OAD, factors including the ability to lower glycosylated haemoglobin (HbA1c) levels decreased the risk of hypoglycaemia, weight reduction or less weight gain, coupled with convenience, influence the final choice of medications used to treat their diabetes [6]. Another important consideration in choosing multiple medications is the physiological interplay of therapies that have complementary mechanisms of action.

Correspondence to: Dr. Priscilla Hollander, Baylor Endocrine Center, Baylor University Medical Center, 656 Wadley Tower, 3600 Gaston Avenue, Dallas, TX 75246, USA.
E-mail: priscilh@BaylorHealth.edu

Insulin detemir (IDet) is a basal insulin analogue that has a protracted mechanism of action by forming hexamers in the injection depot and reversibly binding to albumin in the circulation. It was designed to reduce fasting and between-meal glucose levels, and treatment has resulted in documented efficacy and safety in type 1 and type 2 diabetes, with little or no weight gain and with a low incidence of hypoglycaemia [7,8]. Sitagliptin (SITA), an incretin-based therapy, inhibits dipeptidyl peptidase-4 (DPP-4), the enzyme responsible for degradation of glucagon-like peptide-1 (GLP-1). This inhibition extends the plasma half-life of GLP-1 and thus improves glycaemic control especially in the postprandial state [9–11].

This study is the first in which the treatment of insulin-naive subjects inadequately controlled with OAD treatment is intensified with a combination of a basal insulin analogue, IDet, and a DPP-4 inhibitor, SITA. The complementary effects of IDet and the incretin-based therapy on fasting and postprandial glucose control provide a rational basis for these agents to be used together. Thus, the aim of this trial (TRANSITION) was to

evaluate the efficacy and safety of once-daily IDet + once-daily SITA (IDet + SITA + MET regimen) versus SITA with or without sulphonylureas (SUs) (SITA + MET ± SU regimen). This paper will also examine the outcome in the subgroup that took SUs as part of its prestudy regimen.

Materials and Methods

Design

This was a randomized, open-label, parallel-group, efficacy and safety study. The subjects recruited were insulin-naive, diagnosed with type 2 diabetes for a minimum of 6 months, and were inadequately controlled on current treatment with MET ± another OAD including SU. Inclusion criteria were the following: MET at a stable dose ≥1000 mg/day for a minimum of 3 months; naive to insulin and DPP-4 inhibitors; HbA1c in the range 7.5–10%; body mass index (BMI) ≤45 kg/m^2. Exclusion criteria were the following: any contraindication to insulin or SITA; treatment with thiazolidinediones or GLP-1 analogues within the last 2 months; anticipated change in any systemic treatment that might interfere with glucose metabolism. Subjects were recruited from 48 sites in eight countries (Canada, Finland, France, Hungary, Slovakia, South Korea, Turkey and USA) and they provided written consent. The trial was conducted in accordance with the Declaration of Helsinki.

Treatment

Within 2 weeks of screening, the subjects were randomized (using an interactive web/voice response system) 1 : 1 to treatment with either the IDet + SITA + MET regimen (MET continued while all other OADs discontinued) or the SITA + MET ± SU regimen (MET and SU continued while all other OADs discontinued; SU was allowed to be discontinued at the discretion of the investigator) using stratification based on previous therapy (MET monotherapy or MET in combination with other OADs).

The study was conducted open-label because of the burden on patients having to inject placebo and the potential unblinding of results during the titration stage of the study because of lack of effect in the comparison arm.

SITA was administered orally at a fixed time point and at a fixed dose of 100 mg/day in both treatment arms. The doses and dosing frequency of SU (only allowed in the SITA + MET ± SU arm) and MET were kept at prestudy levels. However, reduction in SU dose was allowed in cases of frequent hypoglycaemic episodes, at the discretion of investigators. IDet was injected once daily in the evening between 1 h before dinner and bedtime. IDet was titrated weekly by a treat-to-target approach by the investigator based on the subject's prebreakfast plasma glucose (PG) measurements. When possible, this was based on the average of three recent measurements (preferably 3 days prior to each visit/contact), otherwise, on the measurements available. The target was a prebreakfast PG level of 4.0–6.0 mmol/l (72–108 mg/dl). If prebreakfast PG was in the range 6.1–7.0 mmol/l (110–126 mg/dl), the insulin dose would be increased by 2 U, and for each 1.0 mmol/l (18 mg/dl) above that range, a further 2 U dose (up to a maximum of 10 U) would be added. If PG was in the range 3.1–3.9 mmol/l (56–70 mg/dl), the dose was recommended to be reduced by 2 U, and with PG levels <3.1 mmol/l (<56 mg/dl), the recommended reduction was 4 U [12]. No specific dietary counselling was given to either group.

Efficacy Endpoints and Statistical Analyses

The study was powered to show superiority in the primary endpoint, HbA1c, after 26 weeks. In previous trials with IDet and OADs in insulin-naive subjects with type 2 diabetes, baseline-corrected standard deviations of HbA1c up to 1.0 have been reported. In order to detect a difference of 0.4% between the two treatment groups after 26 weeks, 100 subjects per group would yield a power of 80%. Assuming a maximum withdrawal rate of 10%, enrolment of 112 subjects per group was planned. The sample size was based on a two-group *t*-test and a 5% two-sided significance level.

