ORIGINAL ARTICLE doi: 10.1111/j.1463-1326.2007.00743.x

Adding biphasic insulin aspart 30 once or twice daily is more efficacious than optimizing oral antidiabetic treatment in patients with type 2 diabetes

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Aim: To evaluate the efficacy and safety of adding biphasic insulin aspart 30 (BIAsp30; NovoMix® 30) to existing oral antidiabetic agents (OADs) vs. optimizing OADs in a subgroup of Western Pacific patients with type 2 diabetes inadequately controlled on oral monotherapy or oral combination therapy.

Methods: This 26-week, multi-centre, open-labelled, randomized, two-arm parallel trial consisted of a 2-week screening period, followed by 24 weeks of treatment. Subjects randomized to BIAsp30 treatment (n = 129) received BIAsp30 once daily (o.d.) at dinnertime between Week 2 and Week 14, and those not reaching treatment targets were switched to twice daily (b.i.d.) BIAsp30 at Week 14 (n = 50). Subjects randomized to the OAD-only arm (n = 63) continued with their previous OAD treatment and, in an attempt to reach treatment goals, the dose was optimized (but OAD unchanged) in accordance to local treatment practice and labelling.

Results: Significantly greater reductions in HbA_{1c} over Weeks 0–13 with BIAsp30 (o.d.) vs. OAD-only treatment (1.16 vs. 0.58%; $p < 0.001$), and over Weeks 0–26, with BIAsp30 (o.d.) and BIAsp30 (b.i.d.) treatments vs. OAD-only treatment (1.24 vs. 1.34 vs. 0.67%; $p < 0.01$). Hypoglycaemic episodes were reported in 54% of the patients in BIAsp30 (o.d. and b.i.d. pooled) and 30% of the patients in OAD-only group. All episodes were minor or symptomatic, except for one in each treatment group, which was major.

Conclusions: Initiating BIAsp30 treatment is a safe and more effective way to improve glycaemic control in Western Pacific patients with type 2 diabetes inadequately controlled with oral monotherapy or oral combination therapy compared with optimizing oral combination therapy alone. In patients not reaching treatment target on BIAsp30 (o.d.), treatment with BIAsp30 (b.i.d.) should be considered.

Keywords: biphasic insulin aspart, insulin initiation, OAD failures, pre-mixed insulin analogue, type 2 diabetes
Received 22 February 2007; returned for revision 30 April 2007; revised version accepted 11 May 2007

Introduction

The Western Pacific is the world's most populous region and home to some forty million people with diabetes mellitus [1]. Clinicians within this region can consult guidelines published (and updated periodically) by the International Diabetes Federation – Western Pacific Region (IDF-WPR) for advice on how to achieve a recognized level

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of glycaemic control in their patients with type 2 diabetes. In their guidelines, the IDF-WPR recommends that clinicians commence insulin when adequate glycaemic control can no longer be achieved with oral agents alone, and pertaining to the choice and timing of insulin, the guidelines only suggest 'intermediate-acting/long-acting insulin at bedtime', without making any mention of the role of pre-mixed insulins, nor of the newer insulin analogues [2].

Indeed, while there may be a substantial evidence base supporting the use of pre-mixed insulin analogues among Caucasian populations, published clinical experience to date regarding the use of these agents among the Western Pacific type 2 diabetic population appears to be limited. Because there is some evidence to suggest the existence of ethnic differences in glycaemic control among patients with type 2 diabetes [3–6], as well as ethnic differences in the glycaemic response to exogenous insulin treatment in these patients [7,8], it may be argued that studies involving pre-mixed insulin analogues conducted in Caucasian populations cannot be extrapolated to other populations with a complete degree of certainty.

The purpose of this trial, therefore, was to investigate the efficacy and safety of initiating a novel pre-mixed insulin regimen – NovoMix® 30 [biphasic insulin aspart 30 (BIAsp30)] – vs. optimizing oral treatment in a subgroup of Western Pacific patients with type 2 diabetes inadequately controlled on oral monotherapy or oral combination therapy. The design of this trial attempted to simulate current clinical practice in the Western Pacific context, with regard to the initiation of insulin therapy among patients with type 2 diabetes who are poorly controlled with oral treatment, as closely as possible.

Research Design and Methods

Study Design

This was a multi-centre, open-labelled, randomized, two-arm parallel trial with a 2-week screening phase and a 24-week treatment phase. The trial was conducted in 14 sites in seven countries in the Western Pacific region [Australia, China (Hong Kong), Malaysia, Philippines, Singapore, Taiwan and Thailand], in accordance with the Declaration of Helsinki and Good Clinical Practice. Approval by institutional ethics committees was obtained for each participating site. All patients provided written informed consent before study entry.

