Patient-directed titration for achieving glycaemic goals using a once-daily basal insulin analogue: an assessment of two different fasting plasma glucose targets - the TITRATE™ study

L. Blonde,1 M. Merilainen,2 V. Karwe2 and P. Raskin3 for the TITRATE™ Study Group

1Ochsner Diabetes Clinical Research Unit, Department of Endocrinology, Diabetes and Metabolic Diseases, Ochsner Medical Center, New Orleans, LA, USA
2Clinical Development, Medical and Regulatory Affairs, Novo Nordisk Inc., Princeton, NJ, USA
3University of Texas Southwestern Medical Center at Dallas, Department of Endocrinology, Dallas, TX, USA

Aims: To compare efficacy and safety of two fasting plasma glucose (FPG) titration targets [4.4–6.1 mmol/l (80–110 mg/dl) and 3.9–5.0 mmol/l (70–90 mg/dl)] using a patient-directed, treat-to-target algorithm for once-daily basal insulin in insulin-naïve subjects with type 2 diabetes suboptimally treated with oral antidiabetes drugs (OADs).

Methods: In this 20-week, randomized, controlled, open-label, multicentre, treat-to-target study, 244 insulin-naïve subjects with type 2 diabetes, HbA1c ≥7.0 and ≤9.0% on OAD treatment, were randomized (1:1) to one of two treatment arms using 3.9–5.0 or 4.4–6.1 mmol/l FPG as titration targets. Once-daily insulin detemir doses were adjusted using algorithm-guided patient-directed titration to achieve target FPG values.

Results: Overall, the combined treatment groups achieved a mean HbA1c level of 6.9% at the end of the study. Substantial reductions in HbA1c were seen in both treatment groups, with the majority of subjects in both titration groups at the end of the study achieving the American Diabetes Association (ADA)-recommended HbA1c level of <7%. In the 3.9–5.0 mmol/l FPG target treatment group, HbA1c values decreased from a baseline mean of 8.0% to 6.8% at 20 weeks. In the 4.4–6.1 mmol/l FPG target group, HbA1c values decreased from 7.9% at baseline to 7.0% at 20 weeks (Intention to treat - last observation carried forward data set). These decreases were significantly different between the two treatment groups (Least squares mean difference = −0.271, 95% CI −0.441 to −0.101, p = 0.0019), favouring the FPG target of 3.9–5.0 mmol/l vs. the 4.4–6.1 mmol/l target. At the end of the study period, 64.3% of subjects in the 3.9–5.0 mmol/l treatment group achieved HbA1c levels <7% compared with 54.5% of subjects in the 4.4–6.1 mmol/l group (95% CI 1.03–3.37, odds ratio 1.86, p = 0.04). Insulin detemir dosing patterns were similar between treatment groups, with the 3.9–5.0 mmol/l group using slightly greater doses throughout the study period (0.57 U/kg vs. 0.51 U/kg at the end of the study). Overall rates of hypoglycaemia episodes were low and were comparable between treatment groups (7.73 and 5.27 events/subject/year for the 3.9–5.0 and 4.4–6.1 mmol/l groups, respectively). A single event of major hypoglycaemia was reported in the 3.9–5.0 mmol/l group. Mean weight changes from baseline to the end of the study were small and did not differ significantly between treatment groups.

Conclusions: The 3.9–5.0 mmol/l FPG target showed superior efficacy compared with the 4.4–6.1 mmol/l target, although both FPG titration targets resulted in substantial reductions of HbA1c in patients with type 2 diabetes using a patient-directed insulin titration algorithm. A majority of subjects in both titration groups achieved the ADA-recommended guideline of <7% HbA1c at the end of the study with low rates of hypoglycaemia. These data indicate that lowering the fasting glucose target using a self-directed titration algorithm with once-daily detemir is safe and increases the likelihood of achieving the target level of HbA1c. Indeed, using this approach, a majority of patients can achieve an HbA1c of <7%.