Other efficacy endpoints included laboratory-measured fasting plasma glucose (FPG), 9-point self-measured plasma glucose (SMPG), proportions of subjects reaching HbA1c ≤7.0% or ≤6.5%, body weight, BMI and waist–hip ratio. HbA1c was analysed using an analysis of covariance (ANCOVA), including treatment, previous therapy (stratification), country and baseline HbA1c. The analysis was performed on the full analysis set (FAS): all randomized subjects exposed to at least one dose of treatment. The last observation carried forward principle was applied to analyses: any missing postbaseline data was substituted with the last available non-missing postbaseline observation. The proportion of subjects meeting HbA1c ≤7.0 or ≤6.5% after 26 weeks was analysed by a logistic regression model including treatment, previous therapy, baseline HbA1c and country as factors. The results are expressed as an odds ratio (OR) for the two treatment arms, IDet + SITA + MET versus SITA + MET ± SU. An analysis was also conducted for subjects reaching these HbA1c targets without symptomatic hypoglycaemia with a PG value <4.0 mmol/l (<72 mg/dl) or any single PG value 3.1 mmol/l (<56 mg/dl) in the last 3 months of treatment. SMPG was analysed by a linear mixed model, with treatment, previous therapy, treatment-by-time interaction and country as factors and using an *unstructured* variance structure assuming complete independence between subjects. FPG, body weight, BMI and waist–hip ratio were analysed as described for HbA1c.

Safety and Tolerability Endpoints and Statistical Analyses

Safety outcomes included adverse events (AEs), hypoglycaemic episodes, lipids and vital signs measured during the study. AEs were evaluated from summaries of statistical tabulations. Hypoglycaemic episodes were defined as major when a subject was unable to treat himself/herself; minor hypoglycaemia was defined as self-treatable and PG <3.1 mmol/l (<56 mg/dl), with or without symptoms. Symptomatic hypoglycaemia was when the patient experienced hypoglycaemic symptoms, but no PG measurement was taken or PG ≥3.1 mmol/l (≥56 mg/dl).

Hypoglycaemic episodes were analysed by a negative binomial regression model adjusting for country, previous therapy and baseline HbA1c and with the log-transformed exposure time as offset variable. The result is expressed as a ratio between the rates of hypoglycaemia in the two treatment arms (rate ratio IDet + SITA + MET : SITA + MET ± SU). Events are expressed as episodes per subject per year.

In addition to the preplanned analyses made on the FAS, *post hoc* analyses on efficacy and safety were performed in the subpopulation of subjects treated with SU before entering the study (the pretrial SU subgroup). Comparisons of HbA1c, FPG, BMI, weight and hypoglycaemia were carried out between the two treatment arms in those subjects in the pretrial SU subgroup (irrespective that subjects discontinued SU if randomized into the IDet + SITA + MET arm).

Results

Baseline Characteristics and Patient Flow

Baseline characteristics and demographic data are shown in Table 1. Patient flow is shown in figure 1. Although the gender proportions were slightly different in the two arms, this observation was not deemed clinically relevant as neither IDet nor SITA is affected by gender (IDet US/European prescribing information [13]; SITA US/European prescribing information [14]). The higher proportion of males in the IDet + SITA + MET arm was reflected in the higher mean weight in this arm, but BMI was not different between the groups. Seventy-eight per cent of the randomized patients were on a regimen of MET + other OAD before entering the trial and almost all of them used SU (98%). Twenty-two per cent of the randomized patients in both arms were on prestudy MET monotherapy. After randomization, 77% of the subjects in the SITA + MET ± SU arm continued with SU, whereas all patients randomized to the IDet + SITA + MET arm discontinued SU (and any OAD other than MET) if they were treated with this prior to inclusion.

Table 1. Demographics and baseline characteristics.

	IDet + SITA + MET	SITA + MET ± SU
Number of subjects	107	110
Age (years)		
Mean (SD)	56.7 (10.0)	57.1 (8.4)
Gender (%)		
Female	36	55
Male	64	45
Race (%)		
White	78	76
Asian	12	15
Black or African American	3	2
Other	0	1
Not known	7	5
Body weight (kg)		
Mean (SD)	93.1 (20.2)	88.2 (19.2)
BMI (kg/m^2)		
Mean (SD)	31.8 (5.2)	31.9 (5.9)
Waist–hip ratio		
Mean (SD)	0.97 (0.10)	0.94 (0.07)
Previous treatment (%)		
MET + other OADs	78	78
MET + SU	75	77
MET monotherapy	22	22
HbA1c (%)		
Mean (SD)	8.5 (0.7)	8.5 (0.7)
FPG (mmol/l/mg/dl)		
Mean (SD)	9.7 (2.2)/174.7 (40.2)	9.8 (2.4)/176.5 (42.5)
Diabetes history (years)		
Mean (SD)	9.6 (5.6)	9.9 (5.7)

BMI, body mass index; FPG, fasting plasma glucose; HbA1c, glycosylated haemoglobin; IDet, insulin detemir; MET, metformin; OAD, oral antidiabetic drug; SD, standard deviation; SITA, sitagliptin; SU, sulphonylurea.