Study Population

The trial enrolled insulin-naïve patients with type 2 diabetes who met the following criteria: (i) age $\geq$18 years; (ii) duration of diabetes $\geq$24 months but $\leq$60 months; (iii) oral antidiabetic agents (OADs) treatment for $\geq$4 months with sulphonylurea, biguanide, glinide or α-glucosidase inhibitor monotherapy, or a combination of these agents involving no more than two OADs; (iv) body mass index $\geq$18 and $\leq$30 kg/m^2; (v) fasting C-peptide $\geq$0.33 nmol/l and (vi) HbA_{1c} $\geq$7% and $\leq$12%. Enrolled patients had no evidence of renal and hepatic dysfunction and had not been in receipt of thiazolidinedione treatment within the past 6 months.

Treatments

Following a 2-week screening phase, patients were randomized in a 2 : 1 ratio either to receive BIAsp30 or OAD only. Patients randomized to BIAsp30 treatment were given BIAsp30 as an add-on to current OAD treatment, starting with a dose of 0.2 U/kg/day, once daily (o.d.), pre-dinner. The starting doses were titrated 2–4 U weekly for the following 4 weeks, and the doses were maintained constant between Weeks 6 and 14. At Week 14, patients on BIAsp30 (o.d.) with HbA_{1c} >8.5% or fasting plasma glucose (FPG) >7 mmol/l were switched to BIAsp30 twice daily (b.i.d.) dosing. The split in insulin dose between morning and evening was decided at the discretion of the investigator, and patients receiving BIAsp30 (b.i.d.) were titrated 2–4 U weekly for the following 4 weeks, and the doses were maintained constant between Week 18 and Week 26 (endpoint). All patients receiving BIAsp30 used 3-ml Penfill cartridges (100 U/ml) in the NovoPen-3 Insulin Delivery System. They continued usage of pre-study OADs without dose modification.

In the OAD-only group, patients continued with their previous OAD treatment and, in an attempt to reach treatment goals, the dose was optimized (but OAD unchanged) in accordance to local treatment practice and labelling. For those on OAD monotherapy, a second OAD could be started at the discretion of the investigator, if necessary, from randomization until Week 6.

All patients were given blood glucose meters (MediSense® Optium®; Abbott, Illinois, USA) for self-measured eight-point plasma glucose (PG) assessments (before and 90 min after breakfast, lunch and dinner; at bedtime; and at 2:00 a.m.). The eight-point glucose profiles were obtained on any one day within the week preceding the visits at Weeks 2, 13 and 26. Treatment targets for this trial were benchmarked according to the guidelines proposed by the IDF-WPR [2], and specifically, the treatment targets were a self-measured pre-breakfast PG level of 4.4–6.1 mmol/l (79–110 mg/dl) and a post-prandial PG (90 min, post-dinner) level of 4.4–8.0 mmol/l (79–144 mg/dl).

Haematologic, clinical chemistry, FPG and HbA_{1c} values were measured at a central laboratory (for sites in Australia: Sonic Clinical Trials Laboratory, Australia; for those outside Australia: Covance Central Laboratory Services, IN, USA). HbA_{1c} was measured by high-performance liquid chromatography (Bio-Rad Variant; Bio-Rad, Hercules, CA, USA) traceable to the Diabetes Control and Complications Trial reference method, with a reference range of 4.3–6.1%.

Study Assessments

The primary efficacy endpoint was the change in HbA_{1c} over Weeks 0–13, secondary efficacy endpoints were change in HbA_{1c} over Weeks 0–26, proportion of patients achieving HbA_{1c} <7% at Weeks 13 and 26, changes in laboratory-measured FPG from Week 2 to Weeks 13 and 26, and changes in self-measured PG values between Week 2 and Weeks 13 and 26 for each of eight PG self-measurements.

The safety endpoints included hypoglycaemic episodes, adverse events, physical examination findings and clinical laboratory evaluations. Minor hypoglycaemia was defined as symptoms consistent with hypoglycaemia with confirmation by PG measurement <3.1 mmol/l (56 mg/dl) and that was handled by the patient himself/herself, or as any asymptomatic PG measurement <3.1 mmol/l (56 mg/dl). Major hypoglycaemia was defined as severe central nervous system symptoms consistent with hypoglycaemia in which the patient was unable to treat himself/herself and had one of the following characteristics: PG <3.1 mmol/l (56 mg/dl) or reversal of symptoms after either food intake or glucagon/i.v. glucose administration.

