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Improved glycaemic control of thrice-daily biphasic insulin aspart compared with twice-daily biphasic human insulin; a randomized, open-label trial in patients with type 1 or type 2 diabetes

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Aim: This trial evaluated the potential for improving glycaemic control by intensifying a conventional twice-daily therapy with premixed human insulin (HI) to a thrice-daily regimen using premixed formulations of biphasic insulin aspart (BIAsp) in patients with type 1 or type 2 diabetes.
Methods: This was a multicentre, open-label, parallel group trial. After a 4-week run-in period, patients were randomized 1 : 1 to 16 weeks of treatment. A total of 748 patients were screened, 664 were exposed to trial drug and 604 completed the trial.
Results: Haemoglobin A_{1c}, the primary efficacy endpoint, was shown to be significantly lower for the BIAsp treatment group compared with the biphasic HI (BHI) 30 group [estimated mean difference: −0.32, 95% confidence interval (CI) (−0.48; −0.16), p = 0.0001]. The average blood glucose level was significantly lower in the BIAsp group [estimated mean difference: −0.79, 95% CI (−1.17; −0.40), p = 0.0001]. There were few major hypoglycaemic episodes, 11 in the BIAsp group and 7 in the BHI 30 group. Although intensification of insulin therapy with BIAsp three times a day was associated with a higher risk of minor hypoglycaemia (relative risk = 1.58, p = 0.0038), the overall rate of minor hypoglycaemia remained low with both the BIAsp and the BHI treatments (13.1 vs. 8.3 episodes/patient year respectively). Overall safety and patient satisfaction were similar with the two insulin therapies.
Conclusions: This trial confirmed that a thrice-daily BIAsp regimen can safely be used to intensify treatment for patients inadequately controlled on twice-daily BHI. A treat-to-target trial is required to explore the full potential of the BIAsp regimens and evaluate their use as a viable alternative to intensification with a basal-bolus regimen.

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Introduction

Biphasic human insulin (BHI) injected twice daily (before breakfast and dinner) has for many years been a preferred treatment regimen for patients with type 2 diabetes requiring insulin treatment and has been extensively used for patients with type 1 diabetes. This relatively simple regimen provides a fairly good overall blood

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glucose (BG) control for many patients. The insulin profile resulting from this regimen does, however, differ substantially from the normal endogenous insulin response profile of healthy people. Two major issues with the twice-daily BHI regimen are the relatively slow postinjection absorption from the subcutis and the fact that no insulin is injected before lunch. BHI injection results in unphysiologically high insulin levels in the hours after a meal, which limits the possible dose due to increasing risk of postprandial hypoglycaemia [1]. The peak level of insulin in blood will therefore always be relatively reduced and delayed with BHI compared with a healthy endogenous insulin profile. BHI is usually recommended to be injected 30 min before a meal to compensate for its slow absorption [2], although patients often choose a shorter injection–meal interval [3,4], exacerbating the inadequate pharmacokinetics of BHI.

Biphasic insulin aspart (BIAsp) is a premix of the rapid-acting insulin analogue, insulin aspart (IAsp), and intermediate-acting, protamine co-crystallized IAsp. The soluble IAsp fraction has been shown to provide a more physiological insulin profile with a faster onset of action and a sharper insulin peak than that of human insulin (HI) [5,6]. In addition, the intermediate-acting, protaminated IAsp fraction of BIAsp will cover between-meal basal insulin needs. BIAsp is available in three ratios; BIAsp 30, BIAsp 50 and BIAsp 70 (the index number represents the percentage of rapid-acting IAsp in the premix). Thrice-daily dosing with a suitable combination of BIAsp products could potentially provide an insulin profile very close to the endogenous insulin profile of a healthy person. Furthermore, the sharper insulin peak of IAsp should allow for increased mealtime insulin dosing without increasing the risk of postprandial hypoglycaemia. Thus, intensification from a twice-daily BHI regimen to thrice-daily BIAsp may offer an alternative to intensification with a traditional basal-bolus treatment regimen, which requires at least four daily injections.

This article presents the results from a large therapeutic trial that compared glycaemic control of a thrice-daily BIAsp treatment regimen and a twice-daily BHI 30 treatment regimen in patients with type 1 or type 2 diabetes. The primary endpoint was glycaemic control evaluated on the basis of haemoglobin A_{1c} (HbA_{1c}) after 16 weeks of treatment.