Keywords: clinical trial, diabetes, insulin analogue, insulin detemir, treat-to-target, TITRATE™

Received 4 February 2009; returned for revision 18 February 2009; revised version accepted 22 February 2009

Correspondence: Lawrence Blonde, Ochsner Diabetes Clinical Research Unit, Department of Endocrinology, Diabetes and Metabolic Diseases, Ochsner Medical Center, New Orleans, LA, USA.
E-mail: l blonde@ochsner.org
**Introduction**

Good glycaemic control in type 2 diabetes is associated with reduced risk of complications [1,2]. Achieving this control can be difficult however, and the progressive nature of the disease (beta-cell deterioration) often requires insulin initiation in addition to lifestyle modifications and oral antidiabetes drugs (OADs).

The newer long-acting basal insulin analogues address many of the limitations of earlier intermediate-acting insulins such as Neutral Protamine Hagedorn (NPH). For example, insulin detemir has a 24-h duration of efficacy with no pronounced activity peak [3]. In euglycaemic clamp studies, insulin detemir has been associated with less within-patient variability, resulting in a more predictable pharmacodynamic response compared with either NPH or insulin glargine, another basal insulin analogue [3,4]. Within-subject fasting plasma glucose (FPG) variability also was consistently lower with insulin detemir compared with NPH insulin in a number of clinical trials in patients with type 1 and type 2 diabetes [5–13]. Importantly, the risk of hypoglycaemia has been shown to be lower in patients taking insulin detemir compared with NPH [6,8,13–15], and the weight gain often experienced by patients beginning insulin therapy has been shown to be lower with insulin detemir than for patients taking NPH or insulin glargine [16,17]. The low intrapatient variability and low rate of nocturnal hypoglycaemia observed with insulin detemir allow an evaluation of the efficacy and safety of lower FPG targets for insulin dose titration than are typically recommended to prescribers.

Recent data from the United Kingdom Prospective Diabetes Study suggest the importance of stringent glycaemic control [1] and current treatment guidelines call for early insulin treatment [18] in type 2 diabetes patients. However, optimal initiation and titration methods for the long-acting basal insulins are still being determined. Evidence suggests that many patients often do not have insulin doses titrated sufficiently to achieve target levels of glucose control (remaining on suboptimal doses and failing to reach treatment targets) [2,19]. What has become increasingly clear is that patient empowerment is essential for motivation to reach treatment targets. Self-titration regimens facilitate empowerment of patients, allowing them to become more involved in their treatment, which can result in improved glycaemic control. In one recent study, patient-directed titration of a biphasic insulin led to HbA1c decreases of approximately 2.5 percentage points [20]. In addition, patient self-management and patient-directed insulin titration are increasingly important as health-care practitioners often do not have the resources to advise patients with the frequency needed to effectively titrate their insulin doses.

This study assessed two different target FPG levels, each using the same overall titration regimen – the 3-0-3 patient-directed self-titration algorithm first used in the PREDICTIVE™ (Predictable Results and Experience in Diabetes Through Intensification and Control to Target: An International Variability Evaluation) 303 Study [21]. Described fully in the Methods of this manuscript (table 1), this simplified treatment strategy has been shown to be both effective and safe [21]. The trial utilized once-daily insulin detemir and a patient population with an entry HbA1c <9% as several studies have indicated that these patients are most likely to respond to basal insulin alone [22,23].

**Methods**

The study protocol was approved by independent ethics committees for each participating centre, and the study was conducted in accordance with the Declaration of Helsinki and Guidelines on Good Clinical Practice. All volunteers provided written informed consent prior to any study-related activities.

This was a 20-week, randomized, controlled, open-label, multicentre, randomized, parallel-group study comparing the safety and efficacy of insulin detemir administered once daily in combination with OADs when titrated to two FPG targets for the treatment of type 2 diabetes.

Study subjects were adults (≥18 years) diagnosed with type 2 diabetes at least 3 months before study participation, who were currently taking metformin ± sulphonylurea ± glinides ± thiazolidinedione (TZDs) at a stable dose for the past 3 months (at either the maximal tolerated dose or at least half of the maximum recommended dose according to package insert). To qualify for participation, insulin naïveté, a body mass index (BMI) ≤45 kg/m² and HbA1c between 7.0 and 9.0% (inclusive) were required. Women who were pregnant, breast feeding or unwilling to use adequate contraception were ineligible. Other

