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Three different premixed combinations of biphasic insulin aspart – comparison of the efficacy and safety in a randomized controlled clinical trial in subjects with type 2 diabetes

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Aim: To evaluate clinical efficacy and safety of biphasic insulin aspart (BIAsp) 30 twice daily (b.i.d.) vs. BIAsp 50 or BIAsp 70 (high-mix regimens) thrice daily (t.i.d.) all in combination with metformin in a 36-week clinical trial in subjects with type 2 diabetes.
Methods: Efficacy measurements included haemoglobin A_{1c} (HbA_{1c}) and eight-point plasma glucose (PG); safety included adverse events (AEs) and hypoglycaemic episodes. The three treatment groups (approximately 200 subjects in each group) were well matched regarding sex ratio, ethnicity, age and body mass index.
Results: After 12 weeks, 43% and 54% in the BIAsp 50 and 70 groups, respectively, switched their dinner insulin to BIAsp 30. Both high-mix regimens were non-inferior to BIAsp 30 b.i.d., as measured by change in HbA_{1c}, and the BIAsp %50 regimen was superior. The odds for meeting the American Diabetes Association and The American Association of Clinícal Endocrinologist HbA_{1c} targets of $<7\%$ and $\leq 6.5\%$, respectively, were significantly higher with the BIAsp 50 regimen than with BIAsp 30. A significantly lower PG level was achieved from lunch until 02:00 hours with both high-mix regimens compared with BIAsp 30 b.i.d. AEs were mild or moderate with all three regimens. Frequency of hypoglycaemic episodes was comparable for the BIAsp 50 and the BIAsp 30 b.i.d. regimens but was significantly higher with BIAsp 70 t.i.d.
Conclusions: Glycaemic control improved with BIAsp 50 t.i.d. without higher incidence of hypoglycaemia compared with BIAsp 30 b.i.d.; with BIAsp 70 t.i.d. lower PG levels from lunch to 02.00 hours, but more hypoglycaemic episodes were obtained compared with BIAsp 30 b.i.d. (Clinical Trials.gov ID no: NCT00184574).

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Introduction

In people with type 2 diabetes mellitus, insulin treatment usually starts only when other treatment regimens fail to provide sufficient glycaemic control. Later, as beta-cell mass and function decline, an intensified insulin treatment is needed to maintain glycaemic control. The American Diabetes Association recommends a target

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haemoglobin A_{1c} (HbA_{1c}) of insulin treatment of <7.0% [1] and the International Diabetes Federation has recently suggested an even lower HbA_{1c} target of <6.5% [2]. Insulin treatment is normally initiated as either a once daily injection of basal insulin or a once or twice daily (b.i.d.) injection of a premixed insulin formulation of a short-acting insulin combined with a longer acting insulin with or without oral antidiabetic drugs (OADs). Premixed formulations may provide both sufficient postmeal and basal insulin to control fasting, preprandial and postprandial glucose and may potentially improve postprandial glycaemic excursions throughout a 24-h period. A rapid-acting insulin analogue such as insulin aspart (IAsp) is more rapidly absorbed and has a shorter duration of action than soluble human insulin (HI). A series of three premixed pharmaceutical dosage forms of IAsp with different ratios of the rapid acting (soluble IAsp) and corresponding intermediate-acting phase (protamine co-crystallized IAsp) have been developed, i.e. BIAsp 30, BIAsp 50 and BIAsp 70 respectively (the numbers denote the percentage of the rapid-acting component). BIAsp 30 (NovoMix®30, Novo Nordisk 9/5 DK-3050 Bagsvaerd, Denmark) has been shown to provide better postprandial glucose control than the corresponding formulation with HI, biphasic human insulin (BHI) 30 [3]. The new formulations with a higher percentage of the rapid-acting component may provide even better postprandial coverage [4]. The trial compared the clinical potential of thrice daily (t.i.d.) regimens with BIAsp 50 and BIAsp 70 (high-mix regimens) with a b.i.d. regimen with BIAsp 30 (BIAsp 30 regimen), all in combination with metformin, in subjects with type 2 diabetes.