Methods

Patients

The trial included patients with type 1 or type 2 diabetes diagnosed according to the 1985 World Health Organization (WHO) classification [7]. The ratio of type 1 and type 2 diabetes patients included in the trial was similar to the ratio found in the general population of patients with diabetes.

Patients were recruited from the individual investigator's clinical practice and were randomized using a telephone randomization system [Intelligent Voice Response System (IVRS)]. The investigator called the IVRS and entered patient number and key patient information and the system assigned the treatment for that patient according to a predefined randomization list. IVRS took into account block randomization within centres.

The trial included men or women at least 18 years old, who at trial entry had been treated with HI twice daily for at least 3 months with or without combination with oral hypoglycaemic agents. The selection criteria did not specify a lower or upper limit of HbA_{1c}.

Patients were not included if any of the following criteria were present: (i) a body mass index (BMI) > 40.0 kg/m^2; (ii) total daily insulin dose of $\geq$1.80 IU/kg; (iii) a history of drug or alcohol dependence; (iv) impaired hepatic (alanine aminotransferase or alkaline phosphatase $\geq$2 times the upper reference level) or renal (serum creatinine $\geq$150 μmol/l) function; (v) cardiac disease; (vi) proliferative retinopathy; (vii) pregnancy, breast feeding and the intention to become pregnant; (viii) known or suspected allergy against soluble HI, IAsp or any component of the biphasic mixtures; (ix) mental incapacity, unwillingness or language barriers precluding adequate understanding or co-operation; (x) any disease or condition which may interfere with the validity of the trial; (xi) receipt of any investigational drug at the time of inclusion in the trial; (xii) a diet containing more or less than three main meals (breakfast, lunch and dinner) per day.

Patients were recruited from 69 trial sites in the following five European countries: 28 in the UK, 3 in Ireland, 6 in Belgium, 21 in France and 11 in the Netherlands. A total of 748 patients were screened, 667 were randomized and 664 were exposed to trial drug. A summary of patients' demographic and baseline diabetic characteristics is presented in table 1. The mean HbA_{1c} level at baseline was 8.7%, indicating that the enrolled patients were generally suboptimally controlled.

Trial Design

This was a multinational, open-label, parallel group trial investigating the efficacy and safety of thrice-daily BIAsp compared with twice-daily BHI 30 in patients with type 1 or type 2 diabetes. The trial was open-label because a double-dummy design would have required patients to take an unacceptably high number of placebo injections.

Table 1 Summary of key baseline demographic and diabetic characteristics

	Biphasic insulin aspart	Biphasic human insulin 30
Patients exposed, total N (%)	335 (50)	329 (50)
Type 1 diabetes, N (%)	88 (13)	98 (15)
Type 2 diabetes, N (%)	247 (37)	231 (35)
Sex		
Men/women	183/152	179/150
Age (years)		
Mean (s.d.)	56.5 (12.8)	57.0 (13.0)
Ethnic origin		
Caucasian/white	322	318
Other	13	11
Body mass index (kg/m^2)		
Mean (s.d.)	28.7 (4.5)	28.8 (4.6)
Duration of diabetes (years)		
Mean (s.d.)	13.8 (9.7)	13.0 (8.8)
Haemoglobin A_{1c} (%)		
Mean (s.d.)	8.7 (1.4)	8.8 (1.4)

Following a run-in period of 4 weeks, the patients were randomized to 16 weeks of treatment on a 1 : 1 basis. An overview of the trial design is given in figure 1.

Oral hypoglycaemic agents were discontinued upon entering the trial. During the 4-week run-in period, all patients were treated with BHI 30 twice daily (injected 30 min before breakfast and dinner) at the doses used before run-in period (pretrial treatment could include BHI of any ratio).

After the run-in period, patients randomized to the BHI group initiated the trial treatment using the same insulin doses as those at the end of the run-in period.

Patients randomized to the BIAsp group were allocated according to their BMI to a thrice-daily treatment regimen with BIAsp 50 ($BMI > 30\ kg/m^2$) or BIAsp 70 ($BMI \leq 30\ kg/m^2$). This allocation according to BMI was based on results from internal Novo Nordisk pharmacokinetic modelling (using normal insulin profiles from Polonsky *et al.* [8]). Patients randomized to BIAsp treatment were switched to BIAsp 30 predinner if their morning fasting BG level at weeks 2, 4 or 6 was above 8 mmol/l, to improve overnight glycaemic control [9].