<table>
<thead>
<tr>
<th>Table 1 Insulin detemir titration algorithm</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Average fasting plasma glucose of three consecutive days</strong></td>
<td><strong>Insulin detemir dose adjustment</strong></td>
</tr>
<tr>
<td>Using 3.9–5.0 mmol/l target (mmol/l)</td>
<td></td>
</tr>
<tr>
<td>&lt;3.9</td>
<td>−3 units</td>
</tr>
<tr>
<td>3.9–5.0</td>
<td>No adjustment</td>
</tr>
<tr>
<td>&gt;5.0</td>
<td>+3 units</td>
</tr>
<tr>
<td>Using 4.4–6.1 mmol/l target (mmol/l)</td>
<td></td>
</tr>
<tr>
<td>&lt;4.4</td>
<td>−3 units</td>
</tr>
<tr>
<td>4.4–6.1</td>
<td>No adjustment</td>
</tr>
<tr>
<td>&gt;6.1</td>
<td>+3 units</td>
</tr>
</tbody>
</table>
exclusion criteria included known or suspected allergies to trial products, previous participation in any trial within the past 3 months and current substance abuse. No subject had any condition that would interfere with participation, and none was receiving other treatments that would interfere with glucose metabolism.

After a 2-week screening period, eligible subjects were randomized to one of two FPG target titration arms: 3.9–5.0 mmol/l (70–90 mg/dl) or 4.4–6.1 mmol/l (80–110 mg/dl), and began using insulin detemir 0.1–0.2 U/kg or 10 U once daily at dinner or bedtime. Participants continued their OAD use at stable doses during the trial; however, dose reduction or discontinuation of sulphonylureas or glinidines was allowed (at investigator’s discretion) if a subject was experiencing hypoglycaemia. Subjects self-titrated their insulin dose every 3 days according to the mean of self-measured FPG values the three previous days using the forced titration algorithm described in the PREDICTIVE 303 study (table 1) [21]. FPG was determined by patient self-monitoring of capillary blood glucose (Precision Xtra; Abbott Diabetes Care, Alameda, CA, USA).

To facilitate the subjects’ involvement in the management of their disease and thereby support patient empowerment, a non-electronic patient tool was developed. This simple patient card was specific for each FPG target and was provided to all trial participants to assist with calculations of FPG means and dosing. In addition to this patient card and standard patient education practices offered during the trial’s five office visits and frequent phone contacts with investigators, all subjects were offered two complimentary education and counselling sessions with an experienced certified diabetes educator and the patient training booklet ‘Living with Diabetes – An Everyday Guide for You and Your Family’ produced by the American College of Physicians.

Efficacy Parameters

HbA1c and FPG were assessed as measures of efficacy. The primary end-point was the proportion of subjects reaching HbA1c levels <7% at 20 weeks.

Safety Parameters

Episodes of hypoglycaemia were recorded at each trial visit and classified as major (requiring third party assistance), minor (Self measured plasma glucose (SMPG) <3.1 mmol/l and not requiring third party assistance) or symptoms only (SMPG ≥3.1 mmol/l or no measurement). Episodes occurring between 11pm and 6am were classified as nocturnal. Adverse event information was collected throughout the trial period. Weight, BMI and vital signs were recorded at each visit, and standard laboratory parameters were assessed at the beginning and at the end of the study.

Statistical Analyses

Sample Size Determination

Two hundred subjects (100 per treatment arm) were required to provide a power of 80% to demonstrate non-inferiority for the primary efficacy end-point. This sample size is also sufficient to show superiority in the proportion of patients reaching HbA1c <7% for the 3.9–5.0 mmol/l arm compared with the 4.4–6.1 mmol/l arm under the assumption that the first proportion is greater than the second by at least 20%. Given a predicted withdrawal rate of 15% and a predicted screen failure rate of 50%, 472 subjects were required for screening.

Efficacy Analyses

The primary efficacy end-point was assessed by two methods: (i) estimating a proportion of responders among subjects with non-missing HbA1c values and (ii) using the odds ratio (OR) estimated from logistic regression with baseline HbA1c as a covariate. Analyses for primary and secondary end-points were performed on intention-to-treat (ITT) and per-protocol populations, with ITT results considered primary results to support efficacy. For ITT analyses, any subjects without post-randomization HbA1c data were considered not to have achieved HbA1c <7%. The proportion of subject with HbA1c ≤6.5% at the end of the trial was analysed analogously to that of the primary end-point.

