ORIGINAL ARTICLE doi: 10.1111/j.1463-1326.2005.00563.x

Attainment of glycaemic goals in type 2 diabetes with once-, twice-, or thrice-daily dosing with biphasic insulin aspart 70/30 (The 1-2-3 study)

A. J. Garber,[1] J. Wahlen,[2] T. Wahl,[3] P. Bressler,[4] R. Braceras,[5] E. Allen,[5]* and R. Jain[6]

[1]Baylor College of Medicine, Houston, TX, USA
[2]Endocrine Research Specialists, Ogden, UT, USA
[3]Internal Medicine Associates Research Center, Omaha, NE, USA
[4]Endocrine and Diabetes Associates, Dallas, TX, USA
[5]Novo Nordisk, Princeton, NJ, USA
[6]Milwaukee Medical Clinic, Advanced Healthcare, Milwaukee, WI, USA

Aim: This observational study in patients with type 2 diabetes failing oral agent therapy with or without basal insulin was conducted to assess whether addition and self-titration of biphasic insulin aspart 70/30 (BIAsp 30) could achieve American Association of Clinical Endocrinologists (AACE)/International Diabetes Federation (IDF) and American Diabetes Association (ADA) glycemic targets (HbA_{1c} $\leq$6.5 and <7%).

Methods: Enrolled patients (n = 100, HbA_{1c} $\geq$7.5 and $\leq$10%) were $\geq$18 years of age, had diabetes $\geq$12 months and had received a stable antidiabetic regimen for at least 3 months [minimum of two oral antidiabetic drugs (OADs) or at least one OAD plus once-daily basal insulin $\leq$60 U]. Patients discontinued prior basal insulin and added one injection of BIAsp 30 (12 U or 70–100% of prior basal insulin dose within 15 min of dinner initiation). Patients self-titrated their BIAsp 30 dose with investigator guidance every 3 or 4 days to achieve pre-breakfast fasting blood glucose (FBG) of 80–110 mg/dl. At 16 weeks, a pre-breakfast injection of 6 U of BIAsp 30 was added if week 15 HbA_{1c} exceeded 6.5%; the added dose was titrated to achieve pre-dinner BG of 80–110 mg/dl. After an additional 16 weeks, 3 U of pre-lunch BIAsp 30 was added if HbA_{1c} exceeded 6.5%. This added dose was adjusted based on 2-h post-lunch BG to achieve postprandial glucose of 100–140 mg/dl. Subjects achieving an HbA_{1c} $\leq$6.5% at 15 and 31 weeks completed the study at weeks 16 and 32 respectively.

Results: Addition of once-daily BIAsp 30 before dinner enabled 21% of the patients to achieve AACE and IDF targets (HbA_{1c} $\leq$6.5%) and 41% to achieve ADA targets (HbA_{1c} <7%). With two daily injections of BIAsp 30, these glycaemic goals were achieved by 52 and 70% of subjects. With three daily BIAsp 30 injections, 60% of patients achieved HbA_{1c} $\leq$6.5%, and 77% achieved HbA_{1c} <7.0%.

Conclusions: This clinical trial demonstrates that initiation of once-daily BIAsp 30 to type 2 diabetes patients poorly controlled on various OAD regimens was an effective treatment approach for achieving glycaemic goals. Additional patients safely achieved these goals by increasing the number of BIAsp 30 injections from one to two, and then, if uncontrolled, from two to three doses per day. Eventually, most patients previously uncontrolled on OADs with or without basal insulin were controlled by the addition and vigorous titration of BIAsp 30 to oral agent therapy.

Keywords: BIAsp, insulin initiation, OAD failures, premixed insulin analogue, treatment algorithm
Received 20 September 2005; returned for revision 17 October 2005; revised version accepted 17 October 2005

*Current address: Bristol Myers Squibb, Princeton, NJ, USA.
Correspondence:
Alan J. Garber, MD, PhD, Baylor College of Medicine, BCM Faculty Center, 1709 Dryden Road, Suite 1000, Houston, TX 77030, USA.
E-mail:
agarber@bcm.tmc.edu

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Introduction

As a result of the landmark United Kingdom Prospective Diabetes Study (UKPDS) [1], the clinical importance of glycaemic control in patients with type 2 diabetes is well established. The American Diabetes Association (ADA) estimates that the risk of diabetes-related mortality increases 25% for each 1% increase in HbA_{1c} [2]. Each percentage point increase in HbA_{1c} has also been estimated to correspond to a 35% increase in the risk of microvascular complications and an 18% increase in the risk of myocardial infarction (fatal plus non-fatal) [2].