No dose-titration algorithm was used in this trial because a treat-to-target trial design was not the convention when the trial was initiated. Rather the trial was meant to reflect a typical clinical setting. For all patients, the target for BG control was a fasting, preprandial and postprandial (self-measured) BG value in the range 5–8 mmol/l. All patients were informed about the target for glycaemic control and were allowed to adjust their insulin dose throughout the trial to reach this target.

BIAsp treatment was initiated with a total daily insulin dose 10% greater than the total daily dose of BHI 30 used at the end of the run-in period. This was to compensate for the more rapid absorption and shorter duration of action of BIAsp compared with BHI [10], as well as the fact that dosing would be distributed over three rather than two meals (initial dose distribution was 40 : 30 : 40; breakfast, lunch and dinner respectively). Starting with the slightly higher insulin dose in the BIAsp regimen allowed patients to quickly reach a more optimal dosing level. Patients were instructed to inject BIAsp immediately (within 5 min) before meals.

The trial was performed in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines [11,12].

Outcome Measures

The primary endpoint was glycaemic control evaluated on the basis of HbA_{1c} after 16 weeks of treatment with a thrice-daily BIAsp regimen or a conventional twice-daily BHI 30 regimen. Blood samples were taken at baseline, and after 8 and 16 weeks of treatment. HbA_{1c} was measured by a central laboratory certified by the National Standardization Program (NGSP) [13] (using Bio-Rad Variant high performance liquid chromatography), and the results were transferred electronically to the data management department at Novo Nordisk A/S.

The secondary objectives were to assess safety [hypoglycaemic episodes, adverse events (AEs), haematology and biochemistry] and additional efficacy endpoints based on BG profiles (average of whole BG profile at each

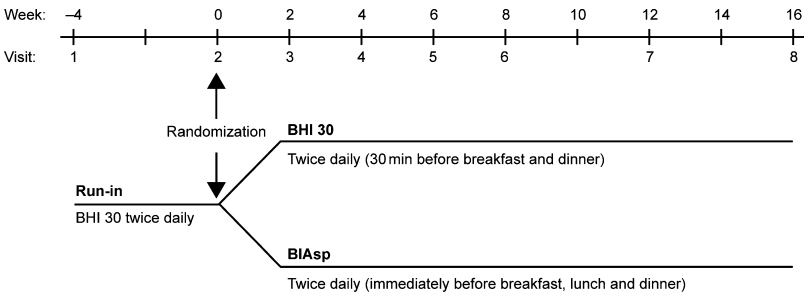

Fig. 1 Overview of the trial design. Details regarding the treatment regimens are given in the text. BHI, biphasic human insulin; BIAsp, biphasic insulin aspart.

visit and average prandial increment). Furthermore, the patients completed two quality-of-life questionnaires at week −4 (baseline) and after 12 and 16 weeks of treatment: The WHO Diabetes Treatment Satisfaction Questionnaire (WHO DTSQ) [14] and the Diabetes Health Profile (DHP) [15,16].

Hypoglycaemic episodes were defined as 'major' (patients unable to treat themselves), 'minor' [BG measurement <2.8 mmol/l (50 mg/dl), with or without symptoms] or 'symptoms only' (symptomatic but not confirmed by BG measurement).

An AE was defined as 'any undesirable medical event occurring to a subject in the trial, whether or not considered related to the trial products'. AEs were classified as 'serious' if they resulted in death, a life-threatening experience, patient hospitalization or prolongation of existing hospitalization and a persistent or significant disability/incapacity.

At the start of the run-in period (week −4), patients were given a BG meter (OneTouch Profile, LifeScan Milpitas, CA, USA) and instructions on its use and calibration. Patients were instructed to self-monitor morning fasting BG and to record date, time and value of these tests in a diary which was reviewed at all subsequent visits. In addition, patients were encouraged to perform daily BG measurements throughout the trial and when suspecting hypoglycaemia. During the week before each visit, the patients recorded a 7- or 8-point BG profile by measuring BG (i) before each meal, (ii) 90 min after the start of each meal, (iii) at bedtime and (iv) at 02:00 hours (weeks 0 and 16).