The change in HbA1c from baseline, HbA1c at the end of the trial and laboratory-measured FPG values at the end of trial were analysed using a generalized linear model with titration groups included as fixed effect and baseline HbA1c as a covariate.

Safety Analyses

Hypoglycaemia was analysed using a generalized linear model. A Poisson model was used for the number of events/subject/year, and Fisher’s exact test was used for the percentage of subjects reporting at least one episode.

Results

Demographics and Baseline Characteristics of the Subject Population

Of 244 randomized subjects, 243 were exposed to insulin detemir (safety population) and 243 were included in the
efficacy analysis (figure 1). Baseline characteristics were generally similar between study groups (table 2), with the exceptions of a slightly higher percentage of men in the 4.4–6.1 mmol/l group (63.9% vs. 55.7% for the 3.9–5.0 mmol/l group) and a longer duration of diabetes (9.0 years for the 4.4–6.1 mmol/l group vs. 7.9 years for the 3.9–5.0 mmol/l group). Current diabetes therapies were identical for both treatment groups, with 30 (25%) subjects in each taking metformin alone and 92 (75%) subjects in each taking metformin plus one or more other OADs.

Baseline glycaemic control was comparable between treatment groups. Mean HbA1c values were 7.99% and 7.94% for the 3.9–5.0 and 4.4–6.1 mmol/l groups – considerably above the American Diabetes Association (ADA)-recommended HbA1c for which intensification of diabetes therapy is appropriate for most patients. Mean baseline FPG values were 9.1 mmol/l for each treatment group.

**Efficacy Results**

**Primary End-point – Proportion of Subjects Reaching HbA1c levels <7% at 20 Weeks (ITT Population)**

At the end of the 20-week study period, 64.3% of subjects in the 3.9–5.0 mmol/l treatment group achieved HbA1c levels <7% compared with 54.5% of subjects in the 4.4–6.1 mmol/l group (95% CI 1.03–3.37, OR 1.86, p = 0.04; figure 2a). Thus, the FPG target of 3.9–5.0 mmol/l was determined to be superior to the 4.4–6.1 mmol/l target for achieving the target HbA1c level.

**Secondary Efficacy End-points**

At the end of the study, 41.1% of subjects in the 3.9–5.0 mmol/l treatment group achieved HbA1c levels ≤6.5% compared with 26.8% of subjects in the 4.4–6.1 mmol/l group (95% CI 1.27–4.30, OR 2.34, p = 0.01; figure 2a).

---

**Table 2** Baseline characteristics of all randomized subjects

<table>
<thead>
<tr>
<th></th>
<th>3.9–5.0 mmol/l</th>
<th>4.4–6.1 mmol/l</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>All randomized</td>
<td>122</td>
<td>122</td>
<td>244</td>
</tr>
<tr>
<td>subjects (N)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex, N (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>68 (55.7)</td>
<td>78 (63.9)</td>
<td>146 (59.8)</td>
</tr>
<tr>
<td>Female</td>
<td>54 (44.3)</td>
<td>44 (36.1)</td>
<td>98 (40.2)</td>
</tr>
<tr>
<td>Age (mean years)</td>
<td>56.6</td>
<td>57.2</td>
<td>56.9</td>
</tr>
<tr>
<td>Ethnicity, N (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hispanic/Latino</td>
<td>35 (28.7)</td>
<td>32 (26.2)</td>
<td>67 (27.5)</td>
</tr>
<tr>
<td>Not Hispanic/Latino</td>
<td>87 (71.3)</td>
<td>90 (73.8)</td>
<td>177 (72.5)</td>
</tr>
<tr>
<td>Race, N (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>96 (78.7)</td>
<td>99 (81.1)</td>
<td>195 (79.9)</td>
</tr>
<tr>
<td>African American</td>
<td>20 (16.4)</td>
<td>17 (13.9)</td>
<td>37 (15.2)</td>
</tr>
<tr>
<td>Asian</td>
<td>2 (1.6)</td>
<td>1 (0.8)</td>
<td>3 (1.2)</td>
</tr>
<tr>
<td>American Indian/Alaskan</td>
<td>0</td>
<td>1 (0.8)</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>Native Hawaiian/PI</td>
<td>0</td>
<td>1 (0.8)</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>Other</td>
<td>4 (3.3)</td>
<td>3 (2.5)</td>
<td>7 (2.9)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>170.1</td>
<td>171.2</td>
<td>170.7</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>95.9</td>
<td>98.6</td>
<td>97.3</td>
</tr>
<tr>
<td>Body mass (kg/m²)</td>
<td>33.0</td>
<td>33.6</td>
<td>33.3</td>
</tr>
<tr>
<td>Duration of diabetes (years)</td>
<td>7.9</td>
<td>9.0</td>
<td>8.4</td>
</tr>
<tr>
<td>Current diabetes therapy, N (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metformin</td>
<td>30 (25)</td>
<td>30 (25)</td>
<td>60 (25)</td>
</tr>
<tr>
<td>Metformin + oral</td>
<td>92 (75)</td>
<td>92 (75)</td>
<td>184 (75)</td>
</tr>
</tbody>
</table>