In order to reduce the consequences of poor glycaemic control, the ADA recommends a treatment goal of HbA_{1c} levels less than 7% [3]. The American Association of Clinical Endocrinologists (AACE) and the International Diabetes Federation (IDF) recommend an even more aggressive goal of 6.5% or lower [4]. The Diabetes Control and Complications Trial and the UKPDS were instrumental in setting HbA_{1c} targets by the ADA and IDF respectively [5,6]. Because postprandial hyperglycaemia has been implicated as a risk factor for macrovascular complications and cardiovascular disease, AACE has recommended aggressive treatment goals for 2-h postprandial glucose (140 mg/dl or less) as well as for fasting plasma glucose (110 mg/dl or less) [7–12]. Despite the known consequences of poor control and these current recommendations, glycaemic control remains inadequate for many patients with diabetes [13].

Traditional therapy for patients with type 2 diabetes has primarily focused on controlling FPG levels with one or more oral antidiabetic drugs (OADs) and/or basal insulin. Although both fasting and postprandial blood glucose levels contribute to glycaemic control, these types of treatment regimens do not provide for control of postprandial blood glucose levels. Recently, the IDF, in their treatment guidelines for type 2 diabetes, has recommended the use of premixed insulin formulations as a treatment option to initiate insulin therapy, particularly for patients with higher HbA_{1c} values [14]. Premixed insulin formulations have both basal and fast-acting insulin capabilities, enabling them to cover both fasting and postprandial blood glucose levels.

Biphasic insulin aspart (BIAsp 30, marketed as NovoLog® Mix 70/30 in the US and as NovoMix® 30 elsewhere) is a premixed insulin analogue consisting of 30% soluble rapid-acting insulin aspart and 70% protaminated insulin aspart. The soluble component of BIAsp 30 targets postprandial BG levels and is absorbed more rapidly and rises to a higher peak serum insulin level in comparison to the soluble component of conventional premixed human insulin 70/30 [15–17]. The earlier and more pronounced peak of the rapid-acting component gives BIAsp 30 an advantage over human insulin 70/30 by being more efficacious at covering postprandial glycaemia. The protaminated insulin aspart component of BIAsp 30 has a prolonged absorption profile and provides basal insulin coverage.

The purpose of this clinical study was to assess if patients with type 2 diabetes and in poor glycaemic control can achieve the AACE target level for HbA_{1c} ($\leq$6.5%) when treated with BIAsp 30 once-, twice-, or thrice-daily in addition to their existing OAD treatment. The study was designed to simulate clinical practice and used a predetermined dose-escalation algorithm specifically designed to help patients self-adjust their insulin dose to attain the AACE target goal.

Methods

Eligible patients had type 2 diabetes for at least 12 months, were 18 years of age or older, and had HbA_{1c} values between 7.5 and 10% on a stable diabetes therapy regimen of at least 3 months duration. The previous regimen was to consist of either (1) treatment with two or more OADs or (2) treatment with one OAD and a basal insulin (insulin glargine or NPH insulin, no more than 60 U/day). The OAD doses were to be at least one-half of the maximum allowed daily dose. Enrolled patients did not have significant cardiac disease (NYHA class III or IV CHF, unstable angina, and/or any myocardial infarction) within 6 months prior to screening or hepatic insufficiency (ALT or AST is greater than or equal to twice the upper reference limit or renal insufficiency (serum creatinine $\geq$1.6 mg/dl for males; 1.4 mg/dl for females).

Study Design and Treatment

This 48-week, open-label, observational study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines at 13 investigative sites in the US [18]. All patients provided written informed consent.

The study consisted of a screening period and three 16-week treatment phases (figure 1). During each treatment phase, the patients either visited or were contacted by the clinic once weekly for the first eight weeks and then at weeks 10, 12, 15, and 16.