Statistical Analyses

The trial was powered to detect a difference of 0.23% units HbA_{1c}, with a probability of more than 90%. The results of the Diabetes Control and Complications Trial (DCCT) [17] suggest that a sustained reduction of 0.23% HbA_{1c} could potentially translate to a 10% reduction in late diabetic complications, which is considered clinically relevant. A total of 660 patients were recruited to allow for an approximate 10% drop-out rate.

The primary and secondary efficacy endpoints were analysed using analysis of variance (ANOVA) models, with treatment as a fixed effect and adjustment for baseline (done by including baseline HbA_{1c} as a covariate). Adjustment for country and treatment-by-country effects is not included in the presented analyses but were investigated in separate analyses and found not to affect any conclusions. All statistical tests were two sided, with a significance level of 5%. The assessment of data was blinded.

Rates of hypoglycaemic episodes were analysed using a generalized linear Poisson regression model accounting for overdispersion and including exposure time as an offset. This analysis was based on the number of episodes per patient year of exposure. The relative risk (RR) of nocturnal (24:00–06:00 hours) hypoglycaemic episodes was estimated using a Mantel–Haenszel method [18], as the number of episodes was expected to be low. This analysis was based on the number of patients experiencing at least one nocturnal episode during treatment.

Analysis of metabolic control vs. risk of hypoglycaemia was performed by evaluating the rate by treatment interaction estimated by an ANOVA model including baseline HbA_{1c}, classified rate of hypoglycaemia (including all hypoglycaemic episodes) and the corresponding interaction.

AEs other than hypoglycaemic episodes were listed and evaluated, but difference between treatment regimens was not tested statistically.

The efficacy analyses and the analyses of the quality-of-life questionnaires were based on the intention-to-treat (ITT) population, which included all patients who were exposed to trial drug and had efficacy data available. The safety evaluation included all patients exposed to trial drug.

The trial was only powered to look at the combined population of patients with type 1 or type 2 diabetes, and analyses of the diabetic subgroups are therefore not presented.

Results

Patients

Of the 664 patients exposed to trial drugs, 60 patients withdrew during the trial and 604 completed the trial. After trial completion, 48 patients were excluded due to failure to meet at least one of the inclusion criteria for the per protocol population. An overview of patient disposition is given in figure 2, and details of patient withdrawals are shown in table 2.

Any previous diabetic complications were recorded and did not appear to differ between the BIAsp and the BHI groups, either for the overall group or when split according to type of diabetes (data not presented).

The total daily insulin dose after 16 weeks of treatment was slightly higher for subjects treated with BIAsp compared with that for those treated with BHI 30, reflecting the 10% higher dose recommended at initiation of BIAsp treatment (table 3). The development in total daily insulin dose was similar in the two treatment groups after 2 weeks, stabilizing in both treatment groups after 6 weeks (figure 3).

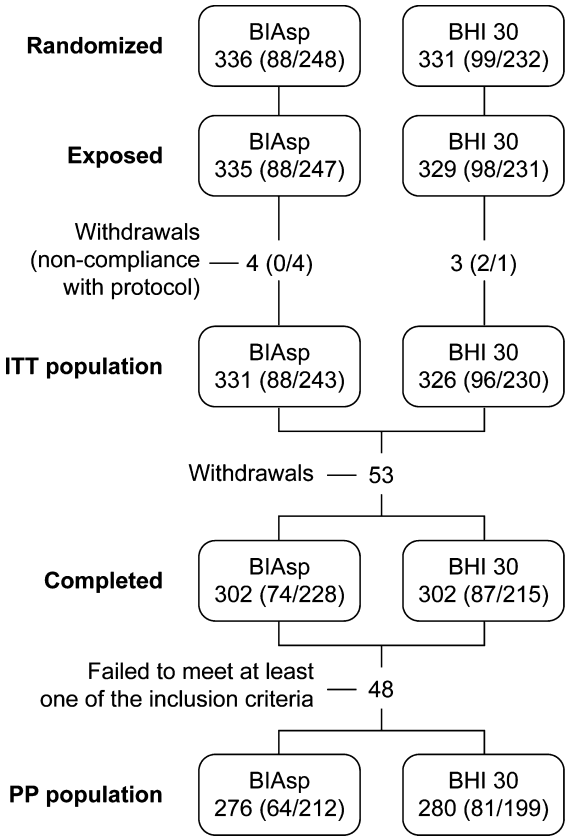

Fig. 2 Patient disposition. Numbers refer to number of patients with diabetes [total (type 1/type 2)]. BHI, biphasic human insulin; BIAsp, biphasic insulin aspart; ITT, intention –to treat; PP, per protocol.