Efficacy

The changes from baseline in HbA1c and FPG during the 26 weeks of treatment for all subjects and for the pretrial SU group are shown in figure 2. At 26 weeks, greater decreases in HbA1c were seen for the IDet + SITA + MET arm than for the SITA + MET ± SU arm: estimated decrease was −1.44% in the IDet + SITA + MET arm and −0.89% in the SITA + MET ± SU arm [estimated treatment difference of −0.55%, 95% CI (−0.77 to −0.33), $p < 0.001$]. FPG also decreased significantly more in the IDet + SITA + MET arm [−3.7 mmol/l (−66.3 mg/dl)] than in the SITA + MET ± SU arm [−1.2 mmol/l (−22.2 mg/dl); estimated treatment difference: −2.5 mmol/l (−44.1 mg/dl), 95% CI: −3.0 to −1.9 mmol/l (−54.3 to −33.8 mg/dl), $p < 0.001$]. The results achieved in the pre-SU group were similar (figure 2B and D).

Overall, 45% of the subjects in the IDet + SITA + MET arm achieved HbA1c ≤7% compared with 24% in the SITA + MET ± SU arm, a difference that was statistically significant [adjusted OR 3.2, 95% CI (1.65 to 6.19), $p = 0.001$]. More than a third (36%) of the subjects on IDet + SITA + MET achieved the HbA1c target without hypoglycaemia in the last 3 months of treatment versus 20% in the SITA + MET ± SU arm, also statistically significant in favour of IDet + SITA + MET [adjusted OR 2.47, 95% CI (1.26 to 4.81), $p = 0.008$]. The proportion of subjects achieving HbA1c ≤6.5% tended to be higher in the IDet + SITA + MET arm than in the SITA + MET ± SU arm (19 vs. 10%); and similarly, the proportion of subjects achieving HbA1c ≤6.5% without hypoglycaemia was also higher in the IDet + SITA + MET arm (15 vs. 8%). However, differences between the arms were not statistically significant.

The 9-point SMPG profiles at baseline and after 26 weeks of treatment are presented in figure 3. At 26 weeks, there was a statistically significant difference in favour of IDet + SITA + MET, both for the overall profile (data not shown) and for the pairwise comparisons (indicated by asterisks) except for before dinner [not significant (NS)]. In the SMPG profile, 2-h postprandial glucose levels were significantly lower in the IDet + SITA + MET arm than in the SITA + MET ± SU arm: breakfast, 8.8 versus 10.5 mmol/l (158.9 vs. 189.2 mg/dl),

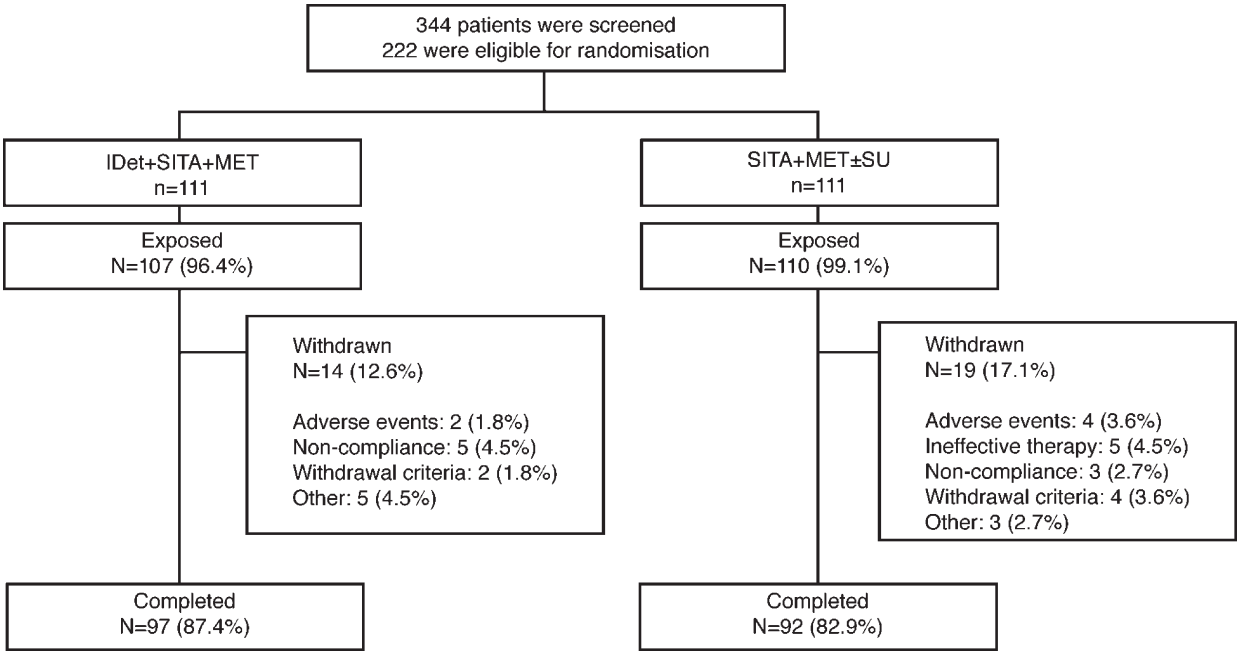

Figure 1. Patient flow. IDet, insulin detemir; MET, metformin; SITA, sitagliptin; SU, sulphonylurea.