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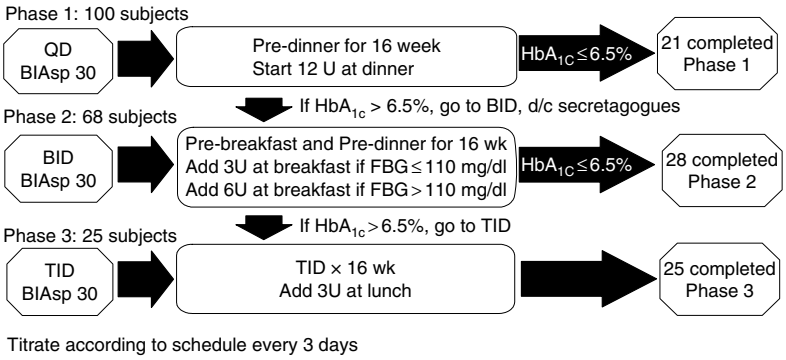

Fig. 1 Study diagram. QD, once daily; BID, twice daily; TID, thrice daily.

In Phase 1, patients added a once-daily injection of BIAsp 30 (within 15 min of dinner) to their OAD regimen. Patients previously on insulin discontinued their insulin upon starting BIAsp 30. Insulin-naive patients began treatment with 12 U of BIAsp 30. Patients previously taking insulin injected either the same number of units of BIAsp 30 as their pre-study basal insulin dose (up to 30 U) or 70% of their pre-study basal insulin dose if they were taking >30 U. Patients were instructed to self-adjust their pre-dinner BIAsp 30 dose every 3–4 days on the basis of an average of three previous pre-breakfast self-measured blood glucose (SMBG) values. The dose-adjustment algorithm and target SMBG values used for the three phases are shown in table 1.

Patients who achieved an HbA_{1c} value of ≤6.5% at the end of Phase 1 were identified as completers of the study. Patients who did not achieve this target continued into Phase 2 and added a second injection of BIAsp 30 before breakfast (BIAsp 30 twice daily). Patients with pre-breakfast SMBG values ≤110 mg/dl injected 3 U before breakfast; patients with pre-breakfast SMBG values >110 mg/dl injected 6 U. Patients were instructed to adjust their pre-breakfast and dinner doses every 3–4 days on the basis of pre-breakfast or pre-dinner SMBG values respectively. Any oral insulin secretagogues used during Phase 1 were discontinued before the patient entered Phase 2.

Patients who achieved an HbA_{1c} value of ≤6.5% at the end of Phase 2 were also identified as completers of the study. The remaining patients continued into Phase 3 and added a third injection of 3 U BIAsp 30 before lunch (BIAsp 30 thrice a day). Patients were instructed to adjust their pre-lunch dose every 3–4 days on the basis of 2-h post-lunch SMBG values. Patients were allowed to adjust their pre-breakfast or pre-dinner doses but were cautioned not to adjust more than one BIAsp 30 dose at a time. All patients completing the 16 weeks of Phase 3 were also identified as completers of the study.

BIAsp 30 was administered with the pre-filled (3 ml, 100 U/ml) NovoLog® Mix 70/30 FlexPen™ delivery system (Novo Nordisk, Bagsvaerd, Denmark).

Assessments

Blood samples for assessment of HbA_{1c} and fasting plasma glucose were obtained at screening and at week 15 of each treatment phase. HbA_{1c} was assayed at Medical Research Laboratories, Highland Heights, KY, USA. The patients were provided with blood glucose

Table 1 BIAsp 30 dose-adjustment algorithm

Pre-dinner dose					
Pre-breakfast SMBG (mg/dl)	<80	80–110	111–140	141–180	>180
Adjustment of pre-dinner dose (U)	−3	No change	+3	+6	+9
Pre-breakfast dose					
Pre-dinner SBMG (mg/dl)	<80	80–110	111–140	141–180	>180
Adjustment of pre-breakfast dose (U)	−3	No change	+3	+6	+9
Pre-lunch dose					
2-h post-lunch SMBG (mg/dl)		<100	100–140	141–180	>180
Adjustment of pre-lunch dose (U)		−3	No change	+3	+6

BIAsp 30, biphasic insulin aspart 70/30; SMBG, self-measured blood glucose. Titration was followed as specified unless an episode of hypoglycaemia occurred. Pre-dinner BIAsp 30 doses were titrated based on pre-breakfast BG values. Pre-breakfast BIAsp 30 was adjusted based on pre-dinner BG values. Pre-lunch insulin was adjusted according to post-lunch BG values.

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meters (OneTouch® Ultra®, LifeScan, Milpitas, CA, USA) and diaries and were instructed to perform eight-point SMBG (before and 2 h after breakfast, lunch, and dinner, 22:00 hours, 3 hours) assessments a few days before screening and before the end of each treatment phase. Blood glucose meters were calibrated to read plasma glucose values.