The majority of patients in the BIAsp group were switched to BIAsp 30 as the evening therapy because their morning fasting BG level was above 8.0 mmol/l after 2, 4 or 6 weeks of treatment (as described in Methods). Of the 331 patients in the ITT population randomized to the BIAsp arm (figure 2), 114 patients received BIAsp 50 and 217 patients received BIAsp 70. Within these sub-populations, 82 and 168 patients, respectively, required BIAsp 30 as their evening treatment.

Table 2 Overview of patient withdrawals

	Biphasic insulin aspart	Biphasic human insulin 30	Combined
Exposed	335 (100%)	329 (100%)	664 (100%)
Withdrawals			
Adverse event	10 (3.0%)	8 (2.4%)	18 (2.7%)
Ineffective therapy	7 (2.1%)	10 (3.0%)	17 (2.6%)
Non-compliance with protocol	4 (1.2%)	3 (0.9%)	7 (1.1%)
Other	12 (3.6%)	6 (1.8%)	18 (2.7%)
Total	33 (9.9%)	27 (8.2%)	60 (9.0%)
Efficacy population			
Intention to treat	331 (98.8%)	326 (99.1%)	

Table 3 Total insulin doses after 2 and 16 weeks of treatment

	Biphasic insulin aspart* (U/kg)		Biphasic human insulin 30 (IU/kg)	
	N	Mean (s.d.)	N	Mean (s.d.)
Week 2†	331	0.80 (0.31)	324	0.70 (0.28)
Week 16	300	0.87 (0.39)	302	0.76 (0.31)

*All BIAsp patients.
†First recorded dose of trial products.

HbA_{1c}

The analysis of the primary efficacy endpoint, HbA_{1c} after 16 weeks, showed superior glycaemic control for BIAsp (mean ± s.e.m.: 8.35 ± 0.06%; N = 296) compared with BHI 30 treatment (8.67 ± 0.06%; N = 291); estimated treatment difference {BIAsp − BHI 30, mean [95% confidence interval (CI)]}: −0.32; p = 0.0001.

Figure 4 shows the HbA_{1c} level in the two treatment groups at baseline, and after 8 and 16 weeks of treatment.

Blood Glucose Profiles

After 16 weeks of treatment, the mean BG level was generally lower for the BIAsp group compared with that of the BHI 30 group, except at 02:00 hours and before breakfast (figure 5).

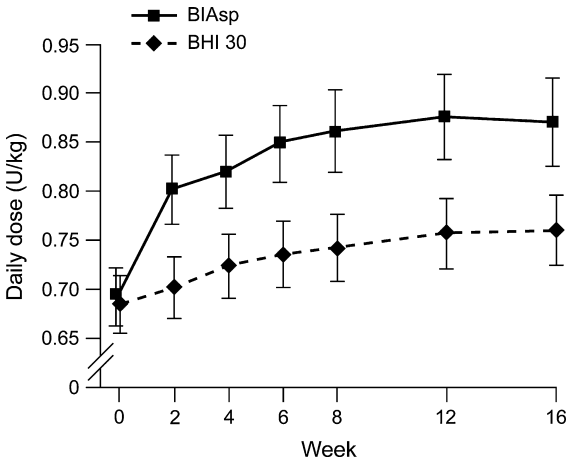

Fig. 3 Total daily dose of insulin (mean ± 2·s.e.m.). For both treatment groups, the insulin dose at baseline (week 0) represents the dosing with BHI in the run-in period. BHI, biphasic human insulin; BIAsp, biphasic insulin aspart.