Changes in treatment satisfaction and patients' perceived frequency of hypoglycaemia and hyperglycaemia were assessed at Week 26 using the Diabetes Treatment Satisfaction Questionnaire (DTSQ) – a widely used satisfaction scale that has been shown to be sensitive to changes following modifications in diabetes management [9]. Scores of the six satisfaction questions on the questionnaire were summated (highest possible score 36) to provide the overall treatment satisfaction score, while one question each on the perceived frequency of hypoglycaemia and the perceived frequency of hyperglycaemia was analysed separately to provide their respective scores (which is on a scale of 0–6, where higher scores indicate a higher perceived frequency of hypoglycaemia and hyperglycaemia respectively).

Data from the o.d. and b.i.d. treatment arms of BIAsp30 are analysed separately for efficacy endpoints and for DTSQ assessments at Week 26 but are pooled for analyses of safety endpoints.

Statistical Analysis and Sample Size Calculation

Using PC SAS 8.2 (SAS Institute Inc., Cary, NC, USA), statistical analysis was performed. Change in efficacy endpoints from baseline were analysed using an analysis of variance model. Unless otherwise noted, results are presented as mean ± s.d. To compare the number of patients achieving HbA_{1c} levels of <7.0%, as well as the proportion of patients experiencing hypoglycaemia, a chi-square test was used. Non-parametric testing was used to compare DTSQ scores, as well as changes in weight. Safety endpoints were evaluated using descriptive statistics and no statistical testing was performed.

The sample size was calculated based on the primary endpoint of change in HbA_{1c} over Weeks 0–13. It was estimated that to provide an 80% power in detecting a clinically relevant difference of 0.6% in HbA_{1c}, 195 subjects (randomized in a ratio of 2 : 1; with 130 subjects randomized to BIAsp30 treatment and 65 subjects to OAD-only treatment) would be required. With an estimated screen failure rate of 20%, it was planned to recruit 234 patients into the study.

Results

Subjects Studied

A total of 269 patients were screened: 192 patients were eligible for randomization, and 191 patients comprised the intent-to-treat population, of which 128 patients received o.d. BIAsp30 treatment and 63 received OAD-only treatment (figure 1). At screening, the demographic and clinical characteristics were similar between the BIAsp30 ($n = 128$) vs. OAD-only groups ($n = 63$) (table 1). Nonetheless, when patients receiving BIAsp30 were stratified according to those who were later intensified to BIAsp30 (b.i.d.) and those who remained on BIAsp30 (o.d.), patients later intensified to BIAsp30 (b.i.d.) appeared to have higher baseline HbA_{1c} values compared with those remaining on BIAsp30 (o.d.), as well as patients receiving OAD-only treatment. After randomization, 13 patients on BIAsp30 (6 because of adverse events, 1 lack of efficacy, 5 non-compliance with protocol and 1 other reasons) and 6 on OAD only (3 lack of efficacy and 3 non-compliance with protocol) discontinued from treatment.

Glycaemic Control

A significantly greater mean reduction in HbA_{1c} over Weeks 0–13 was seen with BIAsp30 vs. OAD-only treatment (1.16 vs. 0.58%; $p < 0.001$), and this trend continued