---

**Fig. 1** Subject flow diagram. The number of patients at baseline, reasons for withdrawal, number of patients completing the study and the number of patients included in the efficacy and safety analysis sets are indicated. *Withdrawal numbers reflect primary reasons for withdrawal as entered in patient case report forms. ITT, intention to treat. AE, adverse event.
HbA1c values throughout the study period are shown in figure 2b. The mean HbA1c value at the end of the study was 6.9% for the combined treatment groups. In the 3.9–5.0 mmol/l treatment group, HbA1c values dropped from a baseline mean of 7.99% to 6.77% at 20 weeks (Intention to Treat - Last Observation Carried Forward [ITT-LOCF]), while HbA1c values decreased from 7.94% at baseline to 7.00% at 20 weeks (ITT-LOCF) in the 4.4–6.1 mmol/l group. These decreases in HbA1c were significantly different from both baseline and between the two treatment groups (Least Squares [LS] mean difference $= -0.271$, 95% CI $= -0.441$ to $-0.101$, $p = 0.0019$).

Approximately 45% (50/112) of subjects in each treatment group achieved an HbA1c level $< 7\%$ without hypoglycaemia during the last 4 weeks of observation, and HbA1c levels $\leq 6.5\%$ without hypoglycaemia were attained by 26% (29/112) and 21% (24/112) of subjects in the 3.9–5.0 and 4.4–6.1 mmol/l groups, respectively (table 3).

### Fasting Plasma Glucose

FPG values for both treatment groups throughout the study period are shown in figure 3. FPG values decreased throughout the first 8 weeks of the study and then generally remained flat for each treatment group. An end-of-study ITT-LOCF calculation showed no significant differences in mean FPG values between treatment groups [LS mean of (3.9–5.0 mmol/l) – (4.4–6.1 mmol/l): $=-8.020$, 95% CI $=-16.587$ to $0.548$, $p = 0.0664$].

### Insulin Dosing

As specified in the trial protocol, all study participants were to administer insulin detemir once daily at dinner or bedtime. Weight-adjusted insulin detemir dosing from baseline to the end of the study is shown for both treatment groups in figure 4. Dosing patterns were similar between treatment groups, with the 3.9–5.0 mmol/l group using slightly greater doses throughout the study period.

### Table 3 Proportion of subjects achieving HbA1c levels $< 7\%$ and $\leq 6.5\%$ without hypoglycaemia during last 4 weeks of observation

<table>
<thead>
<tr>
<th>Population</th>
<th>3.9–5.0 mmol/l</th>
<th>4.4–6.1 mmol/l</th>
<th>Significance (OR; p value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ITT-LOCF ($&lt; 7%$)</td>
<td>44.6 (50/112)</td>
<td>44.6 (50/112)</td>
<td>NS (1.07; 0.7968)</td>
</tr>
<tr>
<td>ITT-LOCF ($\leq 6.5%$)</td>
<td>25.9 (29/112)</td>
<td>21.4 (24/112)</td>
<td>NS (1.42; 0.2814)</td>
</tr>
</tbody>
</table>

ITT-LOCF, Intent to Treat - Last Observation Carried Forward; OR, odds ratio. NS, not significant.
the end of the study, the mean weight-adjusted insulin detemir dose was 0.57 U/kg for the 3.9–5.0 mmol/l treatment group and 0.51 U/kg for the 4.4–6.1 mmol/l [LS mean of (3.9–5.0 mmol/l) – (4.4–6.1 mmol/l): 0.077, 95% CI −0.001 to 0.156, p = 0.0533].