Methods

Eighteen European countries participated in this controlled, open-label, three-arm, parallel-group treat-to-target trial, which consisted of a screening visit, an initial 12-week treatment period with intensive weekly insulin titration and a 24-week continuation period with less frequent titration. The trial was designed and sponsored by Novo Nordisk A/S. The protocol was approved by local ethics committees and health authorities and was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice. All subjects gave written informed consent before initiation of the trial.

Subjects

Subjects attended a screening visit and if eligible, randomization occurred 4–10 days later, using an interactive Web/voice response system. Subjects were stratified according to previous insulin treatment (once daily or b.i.d.) and whether or not the treatment included sulfonylureas. A total of 603 adult men and women with type 2 diabetes, with a body mass index in the range 22–44 kg/m^2 and previously treated with HI or analogue insulin once daily or b.i.d. in combination with metformin (1000–2550 mg/day) for ≥3 months, were randomized. Previous or concomitant treatment with other OADs was permitted with the exception of thiazolidinediones. Well-controlled (HbA_{1c} < 7%) and poorly controlled (HbA_{1c} > 12%) subjects, subjects with excessive insulin dosing (≥1.80 U/kg body weight) and subjects with significant impaired renal or hepatic function, cardiac disease, proliferative retinopathy, macula oedema or other medical conditions likely to interfere with the trial were excluded.

Dosing

The subjects were randomized (1:1:1) to one of three trial regimens; BIAsp 30 b.i.d. (henceforth referred to as BIAsp 30:30), BIAsp 50 t.i.d. (henceforth referred to as BIAsp 50:50:50) or BIAsp 70 t.i.d. (henceforth referred to as BIAsp 70:70:70). The total daily metformin dose was similar in all treatment groups and was maintained throughout the treatment at the pretrial dose level. All other OADs were discontinued at randomization. Insulin treatment was initiated with the same total daily dose as used before trial entry. In the BIAsp 30 regimen, the daily dose was distributed 1:1 between breakfast and dinner. In the high-mix regimens, the dose was distributed 1:1:2 between breakfast, lunch and dinner. The initial dose distribution was selected according to previous trials [5] to reduce potential variability in dosing and to reflect the fact that dinner was for most subjects the largest meal of the day. The appropriateness of the initial dosing regimens was closely monitored throughout the trial, as subjects were required to record self-measured plasma glucose (SMPG) before breakfast, lunch and dinner on three consecutive days in the week before each site visit. Dose adjustments were based on the mean SMPG before each meal as indicated in the titration algorithm (table 1). The target plasma glucose (PG) range was 4.4–6.1 mmol/l. In subjects on the high-mix regimens with insufficient nightly control, as reflected in a fasting plasma glucose (FPG) level > 7.0 mmol/l, the dinner injection was substituted with BIAsp 30 for the remaining 24 weeks. The entire high-mix treatment groups will be referred to as BIAsp 50:50:50(30) and BIAsp 70:70:70(30) respectively; the terms BIAsp 50:50:50 and BIAsp 70:70:70 will be used to denote the

Table 1 Titration algorithm

Premeal blood glucose level		Dose adjustment
<4.4 mmol/l	<80 mg/dl	−2 U*
4.4–6.1 mmol/l	80–110 mg/dl	0
6.2–7.8 mmol/l	111–140 mg/dl	+2 U
7.9–10 mmol/l	141–180 mg/dl	+4 U
>10 mmol/l	>180 mg/dl	+6 U

*Same or more extensive adjustment in case of symptomatic hypoglycaemia.

subpopulations who continued with the original treatment regimen and BIAsp 50:50:30 and BIAsp 70:70:30 to denote the subpopulations who switched at 12 weeks to BIAsp 30 at dinner.