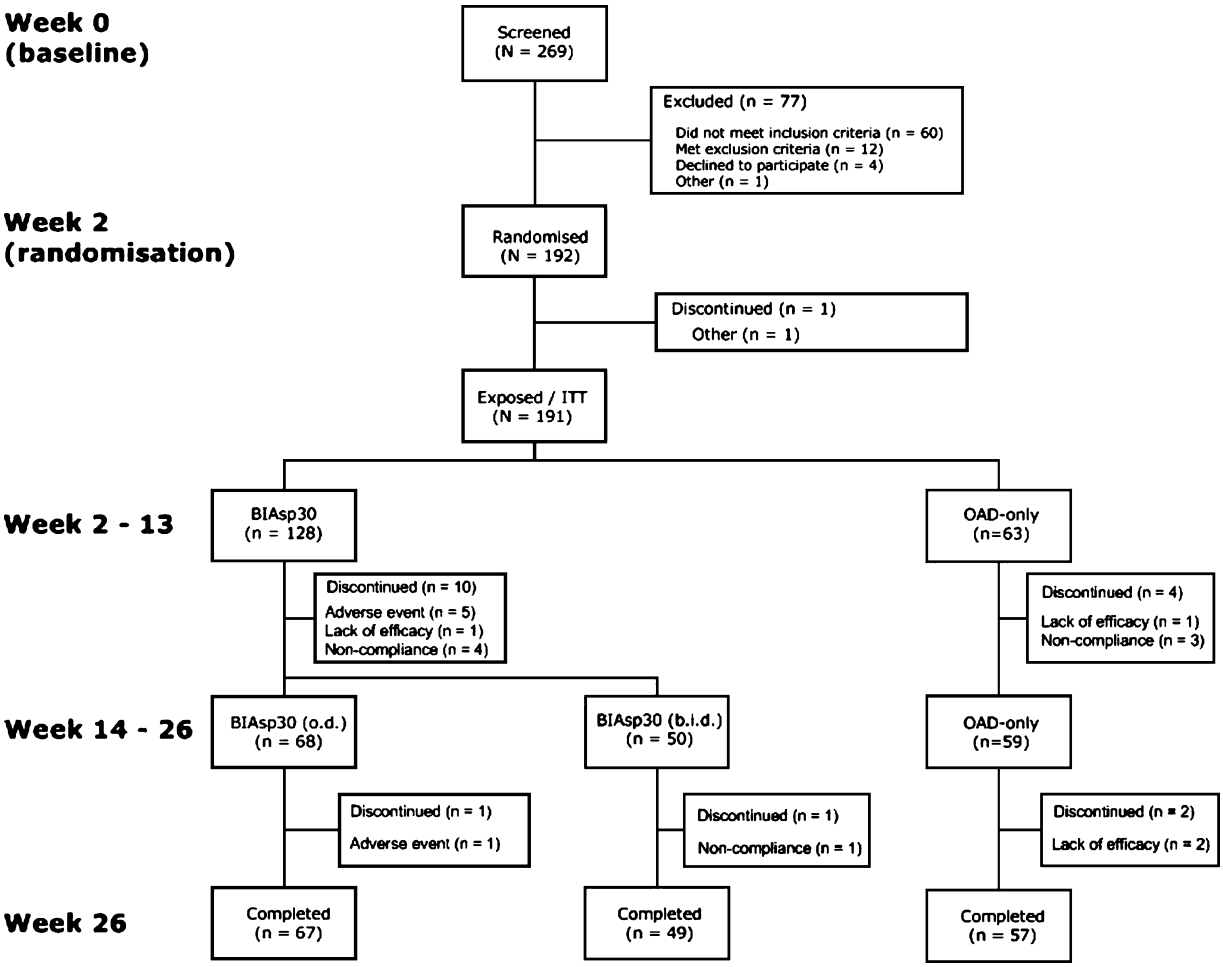

Fig. 1 Flow of subjects from screening through study completion. The intent-to-treat (ITT) population was defined as all randomized subjects who had been exposed to at least one dose of study medication. One patient randomized to BIAsp30 (o.d.) treatment was discontinued before exposure to any treatment and, therefore, excluded from the ITT population. BIAsp30, biphasic insulin aspart 30; b.i.d., twice daily; o.d., once daily.

at Week 26, with significantly greater mean reductions in HbA_{1c} over Weeks 0–26 observed with BIAsp30 (o.d.) vs. OAD-only treatment (1.24 vs. 0.67%; $p < 0.01$), as well as BIAsp30 (b.i.d.) vs. the OAD-only treatment (1.34 vs. 0.67%; $p < 0.005$).

An HbA_{1c} level of <7.0% was achieved by 25% of patients in the BIAsp30 group compared with 21% in the OAD-only group at Week 13 ($p = 0.502$ for the between-treatment difference). Significantly more patients on BIAsp30 (o.d.) than on OAD only reached an HbA_{1c} <7.0% at Week 26 (46 vs. 29%; $p < 0.05$ for the between-treatment difference). A comparable proportion of patients in the BIAsp30 (b.i.d.) and OAD-only groups achieved an HbA_{1c} <7.0% at Week 26 (24 vs. 29%; $p = 0.516$).

Consistent with the trends in HbA_{1c}, significantly greater mean reductions in $FPG_{(lab)}$ at Week 13 with BIAsp30 vs. OAD-only treatment (1.91 vs. 1.01 mmol/l; $p < 0.05$) were achieved. At Week 26, mean $FPG_{(lab)}$ levels decreased by 1.64 mmol/l in the BIAsp30 (o.d.) group, as compared with 1.10 mmol/l in the OAD-only group ($p = 0.209$ for the between-treatment difference). Improvement in $FPG_{(lab)}$ was significantly better with BIAsp30 (b.i.d.) as compared with OAD-only treatment (−2.32 vs. −1.10 mmol/l; $p < 0.05$).

Patients treated with BIAsp30 had greater reductions in almost all self-measured PG values compared with those receiving OAD-only treatment, with statistical significance being reached in a number of endpoints (tables 2 and 3).