Body Weight

Overall, mean weight changes at the end of the study were small and not significantly different between treatment groups. Body weight increased by 0.89 ± 0.36 kg in the 3.9–5.0 mmol/l group and by 0.12 ± 0.36 kg in the 4.4–6.1 mmol/l group [LS mean of (3.9–5.0 mmol/l) – (4.4–6.1 mmol/l): 0.77, 95% CI –0.226 to 1.765, p = 0.13].

A summary of changes in body weight by baseline BMI subgroup is shown in figure 5. In the 3.9–5.0 mmol/l treatment group, mean body weight changes ranged from −0.33 kg in the >40 BMI subgroup to 1.86 kg in the 25 to ≤30 BMI subgroup. In the 4.4–6.1 mmol/l group, mean body weight changes ranged from −0.63 kg in the 30 to ≤35 BMI subgroup to 1.35 kg in the ≤25 BMI subgroup. A trend to better weight benefit of insulin detemir with increasing BMI was noted.

Vital Signs and Laboratory Parameters

There were no clinically significant changes from baseline to study end-point of any vital sign or laboratory parameter.

Safety Results

Hypoglycaemic Events

The overall rates of hypoglycaemic episodes (events/subject/year) were low and were comparable between treatment groups (table 4). Altogether, 52% of subjects in the 3.9–5.0 mmol/l treatment group and 41% in the 4.4–6.1 mmol/l group reported hypoglycaemic events; the rates for the two target fasting glucose levels were 7.73 and 5.27 events/subject/year, respectively (p = 0.0811). Almost all hypoglycaemic events were considered minor or symptoms only; a single major hypoglycaemic event was reported by a subject in the 3.9–5.0 mmol/l treatment group. The rates of nocturnal hypoglycaemic episodes were also similar; these events were reported by 30.6% and 20.5% of the 3.9–5.0 and 4.4–6.1 mmol/l treatment groups, resulting in rates of 2.74 and 2.02 events/subject/year, respectively (p = 0.3177). All nocturnal hypoglycaemic events were considered minor or symptoms only.
Other Adverse Events

A total of 42.1% (51/121) of patients in the 3.9–5.0 mmol/l safety population reported 152 treatment-emergent adverse events (TEAEs), and 36.1% (44/122) of patients in the 4.4–6.1 mmol/l safety population reported 110 TEAEs. Overall, five subjects in the 3.9–5.0 mmol/l treatment group and three subjects in the 4.4–6.1 mmol/l group withdrew from the trial because of adverse events.

A total of four serious adverse events (SAEs), including one judged by the investigator to be possibly related to the trial drug (pneumonia), were reported by four patients in the 4.4–6.1 mmol/l treatment group. Eleven SAEs were reported by five patients in the 3.9–5.0 mmol/l group; all were considered unlikely to be related to trial drug.

Discussion

This is the first prospective randomized study to examine the effect of FPG targets on glycaemic control using a patient-directed titration of once-daily insulin detemir. Both FPG targets were effective: the combined overall average HbA1c was below the ADA-recommended level of <7%, with the majority of subjects in both treatment groups achieving this level of glycaemic control. The more aggressive 3.9–5.0 mmol/l target was shown to be superior, however, with reasonably minor differences in FPG translating into a significant difference in HbA1c. However, it should be noted that a minority of subjects actually reached the FPG target in the 3.9–5.0 mmol/l group, and that clinical judgement was used to sometimes increase detemir by less than 3 U as patients approached target FPG. Nevertheless, aiming for the lower FPG target was associated with attainment of lower HbA1c levels.

Importantly, the clinically significant reductions in HbA1c seen in this trial occurred safely. Overall rates of hypoglycaemia were low and did not differ significantly between groups. Nearly 50% of the subjects in each treatment arm reached an HbA1c <7% with no hypoglycaemic events within the last 4 weeks of observation. Hypoglycaemic episodes were almost exclusively minor or symptoms only, with a low incidence of nocturnal hypoglycaemic events despite once-daily administration of insulin detemir in the evening. This safety profile, coupled with the superior efficacy of the 3.9–5.0 mmol/l titration arm, suggests that we can safely lower FPG targets in this patient population to more aggressively help patients achieve HbA1c goals. These findings provide a clinical correlate to the pharmacokinetic properties of insulin detemir with 24-h efficacy, a relatively flat time-action profile, and very low intrapatient variability.