Efficacy Measurements

Blood samples were drawn at randomization and after 12, 24, 34 and 36 weeks and laboratory evaluations (including HbA_{1c} analysis) were carried out at a central laboratory. The subjects were asked to perform SMPG on a normal weekday one week before randomization, and after 12, 24, 34 and 36 weeks of treatment. They were asked to record the insulin doses taken before the meals and to measure PG at the following times: before and 120 minutes after the three meals (breakfast, lunch and dinner), at bedtime and at 02:00.

Safety Measurements

Subjects were asked to record SMPG values in their diaries whenever they had symptoms of hypoglycaemia. A hypoglycaemic episode was classified as *major* if the subject was unable to treat the episode him/herself and *minor* if the subject dealt with the episode alone and PG was <3.1 mmol/l. All spontaneously reported medical conditions reported during the trial were recorded as adverse events (AEs) and their possible or probable relation to trial treatment was evaluated by the investigators. The change from baseline to 36 weeks for physical examination, vital signs, clinical laboratory evaluations (haematology and biochemistry) and body weight was assessed.

Statistical Analysis

The trial was designed to test for non-inferiority of the high-mix regimens compared with the BIAsp 30 regimen and for superiority in case of non-inferiority of the two high-mix regimens compared with BIAsp 30 for the primary endpoint, HbA_{1c} after 36 weeks of treatment. Sample size was estimated assuming a standard deviation of 1.1% for HbA_{1c}. With a 20% dropout rate, it was estimated that at least 200 patients randomized were needed in each treatment arm to detect a true difference in $HbA_{1c} > 0.4\%$ at a combined power of 81%. All analyses were based on a 5% significance level. HbA_{1c}, average PG and PG increment analyses were based on an analysis of variance model with insulin regimen, stratum and country as factors and the corresponding baseline values as covariates. The proportion of subjects achieving $HbA_{1c} \leq 6.5$ and <7% was analysed by a binary logistic regression model with treatment, stratum, country and baseline HbA_{1c} as explanatory variables. The number of subjects achieving targets and PG analyses were made using the last observation carried forward approach.

All HbA_{1c} and PG analyses were carried out for the 36-week total treatment period by comparison of BIAsp 30 b.i.d. vs. either BIAsp 70:70:70(30) or BIAsp 50:50:50(30) and additionally for the initial 12-week period where all dosings were with BIAsp 50 or BIAsp 70 in the high-mix regimens. Minor hypoglycaemic episodes were analysed using a generalized linear model based on a Poisson distribution. The model included adjustment for stratum, country and exposure time and was corrected for overdispersion.

Results

Subjects

Of 603 randomized subjects, 92 (15%) were withdrawn from the trial (figure 1). The number of withdrawals because of non-compliance was low (<2.5%). There were no significant differences in the withdrawal pattern between the three treatment groups. The treatment arms were generally well balanced with respect to demographic and other baseline characteristics when examined by treatment at randomization or by subgroup (table 2). This was true for insulin dose, although baseline FPG tended to be higher in the high-mix subgroups switching to BIAsp 30 at dinner. Forty-three per cent needed to switch in the BIAsp 50:50:50 arm and 54% in the BIAsp 70:70:70 arm.

Haemoglobin A_{1c}

All treatments led to clinically significant reductions in HbA_{1c} in the initial 12-week titration period, and this reduction was maintained for up to 36 weeks. At 12 weeks, mean HbA_{1c} was 7.33% (BIAsp 30:30), 7.02% (BIAsp 50:50:50) and 7.12% (BIAsp 70:70:70). Pairwise comparisons were significant when the high-mixes were compared with BIAsp 30:30, mean difference = −0.31,