Patients were taught how to recognize the signs and symptoms of hypoglycaemia and instructed to obtain and record a blood glucose reading whenever symptoms of hypoglycaemia occurred. Hypoglycaemic episodes were classified as major if blood glucose was <56 mg/dl with CNS symptoms which the patient was unable to treat himself/herself. Events were classified as minor if blood glucose was <56 mg/dl with symptoms which were handled by the patient or any asymptomatic blood glucose value <56 mg/dl.

Safety was also assessed by general physical examination, assessment of vital signs, ECG readings, clinical haematology and chemistry, urinalysis, and reporting of adverse events. Assessment of plasma lipids (HDL, LDL, total cholesterol, triglycerides and free fatty acids) was also performed.

Statistical Analysis

All patients who took at least one dose of study medication were included in intent-to-treat (ITT) analyses of efficacy and safety. Patients who completed any of the treatment phases were also included in completer analyses of efficacy. For appropriate assessments (e.g. HbA_{1c}), missing values were imputed by carrying forward the previous value (last observation carried forward, LOCF). Data from patients who had prematurely discontinued the study were included in the analyses up to the point of discontinuation. Point estimates and relative confidence intervals were constructed for endpoints assessing percentages. A binomial distribution method was used to assess the percentage and 95% confidence intervals of patients achieving target HbA_{1c} values of $\leq$6.5% (AACE) or <7% (ADA) in each treatment phase. Unless otherwise noted, values presented in the results represent mean ± 1 s.d.

Results

Patients

The baseline characteristics of the 100 patients enrolled in the study are summarized in table 2. Most patients (72%) were being treated with two or more OADs and 28% were being treated with an insulin/OAD(s) regimen. Twenty-six patients withdrew from the study: seven due to non-compliance (six in Phase 1 and one in Phase 2), five due to adverse events (one in Phase 1 and four in Phase 2), one due to ineffective therapy (Phase 1) and 13 (three in Phase 1 and 10 in Phase 2) due to other reasons. No patients discontinued because of hypoglycaemia or weight gain at any time during the study. Of the 26 patients who discontinued the study, 12 had HbA_{1c} <7% when they discontinued in Phase 1 (3 patients) or Phase 2 (9 patients). Three of the 26 patients who withdrew had achieved an HbA_{1c} value of $\leq$6.5% but were not classified as completers because they withdrew before the end of Phase 2.

Glycaemic Control

Once-daily dosing of BIAsp 30 enabled 21% of all patients (95% CI: 13.5 to 30.3) to achieve the AACE HbA_{1c} target $\leq$6.5% and 41% of all patients (95% CI: 31.3 to 51.3) to achieve the ADA HbA_{1c} target <7.0%

Table 2 Demography and baseline characteristics

	Once-daily Phase 1	Twice-daily Phase 2	Thrice-daily Phase 3
n	100	68	25
Age (years)	56.7 ± 11.5	58.0 ± 11.2	57.7 ± 10.2
Race (B/C/H/O) (n)	12/73/13/2	9/50/8/1	4/17/3/1
Gender (female/male) [n (%)]	50(50)/50(50)	29(43)/39(57)	9(36)/16(64)
BMI (kg/m^2)	34.2 ± 6.7	33.9 ± 6.6	33.4 ± 5.8
Duration of diabetes (years)	11.1 ± 7.1	12.0 ± 7.3	12.1 ± 7.8
HbA_{1c} (%)	8.6 ± 0.8	8.7 ± 0.8	8.7 ± 0.7
Previous treatment [n (%)]			
OAD	72 (72)	46 (68)	18 (72)
OAD + glargine	18 (18)	15 (22)	6 (24)
OAD + NPH	10 (10)	7 (10)	1 (4)

OAD, oral antidiabetic drug. Values represent mean ± s.d. or as otherwise noted. For race: B, Black/African American; C, Caucasian; H, Hispanic; O, other.