The results reported here compare favourably with those of other studies of basal insulin analogues. In a recent study of once-daily insulin glargine in patients with type 2 diabetes, the percentages of subjects who reached the end of the study HbA1c levels <7 and ≤6.5% were similar (66 and 38%, respectively), despite a starting population with better glycaemic control (HbA1c inclusion criteria of 7%–8% vs. the 7%–9% used in this trial) [24]. In a comparison by Davies et al. of two treatment algorithms using insulin glargine in subjects with type 2 diabetes, only 30% of subjects using a patient-directed titration algorithm reached the target HbA1c level of <7% at study end, and this occurred with small but statistically significant weight gain [19].

Our results also compare favourably with the recent 1-year basal analogue results of the 4T study [22], with greater percentages of subjects reaching glycaemic targets and with less weight gain. We believe that the patient-friendly design of the TITRATE™ (Treat to target with once-daily Insulin Therapy: Reduce A1C by Titrating Effectively) study, with its focus on patient education and empowerment, addresses some issues associated with 4T. The use of the simple PREDICTIVE
303 titration algorithm allowed for more frequent dose adjustment than was possible in the 4T study. Furthermore, unlike 4T, this study did not require a computerized system that may have separated both health-care professionals and patients from the titration process. The patient education materials and counselling sessions offered in the TITRATE™ trial may also have contributed to the positive results of this study.

Patients with type 2 diabetes are often reluctant to begin insulin therapy owing to concerns such as weight gain, hypoglycaemia and fear of injections. The results of TITRATE™ show that empowering patients to adjust their basal insulin dose by simple, patient-directed, titration algorithms can lead to measurable improvements in their condition and that insulin detemir can provide the means by which patients can achieve their treatment goals with little effect on weight, a low risk of hypoglycaemia and 24-h efficacy (once-daily use).

Furthermore, these results suggest that the pharmacokinetic/pharmacodynamic properties of insulin detemir may allow it to be used with lower FPG targets, which may be beneficial not only for patient-directed titration but also for physician-directed titration to bring patients closer to goal.

Acknowledgements

We would like to thank the patients and investigators of the TITRATE™ study group for participating in this trial. This trial was funded and monitored by Novo Nordisk. Larry Blonde has received grant/research support from Amylin Pharmaceuticals, Eli Lilly and Company, MannKind Corporation, Merck & Co., Inc., Novo Nordisk, Novartis Corporation, Pfizer Inc, Roche and sanofi aventis, and has received honoraria from Abbott, Amylin Pharmaceuticals, AstraZeneca, Biodel Inc, Boehringer Ingelheim Pharmaceuticals, Inc, Bristol-Myers Squibb, Daiichi Sankyo, Eli Lilly and Company, GlaxoSmithKline, LifeScan, Merck & Co., Inc., Novartis Corporation, Novo Nordisk, Pfizer Inc, Roche and sanofi aventis. Dr. Blonde has also disclosed that his spouse is a stock shareholder of Amylin Pharmaceuticals and Pfizer, Inc, in an account that is not part of their community property.

Philip Raskin has received research support from Amylin Pharmaceuticals, Bayhill Therapeutics, Biodel Inc., Boehringer Ingelheim Pharmaceuticals, EliXer Pharmaceuticals, Generex Biotechnology, Hoffmann-La Roche, Johnson & Johnson Pharmaceutical Research and Development, Keryx Biopharmaceuticals, MannKind Corporation, Novo Nordisk, Osiris Therapeutics Inc., Pfizer, sanofi aventis, and Tolerx; is an adviser for AstraZeneca, MannKind Corporation., Novo Nordisk, Inc., and Quigley Pharma Inc.; and is on speakers bureaus for Merck & Co., Inc. and Novo Nordisk, Inc.

Markus Merilainen and Vatsala Karwe are employees of Novo Nordisk. Brian Geldziler, an employee of Novo Nordisk, provided assistance with manuscript preparation.

References


14 De Li, 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.