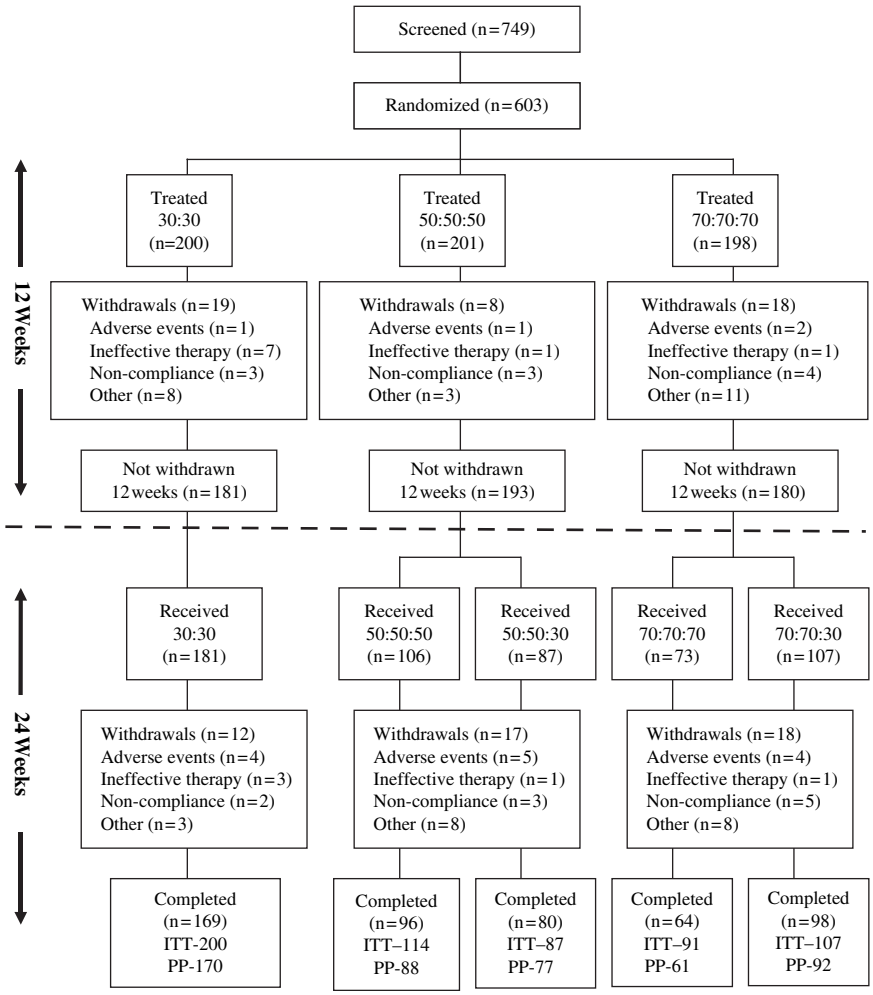

Fig. 1 Subject disposition.

95% confidence interval (CI): −0.43 to −0.18, $p < 0.0001$ for BIAsp 50:50:50 and −0.21, 95% CI: −0.33 to −0.08, $p = 0.0015$ for BIAsp 70:70:70. In the high-mix groups, the pattern was the same for subjects who shifted dinner treatment to BIAsp 30 and subjects who continued with the initial treatment (data not shown). At 36 weeks, mean HbA_{1c} was 7.30% (BIAsp 30:30), 6.99% (BIAsp 50:50:50(30)) and 7.22% (BIAsp 70:70:70(30)). Both high-mix regimens were non-inferior to the BIAsp 30 regimen. Furthermore, HbA_{1c} was significantly lower in the BIAsp 50:50:50(30) arm than in the BIAsp 30:30 arm: −0.3, 95% CI: −0.47 to −0.14, $p = 0.0004$. No significant differences were found between BIAsp 70:70:70(30) and BIAsp 30:30; mean = −0.07, 95% CI: −0.25 to 0.10, $p = 0.4040$ (figure 2). The per protocol analysis supported the findings at 12 and 36 weeks (data not shown).