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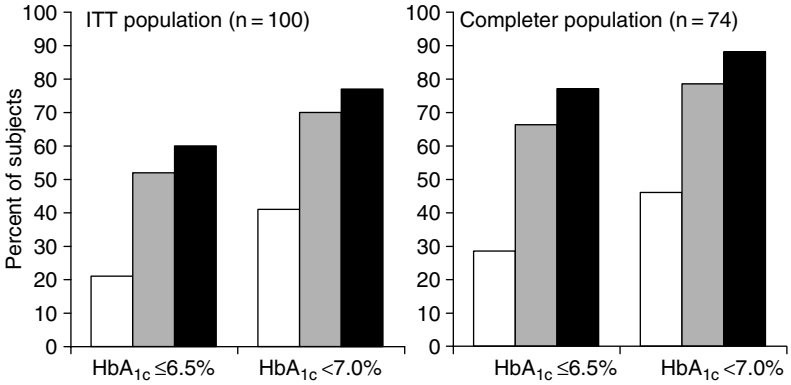

Fig. 2 Cumulative percentage of subjects who reached target HbA_{1c} values. ITT population is comprised of all patients enrolled in the trial. The completer population is comprised of all patients who adhered to the titration schedule and completed the trial.

(figure 2). After twice-daily dosing of BIAsp 30 during Phase 2, the majority of all patients were able to achieve the AACE HbA_{1c} target $\leq$6.5%. By the end of the study, 60% (95% CI: 49.7 to 69.7) of the 100 patients achieved HbA_{1c} values $\leq$6.5% (21 in Phase 1, 31 in Phase 2 and 8 in Phase 3), and 77% (95% CI: 67.5 to 84.8) of the patients achieved the ADA goal of HbA_{1c} <7% (41 in Phase 1, 70 by the end of Phase 2 and 77 by the end of Phase 3).

An additional analysis was performed for those 74 patients who followed the treatment regimen (once daily, twice daily and thrice daily) and titration schedule until they either obtained the target HbA_{1c} at the end of Phases 1 or 2, or completed Phase 3 of the study. In this completer analysis, adherence to the study titration schedule enabled 77% of the patients to achieve the target HbA_{1c} $\leq$6.5%, and 88% of the patients to reach the target HbA_{1c} <7.0% by the end of the study (figure 2).

HbA_{1c} values improved from baseline for patients in each phase of the study. Mean values ($\pm$s.d.) decreased by 1.4% $\pm$ 1.1 (95% CI: -1.6 to -1.2) for patients treated with once-daily dosing, by 1.9% $\pm$ 1.0 (95% CI: -2.2 to -1.3) for patients treated twice-daily dosing, and by 1.8% $\pm$ 1.1 (95% CI: -2.2 to -1.3) for patients treated with thrice-daily dosing. Overall, the mean HbA_{1c} value for all subjects at the end of treatment was 6.6% $\pm$ 0.9.

The mean eight-point self-monitored blood glucose profiles for subjects at the end of each phase demonstrated a significant decrease ($p < 0.001$) in BG values from baseline at all time points in the profiles for all three treatment phases (figure 3). Pre-breakfast SMBG values decreased significantly from 175 to 180 mg/dl at baseline to 115–120 mg/dl after BIAsp 30 treatment in all phases. These values are in accord with the mean laboratory-measured fasting plasma glucose values (125 $\pm$ 59 mg/dl) determined at the end of treatment for all subjects. Improvement from baseline of the post-dinner SMBG value after once-daily BIAsp 30 dosing was 65 mg/dl; the improved post-dinner mean SMBG value after once-daily dosing (148 mg/dl) was maintained in subsequent phases (figure 3). Addition of the breakfast injection of BIAsp 30 in the twice-daily phase significantly reduced the post-breakfast SMBG value from baseline by 98 mg/dl. The breakfast dose during twice-daily treatment further provided a reduction of about 30 mg/dl in the pre-lunch, lunch and pre-dinner SMBG values when compared to those respective SMBG values after once-daily dosing. The mean eight-point profile after thrice-daily BIAsp 30 dosing was similar to that after twice-daily dosing with the exception of the post-breakfast BG value that was slightly greater in the thrice-daily-treated patients.

With the initiation of a new dose in each phase of the study, the blood glucose excursion decreased from baseline at dinner for once-daily dosing, at breakfast for twice-daily dosing and at lunch for thrice-daily dosing (figure 4). The decreases in the excursions from baseline were significant at dinner and breakfast for the once-daily and twice-daily dosing regimens, respectively, but did not reach significance at lunch for thrice-daily dosing.