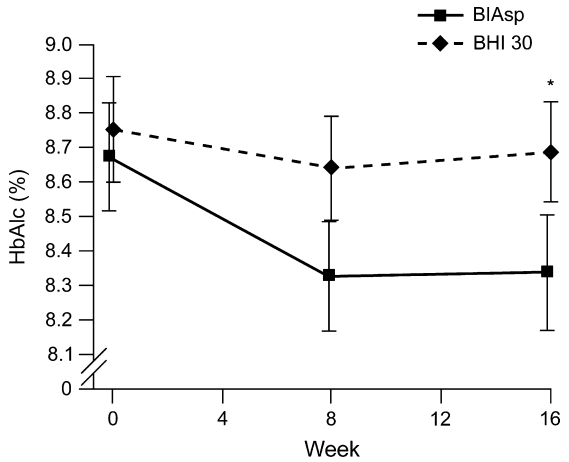

Fig. 4 Mean haemoglobin A_{1c} (±2·s.e.m.) at 0, 8 and 16 weeks. The symbol '*' indicates p = 0.0001. The potential difference between treatment regimens was only evaluated statistically at week 16.

Average BG level (based on the 8-point BG profile) was significantly lower in the BIAsp group compared with that of the BHI 30 group [estimated mean difference: −0.79 (−1.17; −0.40), p = 0.0001].

At the end of the trial, the average (daily) prandial BG increment was lower for the BIAsp compared with that of the BHI group [estimated mean difference: −1.87 (−2.24; −1.49), p < 0.0001]. This difference was prominent immediately after initiating BIAsp treatment and was maintained throughout the trial (data not shown).

Hypoglycaemic Episodes

Very few major hypoglycaemic episodes were reported, and the numbers were similar for the BIAsp and BHI 30 treatment groups (table 4). The risk of experiencing any hypoglycaemic episode was significantly higher in the more intensively treated BIAsp group than that in the BHI 30 group (table 5).

A *post hoc* exploratory analysis showed that the risk of a patient having at least one hypoglycaemic episode at night (24:00–06:00 hours) was lower with the BIAsp treatment [RR, any episode (BIAsp/BHI 30) = 0.7, CI = (0.56; 0.95); p = 0.0186. RR, minor episode (BIAsp/BHI 30) = 0.7, CI = (0.50; 1.04); p = 0.0813).

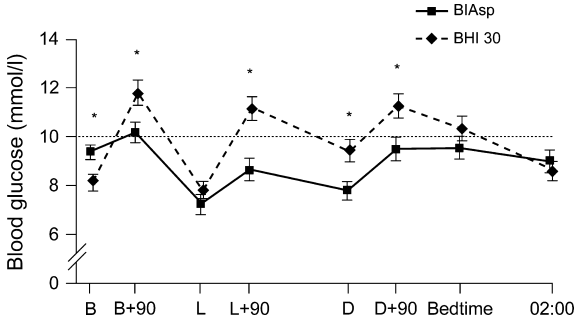

Fig. 5 Mean (±2·s.e.m.) 8-point blood glucose profiles after 16 weeks of treatment. The symbol '*' indicates p< 0.0001. B, breakfast; BHI, biphasic human insulin; BIAsp, biphasic insulin aspart; D, dinner; L, lunch; +90, 90 min after the meal (a sample at mealtime was taken immediately before the meal).

Metabolic Control Vs. Risk of Hypoglycaemia

In an exploratory analysis, the mean rate of all hypoglycaemic episodes was found to affect HbA_{1c} (p = 0.0037), but no interaction with treatment was found (p = 0.6205), indicating that this relationship did not differ between the two treatment groups.

Adverse Events

A total of three deaths was reported. A 52-year-old man died of cardiac arrest after 101 days of treatment with BHI 30. A 54-year-old man died 19 days after completing treatment with BIAsp. A 69-year-old woman died of a malignant lymphoma after 30 days of treatment with BIAsp. All three cases were considered to be unrelated to trial products.

Other serious AEs (SAEs) were uncommon and sporadic with both treatments. For patients with type 1 diabetes, none of the SAEs (four in the BIAsp group and seven in the BHI group) were reported more than once within a treatment group. For patients with type 2 diabetes, the only SAEs reported by more than one patient were myocardial infarction (three patients in the BIAsp group and two patients in the BHI 30 group) and chest pain (two patients in the BIAsp group).

The most common AEs (reported by more than 5% of patients) are listed in table 6. Most were mild or moderate, non-serious and judged unlikely to be related to trial medication. The overall AE profile appeared similar for both treatments and included no unexpected findings.