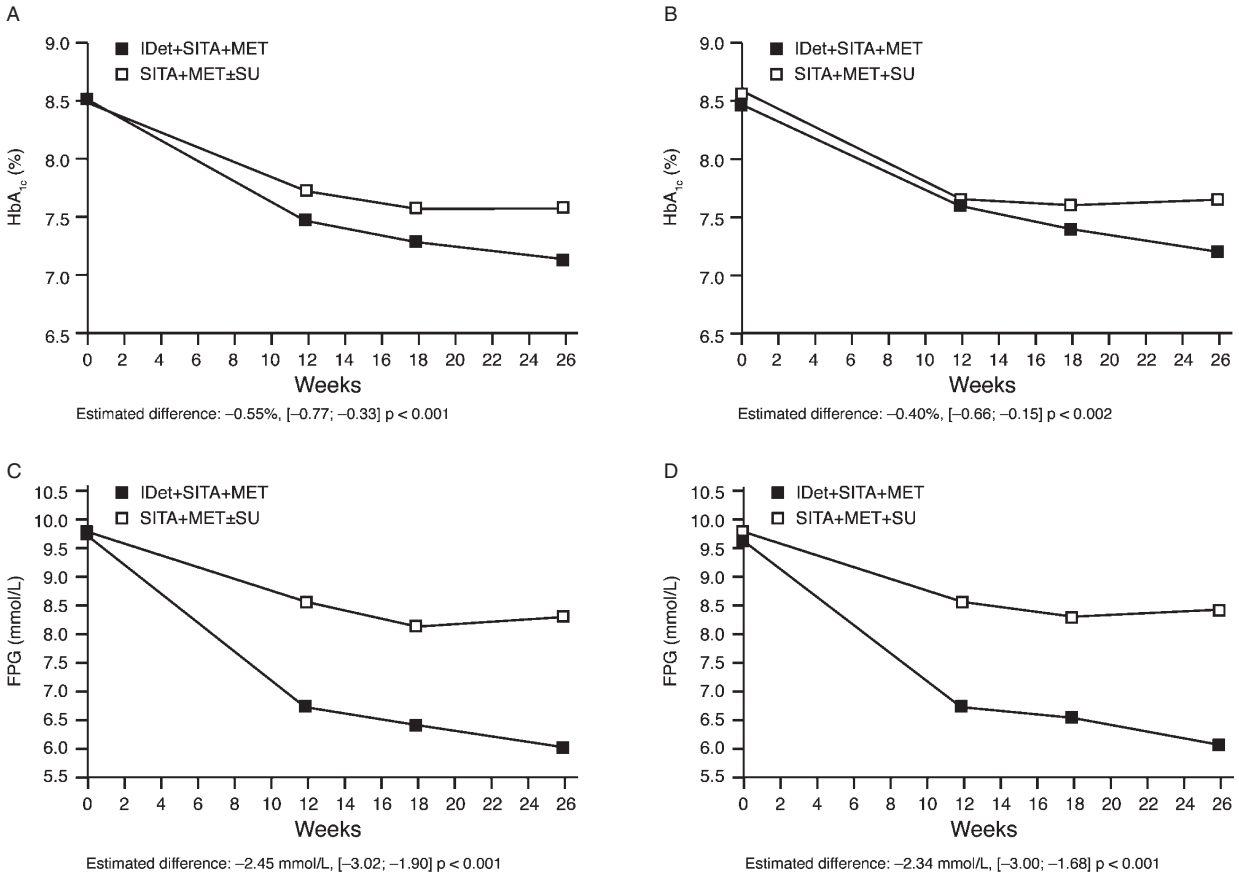

Figure 2. Mean glycosylated haemoglobin (HbA1c) and fasting plasma glucose (FPG) during 26 weeks of treatment. (A) HbA1c in full analysis set (FAS); (B) HbA1c in subjects pretreated with sulphonylurea (pre-SU); (C) FPG in FAS; (D) FPG in pre-SU. IDet, insulin detemir; MET, metformin; SITA, sitagliptin; SU, sulphonylurea.

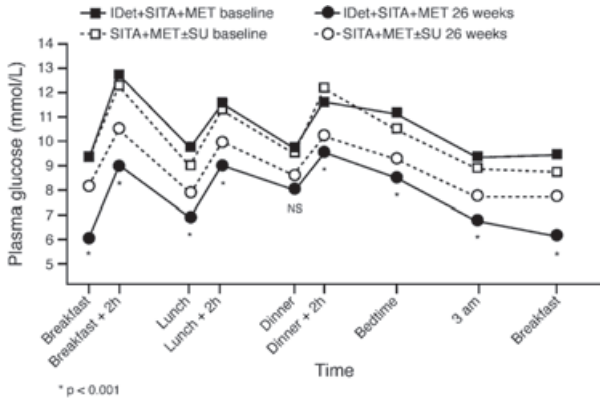

Figure 3. Nine-point self-measured plasma glucose profile. Profiles at baseline and after 26 weeks. Asterisks indicate a significant difference ($p < 0.001$) for the pairwise comparisons between groups at each time point. IDet, insulin detemir; MET, metformin; SITA, sitagliptin; SU, sulphonylurea.