Mean daily BIAsp 30 doses for the patients who achieved HbA_{1c} values $\leq$6.5% were 0.60 U/kg at dinner in Phase 1 (n = 21), 0.51 and 0.64 U/kg for pre-breakfast and at dinner, respectively, in Phase 2 (n = 31), and 0.58, 0.25 and 0.70 U/kg for pre-breakfast, pre-lunch and dinner, respectively, in Phase 3 (n = 8). For patients achieving target in Phase 3, 38, 16 and 46% of the total daily dose were taken before breakfast, lunch and dinner respectively.

Safety

Minor hypoglycaemic events were reported by most (84%) patients during the study at a rate of 15.4, 22.4

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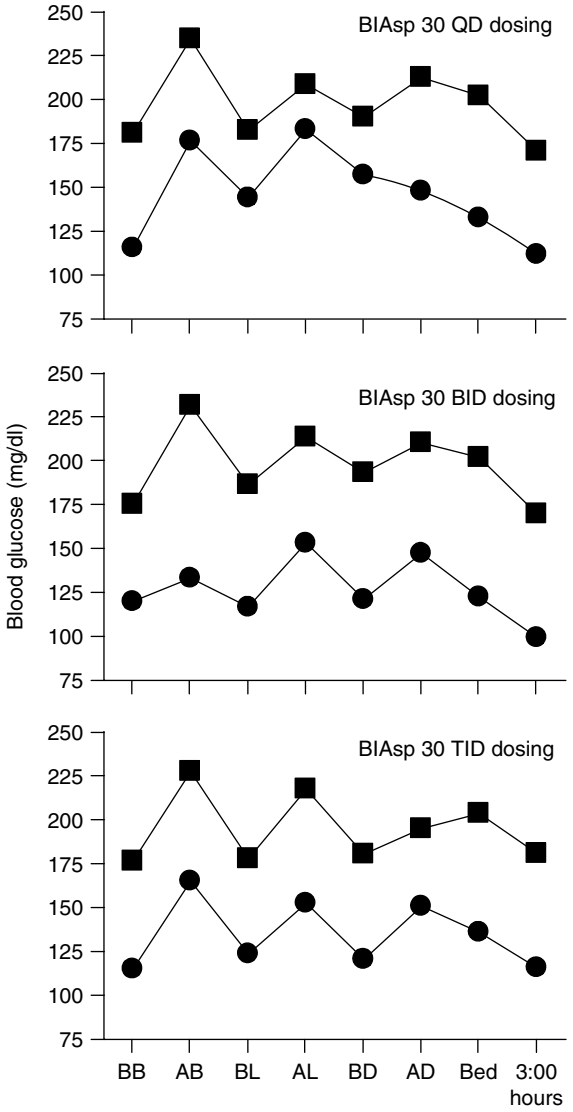

Fig. 3 Eight-point self-monitored blood glucose (SMBG) profiles. Eight-point SMBG readings were taken before breakfast, lunch and supper (BB, BL and BD) and 2 h after breakfast, lunch and supper (AB, AL and AD); at bedtime (Bed); and at 3:00 hours. Baseline profiles (■) represent blood glucose values from the start of the study for patients treated in the respective phase; ●, blood glucose values at the end of the treatment phase. Number of patients for baseline time points (■) in Phase 1: 97–100; Phase 2: 65–68 and Phase 3: 25. Number of patients for end-of-phase time points (●) in Phase 1: 82–86; Phase 2: 55–58 and Phase 3: 20–21. QD, once daily; BID, twice daily; TID, thrice daily.

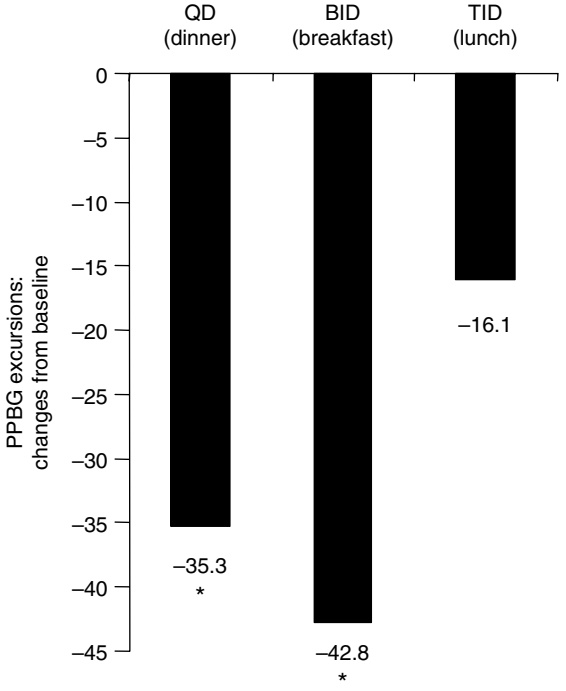

Fig. 4 Mean change in post-prandial blood glucose (PPBG) excursion from baseline (mg/dl). Data for the mean dinner, breakfast and lunch-time values were collected from 83, 55 and 20 patients during the once-daily (QD), twice-daily (BID) and thrice-daily (TID) dosing phases respectively. *$p < 0.001$.