A significantly greater percentage of subjects achieved target HbA_{1c} values of <7.0% and ≤6.5% in the BIAsp 50:50:50(30) arm (51 and 27%, $p < 0.0001$ and $p = 0.004$ respectively) than in the BIAsp 30:30 arm (31% and 13%). A larger proportion also achieved target in the BIAsp 70:70:70(30) arm (38% and 18%) compared with BIAsp 30:30, but this difference was not statistically significant.

Self-monitored PG

Substantial reductions in PG were achieved with all three treatments (figure 3, 36 weeks). The 24-h PG profiles achieved with the high-mix regimens tended to show less fluctuation than seen with the BIAsp 30 regimen. Mean PG values decreased at all time points with all three regimens, but in general, the decrease was most

Table 2 Baseline characteristics – randomized and receiving treatment

	30:30	50:50:50	50:50:30	70:70:70	70:70:30
N	200	114	87	91	107
Age (years)	60.7 (9.0)	59.9 (9.6)	60.9 (8.5)	60.6 (9.1)	60.3 (8.2)
Sex (M/F)	96/104	50/64	34/53	44/47	44/63
Weight (kg)	88.6 (14.2)	88.3 (14.5)	86.7 (13.9)	89.1 (15.2)	87.1 (13.0)
Body mass index (kg/m^2)	31.9 (3.9)	32.1 (4.2)	31.6 (4.0)	32.0 (4.6)	31.8 (4.1)
Diabetes duration (years)	13.2 (7.3)	12.6 (6.8)	13.2 (6.6)	12.9 (7.4)	13.2 (6.8)
Fasting plasma glucose (mmol/l)	9.3 (2.7)	9.2 (2.1)	9.8 (2.5)	8.8 (2.2)	9.4 (2.1)
Haemoglobin A_{1c} (%)	8.9 (1.1)	8.9 (1.0)	8.9 (1.1)	8.7 (1.0)	8.8 (1.1)
Diabetes complications, N (%)	126 (63.0)	74 (64.9)	56 (64.4)	59 (64.8)	67 (62.6)
Treatment dose					
Total daily insulin dose (IU/kg)	0.52 (0.27)	0.44 (0.20)	0.52 (0.26)	0.50 (0.26)	0.53 (0.28)
Total daily metformin dose (mg)	1679 (545.1)	1777 (531.6)	1771 (519.2)	1792 (562.9)	1812 (529.0)

Data given are means (s.d.).

pronounced in the high-mix treatment arms. Mean PG levels were significantly lower (see lower part of figure 3) from lunch to bedtime with the high-mix regimens compared with the BIAsp 30 regimen. At 36 weeks, FPG was higher for BIAsp 70:70:70(30) but not for BIAsp 50:50:50(30) compared with BIAsp 30:30, whereas at 02:00 hours, PG was not significantly different between BIAsp 70:70:70 (30) and BIAsp 30. The pattern was similar at 12 weeks (data not shown). The mean prandial PG increment was significantly lower with the high-mix regimens both after 12 and 36 weeks of treatment (figure 4).

In general, the efficacy evaluations have shown that HbA_{1c}, daytime PG and prandial PG increment were reduced more with BIAsp 50:50:50(30) than with BIAsp 30:30 and that daytime PG but not HbA_{1c} was reduced more with BIAsp 70:70:70(30) than with BIAsp 30:30. More than half (52%) of the subjects were controlled sufficiently with BIAsp 50 at all meals to meet the FPG target at 12 weeks and continued on the 50:50:50