respectively, treatment difference −1.6 mmol/l (−29.5 mg/dl), 95% CI [−2.4 to −0.9 mmol/l (−43.2 to −16.0 mg/dl)]; lunch, 8.7 versus 10.0 mmol/l (156.6 vs. 180.0 mg/dl), respectively, treatment difference −1.3 mmol/l (−23.4 mg/dl), 95% CI [−2.1 to −0.6 mmol/l (−36.9 to −10.0 mg/dl)]; dinner, 9.3 versus 10.2 mmol/l (167.6 vs. 183.8 mg/dl), respectively, treatment difference −0.9 mmol/l (−15.9 mg/dl), 95% CI [−1.8 to −0.02 mmol/l (−31.5 to −0.3 mg/dl)]. SMPG analyses in the pretrial SU subgroup were similar: all PG levels were lower with IDet + SITA + MET than with SITA + MET ± SU and were significantly lower at pre- and postbreakfast, bedtime and 03:00 hours.

In the IDet + SITA + MET arm, mean insulin dose increased gradually throughout treatment from 0.1 to 0.59 U/kg (figure 4A)—median dose increased from 0.11 to 0.54 U/kg—but with considerable individual variation (minimum dose at study end was 0.1 U/kg, maximum dose was 2.0 U/kg). Body weight decreased in both arms with a mean decrease of −1.7 kg with SITA + MET ± SU versus −0.8 kg with IDet + SITA + MET (NS between groups; figure 4B, left). A similar non-significant trend was noted for BMI (figure 4B, right). No changes in hip–waist ratio were found (data not shown). Similar results were seen in the pretrial SU subgroup: an observed decrease in weight and BMI, but with no significant difference between regimens.

Safety and Tolerability

Both regimens were characterized by a low incidence of hypoglycaemic episodes, including diurnal and nocturnal and an absence of major (assistance-requiring) episodes (Table 2). There was no significant difference between treatments in the rate of minor hypoglycaemia (rate ratio IDet + SITA + MET : SITA + MET ± SU 0.97, 95% CI (0.35 to 2.74), $p = 0.96$) or overall hypoglycaemia (rate ratio 0.98, 95% CI (0.48 to 2.02), $p = 0.96$). A single patient from the SITA + MET ± SU group accounted for approximately one third of the minor hypoglycaemic episodes in this group (excluding this patient, the observed episodes per patient per year was 0.35 in this group). In the pretrial SU subgroup, the pattern for hypoglycaemia was similar (data not shown).

Most AEs were mild or moderate; only 8 of a total of 563 were categorized as severe. Twelve AEs were evaluated as possibly or probably related to IDet, whereas 84 AEs were considered possibly or probably related to SITA (11 in IDet + SITA + MET and 73 in SITA + MET ± SU arm). The most common AEs related to SITA were gastrointestinal and nervous events, and at least part of the difference found between the two treatment groups could be explained by a large number of these events being reported in only a few subjects in the SITA + MET ± SU arm. Withdrawal because of AEs was also very low (two and four withdrawals, respectively, with IDet + SITA + MET and SITA + MET ± SU) in both arms.

Discussion

Over the past decade, the role of insulin in the treatment of type 2 diabetes has evolved and expanded. Rather than insulin being added as the last step in therapy, current treatment practice suggests that it can be an attractive addition at any level of the therapy cascade. The initiation of insulin, following the failure of OADs, can help improve glycaemic control and such 'intensive' glucose lowering may prevent or delay chronic complications including the risk of cardiovascular complications [1,2,15,16] especially when initiated early in the course of diabetes [1]. Additionally, early insulin initiation may help protect β-cells from further functional impairment caused by extended exposure to hyperglycaemia [17]. In practice, insulin initiation is however hampered by several barriers such as patient and physician concern about weight gain and hypoglycaemia and patient fear of injections [18]. Therefore, it is important to develop treatment regimens that aim to minimize these concerns.

Our study was designed to mimic the typical clinical situation in type 2 diabetes when a more intensive treatment is needed for patients insufficiently controlled on OADs. The simultaneous addition of once-daily IDet and SITA to insulin-naive subjects provided a pronounced effect on HbA1c (a 1.44% decrease compared to a 0.89% decrease with SITA + MET ± SU). Importantly, this was achieved with a low incidence of hypoglycaemia and without any negative effects on other safety parameters including weight.

SUs are typically included in the initial treatment of type 2 diabetes in many patients (more than 75% of those entering this study were on SU), but they are known to be associated with weight gain and high risk of hypoglycaemia [5]. The improved efficacy and safety profiles of once-daily IDet and SITA were also seen in the subpopulation of subjects treated with SU prestudy. This provides further evidence, albeit exploratory, to support the initiation of insulin- and incretin-based therapy while discontinuing SU.