and 12.0 events per patient year during once-daily, twice-daily and thrice-daily dosing respectively. However, there was considerable interpatient variation in the reporting of minor events; 33 patients reported two or less major and minor hypoglycaemic episodes, while 13 patients reported approximately half of all minor events. Major hypoglycaemic events were reported by seven patients (three patients during both once-daily and twice-daily dosing and one patient during thrice-daily dosing). There were no major nocturnal hypoglycaemic events, and no patient withdrew from the study due to a hypoglycaemic event. No apparent relationship between any BIAsp 30 treatment regimen and the rate of minor or major hypoglycaemic events was observed.

Adverse events were reported by 94 patients. The most commonly reported events were upper respiratory tract infection, peripheral oedema, headache and cough by 31, 21, 10 and 9 patients respectively. The number and types of adverse events were similarly reported for each of the study phases. Five patients withdrew from the study because of an adverse event (one patient in Phase 1 due to a duodenal ulcer and four patients in Phase 2 because of exertional dyspnea and peripheral oedema, myocardial infarction, Hodgkin's lymphoma and chest pain).

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In contrast to the reporting of adverse events, significant improvements from screening in mean values for HDL cholesterol (9% increase), total cholesterol (5% decrease), and triglycerides (20% decrease) were observed at the end of the study. No change in mean LDL cholesterol levels was observed.

No notable safety findings for general physical examination, assessment of vital signs, ECG readings, clinical haematology and chemistry, or urinalysis were reported. However, significant increases in mean body weight (5 kg) and body mass index (BMI, 5%) were observed.

Discussion

This trial employed an aggressive, pre-defined, dose-adjustment algorithm and clearly defined glycaemic goals for a treat-to-target clinical trial in type 2 diabetes to acheive the 6.5% HbA_{1c} goal that is currently advocated by AACE. The results of the trial clearly indicate that insulin therapy using addition of once-daily BIAsp 30 injections to a prior OAD regimen can achieve current diabetes treatment targets in a substantial portion of patients (21% achieved HbA_{1c} $\leq$6.5%, and 41% achieved HbA_{1c} <7%). In those patients failing to achieve glycaemic goals with a simple regimen of once-daily injections, addition of a second daily injection of BIAsp 30 allowed the majority of patients to achieve glycaemic goals (52% with HbA_{1c} $\leq$6.5% or 70% with HbA_{1c} <7%). Addition of a third BIAsp 30 injection further increased the proportion of patients achieving treatment success (HbA_{1c} $\leq$6.5%) to 60%.

Achieving target in this trial can be attributed to the ability of BIAsp 30 to provide both postprandial glucose reduction and basal insulin coverage. The contribution of postprandial glucose control has been shown to impact overall glycaemic control (as measured by HbA_{1c}) as glycaemic targets are approached. According to Monnier *et al.* [19], the contribution of postprandial glucose control becomes more important than that of fasting glucose levels for HbA_{1c} values in the range below approximately 7.3–8.4%. Such a model implies that current glycaemic control targets in the treatment of diabetes may frequently prove difficult to achieve unless therapy includes the control of peak postprandial plasma glucose levels.

Therapy with BIAsp 30 directly addresses postprandial insulin needs for one or more crucial daily meals, unlike alternative treatment approaches using a long-acting basal insulin analogue in the absence of rapid-acting insulin. The combined basal and postprandial glucose reduction actions of BIAsp 30 provided better glycaemic control than a once-daily long-acting basal insulin analogue in the recent INITIATE study. The INITIATE study demonstrated that significantly improved glycaemic control (HbA_{1c} difference between treatments of 0.43%) was achieved by addition of twice-daily BIAsp 30 to metformin therapy compared to the addition of once-daily insulin glargine to metformin therapy in subjects who had shown inadequate glycaemic control using OADs [20]. Significantly more subjects achieved ADA targets of HbA_{1c} $\leq$7% in the BIAsp 30 regimen (66%) than the insulin glargine regimen (40%). This observation has been confirmed by similar findings from a study by Malone [21] using the premixed analogue insulin, insulin lispro 75/25. The percentages of patients reaching the HbA_{1c} target <7% were somewhat less in the Malone study (lispro 75/25, 42%; glargine, 18%) than those in the INITIATE study. However, in the Malone study, the treatment duration was less, and patients did not adjust their insulin using an algorithm-directed titration as was used in the INITIATE study.