Haematology and Biochemistry

Of the haematology and biochemistry parameters (haemoglobin, leucocytes, thrombocytes, creatinine, sodium, potassium, total protein, alkaline phosphate, alanine aminotransferase and lactate dehydrogenase), only plasma sodium indicated a minor increase from baseline for BIAsp compared with BHI treatment [mean

Table 4 Hypoglycaemic episodes by classification

	Biphasic insulin aspart			Biphasic human insulin 30		
	N (%)	E	Rate	N (%)	E	Rate
Major	7 (2.1)	11	0.1	5 (1.5)	7	0.1
Minor	182 (54.3)	1272	13.1	149 (45.3)	805	8.3
Symptoms only	223 (66.6)	1622	16.7	172 (52.3)	1146	11.8

E, absolute number of hypoglycaemic episodes; N, number of subjects with hypoglycaemic episodes; %, percentage of subjects exposed in the given period having hypoglycaemic episodes; Rate, episodes per subject year.

$_{(BIAsp - BHI\ 30)} = 0.6$; 95% CI: (0.1; 1.1)]; however, the majority of the values were within the normal range.

Quality-of-Life Questionnaires

The following three dimensions were evaluated in the WHO DTSQ: 'Hyperglycaemia', 'Hypoglycaemia' and 'Overall treatment satisfaction'. None of these differed between the BIAsp and the BHI treatment groups after 16 weeks of treatment ($p = 0.239$, $p = 0.208$ and $p = 0.188$ respectively). Similarly, none of the three DHP dimensions evaluated, 'Barriers to activity', 'Disinhibited eating' and 'Psychological distress', were found to differ between the two treatment groups ($p = 0.116$, $p = 0.794$ and $p = 0.196$ respectively).

Discussion

The present study evaluated the potential benefit of intensifying a commonly used twice-daily BHI 30 treatment regimen to a thrice-daily BIAsp treatment regimen for patients with diabetes inadequately controlled in their current treatment. The BIAsp treatment regimen attempts to provide a tailored treatment that covers both prandial and basal insulin requirements while still requiring only three injections per day.

The primary analysis showed that 16 weeks of thrice-daily BIAsp treatment provided superior glycaemic control compared with twice-daily BHI 30 treatment [estimated mean difference in HbA_{1c}: −0.32 (−0.48; −0.16), $p = 0.0001$], reflecting significantly lower average prandial BG increment and average BG level across the day with BIAsp treatment. The results of the DCCT [17] suggest that a sustained reduction of 0.23% units HbA_{1c} could potentially translate to a 10% reduction in late diabetic complications, a reduction we consider clinically relevant. The end-of-trial HbA_{1c} of 8.35% achieved by the BIAsp thrice-daily group does not meet the HbA_{1c} target levels recommended by International Diabetes Federation [19] or American Diabetes Association [20] (<6.5 and <7.0% respectively). However, this trial was not a treat-to-target trial, hence, there was no forced titration to reach a specific target. The present study was not sufficiently powered to allow comparative analysis between the four BIAsp regimens comprising various combinations of BIAsp 30, 50 and 70, and BHI 30 treatment.

The improved BG control with the BIAsp treatment regimen is considered the result of several factors. Most importantly, the rapid-acting IAsp fraction of BIAsp is more quickly absorbed and results in a sharper and more physiological insulin peak than is possible with HI [5,6]. This, as well as thrice-daily dosing, allows for a higher BIAsp dose compared with that in a twice-daily regimen of BHI 30. Indeed, the increased insulin dose may be largely responsible for the greater reduction in HbA_{1c} seen in the BIAsp arm, although the relative contributions of insulin dose, injection frequency and insulin type cannot be determined with the present trial design. Simply increasing the dose is not a viable option with BHI 30 because its pharmacokinetics prevent it being used thrice daily (the 'tail' of the intermediate-acting insulin component would add to the following injection, resulting in a high risk of hypoglycaemia). It

Table 5 Analysis of hypoglycaemic episodes

	BIAsp			BHI 30			BIAsp/BHI 30		
	E	T	Rate	E	T	Rate	RR	95% CI	p value
All (major, minor and symptoms only)	2905	97.4	29.83	1958	97.2	20.14	1.48	1.16; 1.89	0.0015
Minor	1272	97.4	13.06	805	97.2	8.281	1.58	1.15; 2.16	0.0038

BHI, biphasic human insulin; BIAsp, biphasic insulin aspart; CI, confidence interval; E, number of episodes; Rate, episodes per year; RR, relative risk; T, exposure time (years).