Our study results were in line with what we anticipated, given the complementary mechanisms of the action of IDet and an incretin-based therapy and that current evidence with both treatments shows they are efficacious and well tolerated with a low incidence of hypoglycaemia and weight

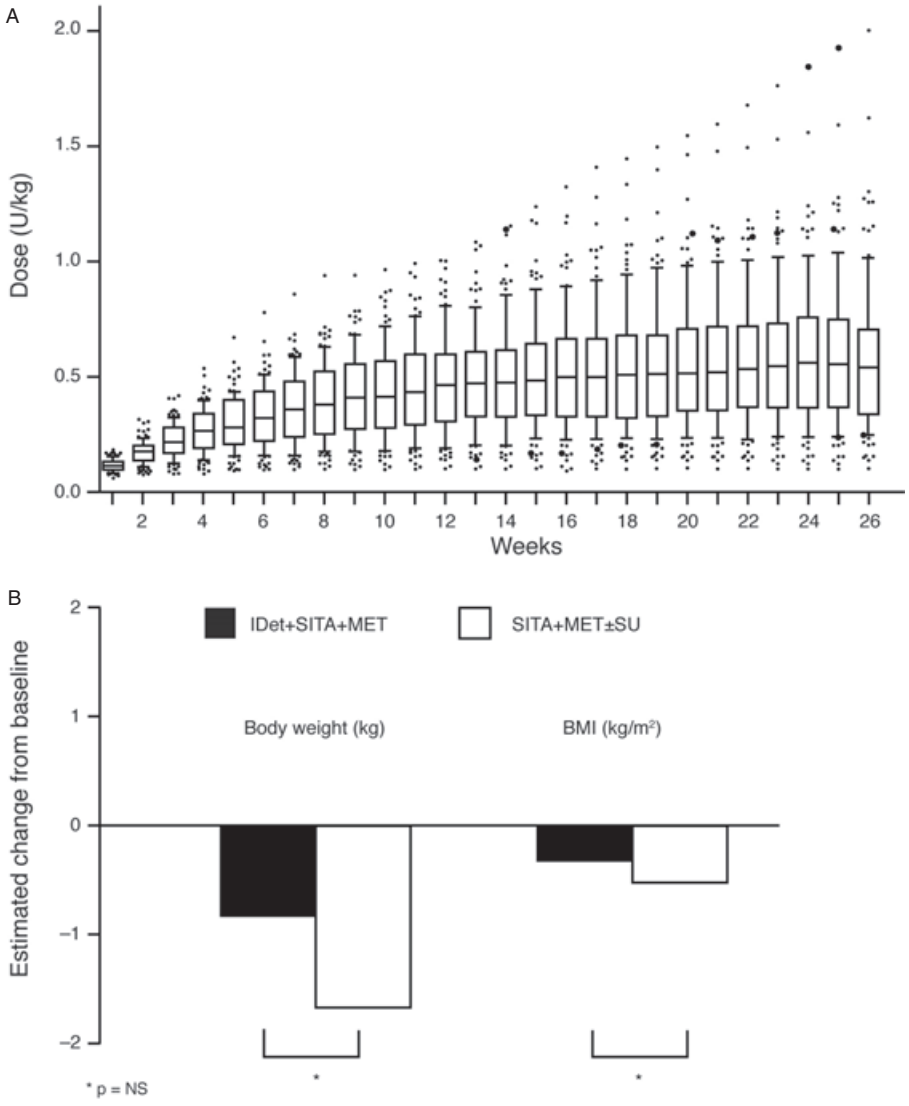

Figure 4. Insulin dose, body weight and body mass index (BMI) during treatment. (A) Box plot of insulin dose titration during treatment in IDet + SITA + MET arm; (B, left) change in body weight; (B, right) change in BMI. IDet, insulin detemir; MET, metformin; NS, not significant; SITA, sitagliptin; SU, sulphonylurea.

neutral/sparing effects [7,8]. The significantly lower HbA1c achieved with IDet + SITA + MET versus SITA + MET ± SU in this study was, however, achieved without any increase in hypoglycaemia rate. In previous studies of patients with type 2 diabetes, SITA or alogliptin—when added to the ongoing insulin treatment—caused a 0.6% and ~0.7% decrease in HbA1c, respectively, an increase in hypoglycaemia (but still a low incidence) and no weight change as compared to placebo [19,20].

Initiation of insulin therapy is often accompanied by weight gain. Our results are also consistent with previous findings that, in the case of IDet, weight gain is not however necessarily a consequence of insulin treatment [21]. In the present study, the improved glycaemic control with IDet when added together with a DPP-4 inhibitor was not accompanied by an increase in body weight relative to baseline. Indeed, weight was even reduced slightly in the IDet arm. The mechanism(s) for less weight gain with IDet are currently unclear, although a recent paper has reported a marked central nervous system response to euglycaemic intravenous infusion of IDet, which was missing with infusion of human insulin, although both insulins elicited an equipotent peripheral/systemic effect [22]. The stronger anorexigenic effect on the central nervous system of IDet compared with human insulin was accompanied by approximately 20% less *ad libitum* food intake.

There are a couple of points to consider when interpreting this study. Around 25% of patients in the study were taking only MET at baseline; in those patients assigned to IDet + SITA + MET, IDet plus SITA was *added* and compared to *added* SITA without SU. So the improvement in glycaemic control with IDet + SITA + MET was expected. Around 75% of patients had been taking an SU prior to inclusion, and this was discontinued

Table 2. Incidence of hypoglycaemic episodes.