Table 1 Demographics and characteristics of the study population at screening (Week 0)

Characteristic	BIAsp30 o.d.	BIAsp30 b.i.d.	All subjects	OAD only
n	78	50	128	63
Male/female (%)	42/36	19/31	48/52	41/59
Age (years)	56.8 ± 9.6	52.1 ± 10.9	55.0 ± 10.4	52.7 ± 10.5
Body mass index (kg/m^2)	25.9 ± 2.6	26.6 ± 2.9	26.2 ± 2.7	25.4 ± 2.3
Duration of diabetes (years)	4.3 ± 1.4	4.5 ± 1.4	4.4 ± 1.4	4.3 ± 1.4
HbA_{1c} (%)	8.3 ± 1.1	9.0 ± 1.2	8.6 ± 1.2	8.5 ± 1.0
Concomitant complications				
Retinopathy, n (%)	13 (17%)	4 (8%)	17 (13%)	8 (13%)
Nephropathy, n (%)	10 (13%)	6 (12%)	16 (13%)	13 (21%)
OAD treatment				
Two OADs, n (%)	56 (72%)	35 (70%)	91 (71%)	53 (84%)
Sulphonylureas only, n (%)	15 (19%)	9 (18%)	24 (19%)	8 (13%)
Biguanides only, n (%)	7 (9%)	5 (10%)	12 (9%)	1 (2%)
Meglitinides only, n (%)	0 (0%)	1 (2%)	1 (1%)	1 (2%)

BIAsp30, biphasic insulin aspart 30; b.i.d., twice daily; OAD, oral antidiabetic agent; o.d., once daily.

BIAsp30 Dose

The insulin dose increased over the study duration from a mean daily starting dose of 0.17 and 0.16 U/kg to 0.22 and 0.43 U/kg at the end of the trial, for BIAsp30 (o.d.) and BIAsp30 (b.i.d.) patients respectively.

Hypoglycaemic Episodes

A significantly larger proportion of patients receiving BIAsp30 treatment experienced hypoglycaemic episodes compared with those receiving OAD only (54 vs. 30%; $p < 0.005$). Of the 178 hypoglycaemic episodes reported by patients receiving BIAsp30, and the 46 episodes reported by patients treated with OAD only, all were classified as minor or symptomatic, except for one in each treatment group, which was classified as major.

Adverse Events

The proportion of patients who experienced treatment-emergent adverse events (TEAEs) was similar between the two treatment groups: 69% (n = 88) in the pooled BIAsp30 group and 68% (n = 43) in the OAD-only group. There were five serious TEAEs in the BIAsp30 group and none in the OAD-only group. None of these serious TEAEs were likely to be related to the trial product.

Table 2 Efficacy data at Week 13

	BIAsp30	OAD only
n	128	63
Primary endpoint		
Change in HbA_{1c} from Week 0 (%)	−1.16 ± 1.01†	−0.58 ± 0.95
Secondary endpoints		
Proportion achieving HbA_{1c} <7.0% (%)	25	12
Change in $FPG_{(lab)}$ from Week 2 (mmol/l)	−1.91 ± 2.22*	−1.01 ± 2.20
Change in breakfast $PG_{(self)}$ from Week 2 (mmol/l)	−2.20 ± 3.00†	−0.50 ± 2.68
Change in breakfast + 90-min $PG_{(self)}$ from Week 2 (mmol/l)	−2.41 ± 4.68*	−0.78 ± 3.97
Change in lunch $PG_{(self)}$ from Week 2 (mmol/l)	−1.42 ± 3.95	−0.28 ± 3.94
Change in lunch + 90-min $PG_{(self)}$ from Week 2 (mmol/l)	−1.78 ± 4.15	−0.99 ± 3.69
Change in dinner $PG_{(self)}$ from Week 2 (mmol/l)	−2.04 ± 3.87†	0.08 ± 3.44
Change in dinner + 90-min $PG_{(self)}$ from Week 2 (mmol/l)	−3.79 ± 4.48†	−0.52 ± 4.18
Change in bedtime $PG_{(self)}$ from Week 2 (mmol/l)	−3.56 ± 4.29†	−1.16 ± 4.03
Change in 2 a.m. $PG_{(self)}$ from Week 2 (mmol/l)	−2.50 ± 3.44†	−0.75 ± 2.78

BIAsp30, biphasic insulin aspart 30; FPG, fasting plasma glucose; OAD, oral antidiabetic agent; PG, plasma glucose.
*$p < 0.05$ vs. OAD only.
†$p < 0.005$ vs. OAD only.