Table 6 Adverse events reported by more than 5% of patients

	Biphasic insulin aspart		Biphasic human insulin 30	
	N (%)	E	N (%)	E
Adverse events (total)	218 (65.1)	668	201 (61.1)	565
Headache	54 (16.1)	119	38 (11.6)	81
Upper respiratory tract infection NOS	49 (14.6)	57	38 (11.6)	43
Pharyngitis	14 (4.2)	17	17 (5.2)	18
Influenza-like illness	23 (6.9)	25	21 (6.4)	24
Cough	20 (6.0)	20	11 (3.3)	12
Diarrhoea NOS	9 (2.7)	9	20 (6.1)	23

E, number of adverse events; N, number of patients with adverse event; %, percentage of patients having the adverse event in the treatment group.

is worth noting, however, that despite higher dosing, greater glycaemic control in the BIAsp arm was achieved without increasing the risk of major postprandial hypoglycaemia probably because of the more physiological insulin profile of thrice-daily BIAsp compared with that of the conventional twice-daily BHI treatment.

An evaluation of the BG profiles indicates that the evening dose of insulin may not have been optimized with the BIAsp treatment. A treat-to-target algorithm was not the convention when this trial was initiated, so patients handled their own dose adjustments, which were not enforced by study investigators. This means that the level of BG control achieved in this trial may be reasonably representative of what may be expected in clinical practice. Patients may also have been reluctant to increase their evening dose of BIAsp due to fear of nocturnal hypoglycaemia, which, however, was not found to be an issue during this study. The lower RR of experiencing a nocturnal hypoglycaemic episode with BIAsp seems to supports the notion that there may have been potential for increasing the evening dose of BIAsp in this trial. A recent trial [21] evaluated the efficacy and safety of a similar BIAsp treatment regimen (BIAsp 50 or BIAsp 70 at breakfast and lunch combined with BIAsp 30 in the evening) compared with a basal-bolus treatment regimen (IAsp before each meal and NPH at bedtime). In this trial, the evening dose of BIAsp 30 was set to 50% of the total daily insulin dose and resulted in similar glycaemic control (HbA_{1c}) to that in the basal-bolus regimen. Furthermore, the frequency of both overall and night-time hypoglycaemic episodes were similar between treatments, further supporting the view that night-time glycaemic control could have been better in the present trial if the BIAsp dosing had been optimized.

Patients randomized to the BIAsp treatment group were allocated to treatment with BIAsp 50 if they had a BMI > 30 kg/m^2 and to BIAsp 70 if they had a BMI ≤ 30 kg/m^2. It was not possible to evaluate the benefit of the stratification according to BMI with the current trial design, but this was done in a recent trial that compared obese and non-obese patients treated with thrice-daily BIAsp 50 or BIAsp 70 in a crossover trial design [22]. Although differences in pharmacokinetics of BIAsp 50 and BIAsp 70 were shown, they were equally good at providing the insulin needs of obese or non-obese patients. It seems likely that individual selection of the BIAsp premixes is the key to better glycaemic control for a given patient.

There were very few major hypoglycaemic episodes during the trial, and the numbers were similar for BIAsp and BHI 30 (11 and 7 respectively). Overall, the RR of experiencing any hypoglycaemic episode was higher with the more intensive BIAsp three times a day regimen than with BHI 30 twice a day regimen (RR = 1.48, p = 0.0015). The large UKPDS Study [23] found that intensive insulin treatment for type 2 diabetes resulted in greater frequency of hypoglycaemia episodes, so our result is not totally unexpected. An exploratory analysis found that for both treatments in the present study, the rate of all hypoglycaemic episodes was correlated with HbA_{1c}.

No differences were detected between treatments in any of the dimensions evaluated in the two quality-of-life questionnaires. While this may indicate that patients did not consider three instead of two injections to be a problem, it must also be acknowledged that this could be due to insufficient statistical power to detect minor differences in treatment preference.

The overall safety profile of BIAsp 50 and BIAsp 70 was similar to that observed for BHI 30 and was consistent with that previously observed with IAsp and BIAsp 30.

In conclusion, a thrice-daily BIAsp treatment regimen tailored to the individual insulin requirements of a patient with diabetes is therefore considered an effective and safe option to achieve tighter glycaemic control. Moreover, this regimen may delay the need for the conventional, more intensive basal-bolus treatment intervention.

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