	IDet + SITA + MET (n = 107)				SITA + MET ± SU (n = 110)			
	N	%	E	R	N	%	E	R
All hypoglycaemia	31	29	63	1.27	25	23	83	1.68
Minor	20	19	26	0.52	12	11	45	0.91
Symptoms only	20	19	36	0.73	16	15	35	0.71
Unclassified	1	1	1	0.02	1	1	3	0.06
Diurnal	27	25	51	1.03	25	23	72	1.46
Minor	17	16	22	0.44	12	11	41	0.83
Symptoms only	17	16	28	0.56	15	14	31	0.63
Unclassified	1	1	1	0.02	—	—	—	—
Nocturnal	10	9	12	0.24	3	3	11	0.22
Minor	4	4	4	0.08	1	1	4	0.08
Symptoms only	6	6	8	0.16	2	2	4	0.08
Unclassified	—	—	—	—	1	1	3	0.06

E, number of hypoglycaemic episodes; IDet, insulin detemir; MET, metformin; n, number of subjects experiencing hypoglycaemia; %, percentage of subjects experiencing at least one episode of hypoglycaemia; R, rate of hypoglycaemia, episodes/year; SITA, sitagliptin; SU, sulphonylurea.

if randomized to the IDet + SITA + MET arm; thus, in those patients assigned to IDet + SITA + MET, IDet was *substituted* for SU. Therefore, the comparison is the potentially added IDet (in IDet + SITA + MET) versus existing SU (in SITA + MET ± SU). This is why the pretrial SU subgroup was analysed; the difference in HbA1c between the groups in the SU subgroup analysis still remains significant, however. One OAD combination we cannot consider was patients previously being treated with thiazolidinediones, as they were excluded.

A second point to contemplate is that the poor control at baseline in the patients [mean baseline HbA1c 8.5% and FPG 9.7 mmol/l (175 mg/dl)] could possibly favour the addition of IDet, which specifically targets FPG, compared with SITA, which has more of an effect on postprandial glucose (PPG). We know that at higher HbA1c levels, FPG contributes more to overall hyperglycaemia than PPG, thereby potentially benefiting the glucose-lowering effect of IDet in this trial [23]. Furthermore, the antihyperglycaemic capacity of SITA appears to be no greater than that of other OADs. It has been shown that the addition of SITA to MET monotherapy over 1 year results in the same change in mean HbA1c from baseline as that following the addition of glipizide to MET monotherapy (−0.67%) in a randomized controlled trial of 1172 patients with type 2 diabetes [24]. Our study, however, is currently one of only three published studies to investigate insulin plus an incretin therapy, and the first to do so in insulin-naive patients.

In conclusion, our results show that IDet combined with SITA provide a clinically significant improvement in glycaemic control while maintaining the beneficial properties of weight neutrality and the low rate of hypoglycaemia experienced with the individual drugs. This may therefore be a useful approach in practice, an approach that might more easily intensify treatment for patients. The effect of the combination approach of insulin and incretin-based therapy should be further explored and confirmed in future clinical studies; for example, the addition of IDet to a GLP-1 analogue, such as once-daily liraglutide (plus MET), has showed a significantly greater improvement in glycaemic control than the GLP-1 analogue (plus MET) [25].

Acknowledgements

The authors wish to acknowledge Jens Keiding, Ed Kimble and Irene Vejgård Sørensen, from Novo Nordisk, and Watermeadow Medical, for assistance with the preparation of the manuscript. They also wish to thank Jens Larsen, Yan Gong, Tine Møller Jørgensen and Jette Lohse Løje from Novo Nordisk for help with trial design and data interpretation.

Conflict of Interest

This study was supported by Novo Nordisk A/S. P. H. has served on advisory boards for, and received honoraria from, Novo Nordisk, Orexigen, Novartis and BMS. K. R. has received research support from Novo Nordisk for a clinical trial related to the current trial and is a member of a scientific advisory panel, Residual Risk Reduction initiative (R3i). J. R. is employed by Novo Nordisk. T. V. S. is employed by and owns shares in Novo Nordisk. J. F. L. has received support from Novo Nordisk for clinical research, including honoraria for education on management of people with diabetes, and has participated in advisory board meetings for Novo Nordisk, Eli Lilly Canada, Pfizer, Astra Zeneca and GlaxoSmithKline.

P. H., K. R., T. V. S. and J. F. L. were involved in conducting the trial and data collection. All authors were involved in designing the study, analysing the data, writing the manuscript, reviewing drafts and approving the final draft.

References

1. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. New Engl J Med 2008; **359**: 1577–1589.
2. Prospective Diabetes UK. Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998; **352**: 837–853.
3. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression

of long-term complications in insulin-dependent diabetes mellitus. New Engl J Med 1993; **329**: 977–986.