Table 3 Efficacy data at Week 26

	BIAsp30 (o.d.)	BIAsp30 (b.i.d.)	OAD only
n	78	50	63
Secondary endpoints			
Change in HbA_{1c} from Week 0 (%)	1.24 ± 1.04*	−1.34 ± 1.33†	−0.67 ± 1.18
Proportion achieving HbA_{1c} <7.0% (%)	46*	24	29
Change in $FPG_{(lab)}$ from Week 2 (mmol/l)	−1.64 ± 2.04	−2.32 ± 3.13*	−1.10 ± 2.37
Change in breakfast $PG_{(self)}$ from Week 2 (mmol/l)	−2.00 ± 2.60*	−2.76 ± 3.25†	−0.92 ± 2.76
Change in breakfast + 90-min $PG_{(self)}$ from Week 2 (mmol/l)	−2.76 ± 4.22	−3.93 ± 4.43*	−2.31 ± 3.55
Change in lunch $PG_{(self)}$ from Week 2 (mmol/l)	−1.05 ± 3.25	−2.09 ± 5.73	−1.01 ± 3.55
Change in lunch + 90-min $PG_{(self)}$ from Week 2 (mmol/l)	−1.16 ± 3.34	−2.93 ± 4.75	−1.41 ± 4.51
Change in dinner $PG_{(self)}$ from Week 2 (mmol/l)	−1.60 ± 4.08	−2.15 ± 7.13	−0.78 ± 3.46
Change in dinner + 90-min $PG_{(self)}$ from Week 2 (mmol/l)	−3.41 ± 4.16*	−3.56 ± 4.58	−1.62 ± 3.44
Change in bedtime $PG_{(self)}$ from Week 2 (mmol/l)	−2.80 ± 3.87	−4.30 ± 4.15†	−2.00 ± 3.66
Change in 2 a.m. $PG_{(self)}$ from Week 2 (mmol/l)	−0.97 ± 6.17	−3.46 ± 3.80*	−1.30 ± 2.73
Change in overall treatment satisfaction score from Week 2	3.52 ± 6.54	−0.63 ± 7.34*	2.22 ± 6.90

BIAsp30, biphasic insulin aspart 30; b.i.d., twice daily; FPG, fasting plasma glucose; OAD, oral antidiabetic agent; o.d., once daily; PG, plasma glucose.
*$p < 0.05$ vs. OAD only.
†$p < 0.005$ vs. OAD only.

No notable safety findings for general physical examination, assessment of vital signs, ECG readings, clinical haematology and chemistry were reported.

Body Weight

A significantly larger increase in mean weight over Weeks 2–13 was seen with BIAsp30 vs. OAD-only treatment (0.98 vs. 0.00 kg; $p < 0.005$), and this trend continued at Week 26, with significantly larger increases in mean weight over Weeks 2–26 observed with BIAsp30 (o.d.) vs. OAD-only treatment (0.96 vs. −0.18 kg; $p < 0.005$), as well as BIAsp30 (b.i.d.) vs. the OAD-only treatment (1.53 vs. −0.18 kg; $p < 0.005$).

DTSQ Scores

The change in overall treatment satisfaction over Weeks 2–26 was comparable between the BIAsp30 (o.d.) and OAD-only treatment groups, but significantly different between the BIAsp30 (b.i.d.) and OAD-only treatment groups, in favour of the latter. Item-by-item analyses of the six DTSQ items that constitute the overall treatment satisfaction score showed that the changes from Weeks 2 to 26 in each item were similar between the BIAsp30 (b.i.d.) and OAD-only treatment groups, with the exception of the treatment flexibility score, which was significantly different between the two groups in favour of OAD-only treatment (table 4).

Discussion

BIAsp30 is a biphasic insulin analogue formulation of insulin aspart containing 30% soluble insulin aspart and 70% insulin aspart crystallized with protamine. The soluble fraction of BIAsp30 is absorbed more quickly, reaches a higher plasma concentration and produces

Table 4 Changes in scores (over Weeks 2–26) for each of the items related to the Diabetes Treatment Satisfaction Questionnaire

	Change in Score Over Weeks 2–26		
Item	BIAsp30 (o.d.)	BIAsp30 (b.i.d.)	OAD only
1. How satisfied are you with your current treatment?	0.78	−0.08	0.47
2. How often have you felt that your blood sugars have been unacceptably high recently?	−0.40	−0.30	−0.63
3. How often have you felt that your blood sugars have been unacceptably low recently?	0.63	0.25	0.72
4. How convenient have you been finding your treatment to be recently?	0.37	−0.10	0.35
5. How flexible have you been finding your treatment to be recently?	0.70	−0.17*	0.67
6. How satisfied are you with your understanding of your diabetes?	0.57	0.15	0.27
7. Would you recommend this form of treatment to someone else?	0.58	−0.19	0.38
8. How satisfied are you to continue with your present form of treatment?	0.48	−0.23	0.42