Although the INITIATE study showed better glycaemic control of twice-daily BIAsp 30 treatment over treatment with glargine, the obvious question remained: were two injections per day necessary? The finding that a substantial number of patients can be controlled by the addition of a single BIAsp 30 injection in this study was unexpected. No patient parameter predicted such a success. Baseline HbA_{1c} values in those achieving goal with one injection were similar to HbA_{1c} values for those requiring two or three injections. However, the odds of achieving HbA_{1c} values $\leq$6.5% with one injection per day were significantly greater for insulin-naïve subjects (72% of patients), as compared to subjects previously treated with insulin (odds ratio = 4.96, $p = 0.042$).

Of perhaps greater interest is the inability of pre-treatment HbA_{1c} values to predict insulin dosages. This finding suggests that some patients with hyperglycaemia have irrecoverable loss of β-cell function, while other patients may have some recoverable β-cell function and thus require less insulin. The challenge for clinicians is to recognize one from the other in advance. At present, there appears to be no satisfactory discriminator available to circumvent a progressive titration as was performed in this study.

The risk of major hypoglycaemic episodes was similar for once-daily, twice-daily or thrice-daily treatment as assessed in this clinical trial. Increasing the number of daily injections in pursuit of glycaemic control likewise did not affect the observed frequency of minor hypoglycaemia. It should be recognized that the short duration of time required to achieve the selected glycaemic

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targets required an aggressive insulin titration regimen that may have increased the risk for hypoglycaemia. In clinical practice, a less aggressive titration schedule may be more suitable for patients prone to hypoglycaemia. In addition, the short-time period over which glycaemic targets were met may have underestimated the number of subjects who can reach an HbA_{1c} value of 6.5%, since insulin doses were still being titrated at the end of this treatment phase and steady-state HbA_{1c} values may not have been achieved.

Weight gain often accompanies insulin therapy as glycaemic control improves. As expected, the mean weight gain was greater for subjects that were in the trial longer. Weight increase during the first phase of this study (approximately 3 kg) was similar to that observed for NPH- and glargine-treated subjects in the Treat-to-Target study that had similar duration [22]. The overall weight increase seen in this study was similar to that observed in the INITIATE study that also used a forced insulin titration schedule [20].

In conclusion, this clinical trial indicates that the addition of once-daily BIAsp 30 to prior OAD therapy is a viable treatment approach for a substantial number of patients and can be safely intensified to achieve glycaemic control in the majority of patients who are failing to achieve glycaemic control with OAD therapy. The current clinical trial should provide a model that can be easily applied to routine clinical practice and where patients can be initiated on once-daily BIAsp 30, titrated in dose, assessed, and escalated in intensity of therapy until glycaemic goals are achieved. The ultimate goal of diabetes therapy is to achieve the best possible glycaemic control with approaches that patients can follow easily and safely. This study indicates that BIAsp 30 is a flexible, efficacious insulin capable of achieving target glycaemia in a majority of patients with type 2 diabetes.

Acknowledgements

Principal investigators of the 1-2-3 Study Group were as follows: Ronald Brazg, Renton, WA, USA; Peter Bressler, Dallas, TX, USA; Jay Cohen, Memphis, TN, USA; Steven Edelman, San Diego, CA, USA; Alan J. Garber, Houston, TX, USA; Gregg Gerety, Albany, NY, USA; Rajeev Jain, Milwaukee, WI, USA; Philip Levy, Phoenix, AZ, USA; Dennis Linden, Medford, OR, USA; Bruce Rankin, Deland, FL, USA; Laurie Sadler, Cleveland, OH, USA; Timothy Wahl, Omaha, NE, USA; Jack Wahlen, Ogden, UT, USA. This clinical trial received financial support of Novo Nordisk, Princeton, NJ, USA.

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