4. Reichard P, Nilsson BY, Rosenqvist U. The effect of long-term intensified insulin treatment on the development of microvascular complications of diabetes mellitus. New Engl J Med 1993; **329**: 304–309.
5. Nathan DM, Buse JB, Davidson MB et al. Medical management of hyperglycaemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 2009; **32**: 193–203.
6. Rodbard HW, Jellinger PS, Davidson JA et al. Statement by an American Association of Clinical Endocrinologists/American College of Endocrinology consensus panel on type 2 diabetes mellitus: an algorithm for glycemic control. Endocr Pract 2009; **15**: 540–559.
7. De Leeuw I, Vague P, Selam JL et al. Insulin detemir used in basal-bolus therapy in people with type 1 diabetes is associated with a lower risk of nocturnal hypoglycaemia and less weight gain over 12 months in comparison to NPH insulin. Diabetes Obes Metab 2005; **7**: 73–82.
8. Haak T, Tiengo A, Draeger E, Suntum M, Waldhausl W. Lower within-subject variability of fasting blood glucose and reduced weight gain with insulin detemir compared to NPH insulin in patients with type 2 diabetes. Diabetes Obes Metab 2005; **7**: 56–64.
9. Drucker DJ, Nauch MA. The incretin system: glucagon-like peptide-1 receptor antagonists and dipeptidyl-4 inhibitors in type 2 diabetes. Lancet 2006; **568**: 1696–1705.
10. Goldstein B, Feinglos M, Lunceford J, Johnson J, Williams-Herman DE, Sitagliptin 036 Study Group. Effect of initial combination therapy with sitagliptin, a dipeptidyl peptidase-4 inhibitor, and metformin on glycemic control in patients with type 2 diabetes. Diabetes Care 2007; **30**: 1979–1987.
11. Hermansen K, Kipnes M, Luo E, Fanurik D, Khatami H, Stein P, Sitagliptin Study 035 Group. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor, sitagliptin, in patients with type 2 diabetes mellitus inadequately controlled on glimepiride alone or on glimepiride and metformin. Diabetes Obes Metab 2007; **9**: 733–745.
12. Philis-Tsimikas A, Charpentier G, Clauson P, Ravn GM, Roberts VL, Thorsteinsson B. Comparison of once-daily insulin detemir with NPH insulin added to a regimen of oral antidiabetic drugs in poorly controlled type 2 diabetes. Clin Ther 2006; **28**: 1569–1581.
13. Insulin detemir prescribing information. Available from URL: http://www.accessdata.fda.gov/drugsatfda_docs/label/2007/021536s015lbl.pdf. Accessed 24 September 2010.
14. Sitagliptin prescribing information. Available from URL: http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/021995s010s011s012s014lbl.pdf. Accessed 24 September 2010.
15. Turnbull FM, Abraira C, Anderson RJ et al. Intensive glucose control and macrovascular outcomes in type 2 diabetes. Diabetologia 2009; **52**: 2288–2298.
16. Ray KK, Wilde MI, Sivakumaran R et al. Effect of intensive control of glucose on cardiovascular outcomes and death in patients with diabetes mellitus: a meta-analysis of randomised controlled trials. Lancet 2009; **373**: 1765–1772.
17. Glaser B, Cerasi E. Early intensive insulin treatment for induction of long-term glycaemic control in type 2 diabetes. Diabetes Obes Metab 2001; **1**: 67–74.
18. Home PD, Boulton AJM, Jimenez J, Landgraf R, Osterbrink B, Christiansen JS. Issues relating to the early or earlier use insulin in type 2 diabetes. Pract Diabetes Int 2003; **20**: 63–71.
19. Vilsbøll T, Rosenstock J, Yki-Järvinen H et al. Efficacy and safety of sitagliptin when added to insulin therapy in patients with type 2 diabetes. Diabetes Obes Metab 2010; **12**: 167–177.
20. Rosenstock J, Rendell M, Gross JL, Fleck PR, Wilson CA, Mekki Q. Alogliptin added to insulin therapy in patients with type 2 diabetes reduces HbA1c without increasing weight gain or hypoglycemia. Diabetes Obes Metab 2009; **11**: 1145–1152.
21. Dornhorst A, Luddecke H-J, Sreenan S et al. for the PREDICTIVE Study Group. Insulin detemir improves glycaemic control without weight gain in insulin-naive patients with type 2 diabetes: subgroup analyses from the PREDICTIVE(TM) study. Int J Clin Pract 2008; **62**: 659–665.
22. Hallschmid M, Jauch-Chara K, Korn O et al. Euglycemic infusion of insulin detemir compared with human insulin appears to increase direct current brain potential response and reduces food intake while inducing similar systemic effects. Diabetes 2010; **59**: 1101–1107.
23. Monnier L, Lapinski H, Colette C. Contributions of fasting and postprandial plasma glucose increments to the overall diurnal hyperglycemia of type 2 diabetic patients: variations with increasing levels of HbA(1c). Diabetes Care 2003; **26**: 881–885.
24. Nauck MA, Meininger G, Sheng D, Terranella L, Stein PP. Sitagliptin Study 024 Group. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor, sitagliptin, compared with the sulphonylurea, glipizide, in patients with type 2 diabetes inadequately controlled on metformin alone: a randomized, double-blind, non-inferiority trial. Diabetes Obes Metab 2007; **9**: 194–205.
25. Novo Nordisk Press Release. Available from URL: http://www.novonordisk.com/science/about_rd/quarterly_rd_update.asp. Accessed 24 September 2010.