BIAsp30, biphasic insulin aspart 30; b.i.d., twice daily; OAD, oral antidiabetic agent; o.d., once daily.
*$p < 0.05$ vs. OAD only.

glucose-lowering actions faster than the soluble fraction of a biphasic formulation of regular human insulin (BHI 30/70) [10,11]. A number of open-labelled, randomized studies conducted outside the Western Pacific region have shown that in patients with type 2 diabetes who are poorly controlled on OAD monotherapy, the addition of BIAsp30 can provide significantly better improvements in HbA_{1c} control, as compared with the addition of a second OAD [12–15]. Consistent with these studies, our study shows that glycaemic control among a subgroup of Western Pacific patients with type 2 diabetes can be improved significantly through the addition of BIAsp30 therapy. Specifically, the addition of BIAsp30 was statistically significantly superior to OAD optimization in achieving the primary endpoint of reducing HbA_{1c} over Weeks 0–13, with a mean reduction of 1.16 vs. 0.58% ($p < 0.001$). The favourable glycaemic response with BIAsp30 therapy persisted at Week 26, with both the BIAsp30 (o.d.) and BIAsp30 (b.i.d.) treatment groups achieving a statistically significantly greater reduction in HbA_{1c} from Week 0 compared with the OAD-only treatment group ($p < 0.01$ for both comparisons). The results of our study are significant given the context of the level of diabetes control within the Western Pacific region. Multinational audits of diabetes care within the region have shown that many patients with diabetes are not achieving adequate glycaemic control, placing them at high risk for diabetes-related complications [16–18]. Therefore, we infer from our study results that BIAsp30 has a role in improving the dismal level of glycaemic control within the Western Pacific.

Consistent with the trends in absolute HbA_{1c} reduction, significantly more patients on BIAsp30 (o.d.) than on OAD only achieved an HbA_{1c} <7.0% at the end of treatment. However, the proportion of patients achieving an HbA_{1c} <7.0% was comparable between the BIAsp30 (b.i.d.) and OAD-only treatment groups at Week 26. The latter could be because of the higher mean baseline HbA_{1c} value observed among patients in the BIAsp30 (b.i.d.) treatment group, as compared with those in the BIAsp30 (o.d.) or OAD-only treatment groups, which may in turn allude to the need for more time to titrate patients in the BIAsp30 (b.i.d.) treatment group to target HbA_{1c} levels, so as to overcome the baseline HbA_{1c} disparity vs. patients in the BIAsp30 (o.d.) and OAD-only treatment groups. Indeed, it should be pointed out that among the three treatment groups, it was patients on BIAsp30 (b.i.d.) who realized the greatest glycaemic benefit with their therapy, with the highest reductions in HbA_{1c}, FPG and self-measured PG levels between baseline and the end of the trial as compared with OAD-only or BIAsp30 (o.d.) treatments.

The recently reported BIAsp30 1-2-3 study has shown that in patients with type 2 diabetes failing oral agent therapy, the addition of BIAsp30 (o.d.), and subsequent stepwise titration of BIAsp30 (i.e. increasing the number of BIAsp30 injections from one to two, and then, if glycaemia remained uncontrolled, from two to three doses per day), can enable a high and progressively increasing percentage of subjects to achieve glycaemic targets [19]. Indeed, the BIAsp30 1-2-3 study showed that the addition of BIAsp30 (o.d.) enabled 41% of patients with type 2 diabetes failing oral agent therapy to achieve HbA_{1c} <7.0%; with two daily injections of BIAsp30, this glycaemic target could be achieved by 70% of patients, and with three daily BIAsp30 injections, 77% achieved HbA_{1c} <7.0%. As compared with the 1-2-3 study, there was a lower proportion of subjects in our study achieving HbA_{1c} <7.0% with BIAsp30, and this can be attributed to the fact that the 1-2-3 study was of longer duration and, moreover, a treat-to-target trial, while a less aggressive dose-adjustment algorithm was used in our study.

In our study, both BIAsp30 and OAD-only treatments were well tolerated, and a similar proportion of subjects in both treatment groups had experienced TEAEs during the course of this trial. Intensive insulin therapy aiming to achieve tight long-term glycaemic control is known to be associated with increased frequency of hypoglycaemia [20], and although the proportion of subjects reporting hypoglycaemic episodes was significantly higher with BIAsp30 treatment as compared with OAD-only treatment, in both treatment groups, most subjects experienced only minor or symptoms-only hypoglycaemic episodes. In fact, there was only one major hypoglycaemic episode reported in both treatment groups. Overall, these results are consistent with the results of similar trials involving BIAsp30, conducted outside of the Western Pacific region [12,13]. The issue of hypoglycaemia is an important one because a treatment will only be effective long term if it is well tolerated because reduced compliance leads to reduced efficacy. Reassuringly, patients, as assessed by the DTSQ, did not perceive the frequency of hypoglycaemia to be higher with BIAsp30 treatment compared with OAD-only treatment.

Weight gain often accompanies insulin therapy as glycaemic control improves, and as expected, a mean body weight gain was observed with BIAsp30 treatment. The overall weight increase seen in this study was comparable with that observed in the BIAsp30–metformin combination therapy arm of a European study (approximately 1 kg in both studies) [13]. In the European study, patients receiving BIAsp30 + metformin treatment gained a larger amount of body weight at the end of the trial, as

compared with patients who were treated with glibenclamide/metformin combination therapy (0.1 kg). Consistent with the European study, patients in the BIAsp30 treatment arm of our study experienced a statistically significant increase in weight as compared with patients in the OAD-only treatment arm.

Many insulin-naïve patients are averse to the possibility of being initiated on insulin therapy [21]; therefore, when insulin therapy is finally initiated, there is the potential that their initial aversion can have a future negative impact on their satisfaction towards their diabetes treatment. It is therefore interesting to observe that in patients treated with BIAsp30 (o.d.), the change in overall treatment satisfaction did not differ significantly to patients treated with OAD only. The change in overall treatment satisfaction, however, was significantly different between patients on BIAsp30 (b.i.d.) vs. those continuing on OAD only, and a major contribution to this difference may be related to the difference in how the two groups rated the flexibility of their treatments (table 3).

This has been the first study involving BIAsp30 in a Western Pacific population, and in designing our study, we attempted to simulate current clinical practice within the Western Pacific context as closely as possible. To that end, our treatment targets for pre-prandial PG and post-prandial glucose levels are identical to the targets recommended by the IDF-WPR [2]. In addition, our specifications that patients randomized to the BIAsp30 arm should have BIAsp30 added to their current OAD – instead of stopping oral treatment altogether – are in line with the guidelines of the IDF-WPR, which recommend that when patients need to start insulin, 'insulin should usually be combined with oral agents'. During the protocol development stage, our lower cut-off level for HbA_{1c} was originally set at >6.5% (so as to be consistent with the IDF-WPR recommendation that patients on maximal oral therapy, whose HbA_{1c} is >6.5%, be 'strongly considered' for 'early treatment with insulin'), but we met with concerns from some investigators, who reflected that this contravened their local practice. Hence, in the final protocol, a compromise of ≥7% in HbA_{1c} was eventually settled for.

One limitation of the study results reside in the fact that while patients in the OAD-only arm were permitted to add a second OAD had they been on OAD monotherapy on entering the study, they were however not permitted to add a third OAD had they been failing on two OADs. It has already been shown that in patients with type 2 diabetes inadequately controlled on two oral medications, adding a third oral agent may be as effective in improving glycaemic control as initiating b.i.d. pre-mixed insulin plus metformin [22]; however, the triple oral therapy is less cost effective and a high percentage of subjects (~16%) following this regimen do not complete the treatment because of side effects or a lack of efficacy.

Overall, this study shows that in a subgroup of Western Pacific patients with type 2 diabetes inadequately controlled with oral monotherapy or combination therapy, the addition of BIAsp30 can provide greater glycaemic reductions than optimizing oral treatment, without increasing the risk of major hypoglycaemia. Treatment with BIAsp30 was associated with weight gain, but otherwise safety assessments did not show any clinically significant changes in overall health, and no serious adverse events related to the trial product were reported during the evaluation. We conclude that a safe and effective option for patients with type 2 diabetes inadequately controlled with oral monotherapy or combination therapy is to initiate insulin treatment with BIAsp30 once or twice daily than to continue optimization with OAD alone.

Acknowledgements

This study was funded by Novo Nordisk Asia Pacific Pte Ltd. Participating countries (and sites): Australia (T. Donnelly Pty Ltd and St Vincent's Hospital), Hong Kong (Queen Mary Hospital and Prince of Wales Hospital), Malaysia (Hospital Universiti Sains Malaysia, Hospital Pulau Pinang and Hospital Universiti Kebangsaan Malaysia), Philippines (East Avenue Medical Center and Vicente Sotto Memorial Medical Center), Singapore (Alexandra Hospital), Taiwan (Changhua Christian Hospital) and Thailand (Vajira Hospital and King Chulalongkorn Memorial Hospital). The authors thank Chan Peng, BSc (Hons), for his assistance with the study; Teng Lot Yin, MSc, for her assistance in the statistical analysis of the data; and Roy Chan, BSc, MA, for his assistance with the manuscript.

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