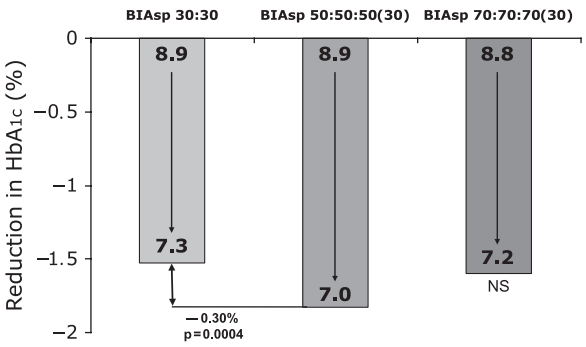

Fig. 2 Reduction in mean haemoglobin A_{1c} (HbA_{1c}) (%) at 36 weeks of treatment, intent-to-treat population. Comparison of biphasic insulin aspart (BIAsp) 30:30 with BIAsp 50:50:50 (30) and BIAsp 30:30 with BIAsp 70:70:70 (30). Analysis was performed by analysis of variance with adjustment for baseline HbA_{1c}, strata and country. Baseline is mean HbA_{1c} and end of trial HbA_{1c} is estimated mean from the model. NS, non-significant.

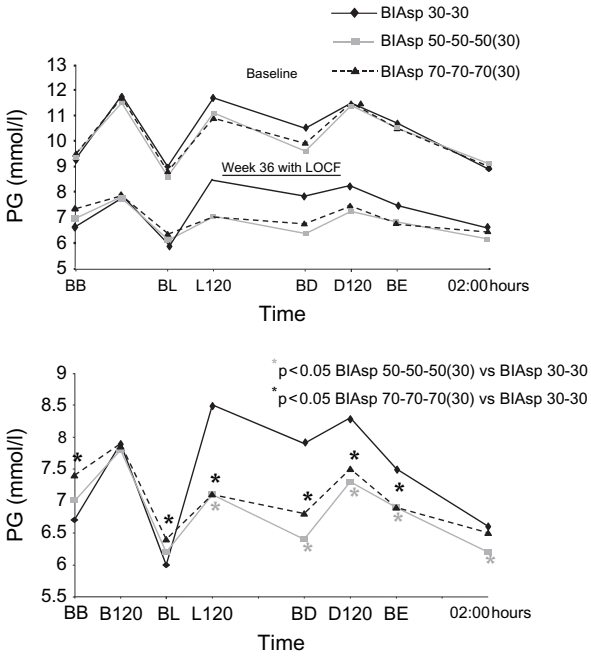

Fig. 3 Mean eight-point plasma glucose (PG) profiles (mmol/l) at baseline and end of trial (week 36 with LOCF) – intent-to-treat. Upper graph: eight-point PG profiles at baseline and after 36 weeks treatment. Lower graph: 36-week PG profile with comparison of thrice and twice daily regimens. BB, before breakfast; B120, breakfast + 120 min; BL, before lunch; L120, lunch + 120 min; BD, before dinner; D120, dinner + 120 min; BE, before night; 02:00 hours, 02:00 hours in the morning; LOCF, last observation carried forward.

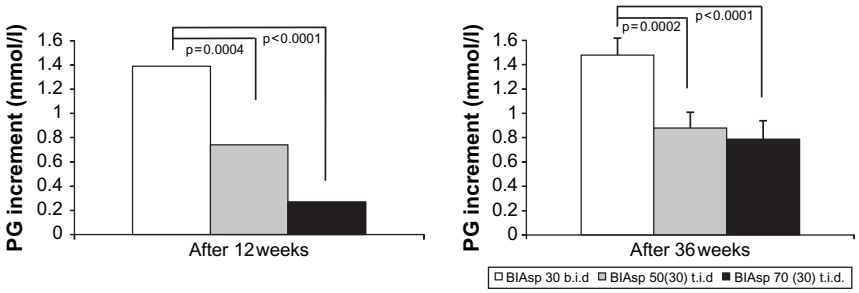

Fig. 4 Average prandial plasma glucose (PG) increment (mmol/l) after 12 and 36 weeks. BIAsp, biphasic insulin aspart.

regimen, whereas less than half (35%) met the target with BIAsp 70:70:70. In the BIAsp 70:70:70 treatment group, significantly more subjects had to switch the dinner injection to BIAsp 30 compared with BIAsp 50:50:50: BIAsp 50:50:50/BIAsp 70:70:70 odds ratio = 0.42, 95% CI: 0.27–0.67, p = 0.0002.

Hypoglycaemia

Major hypoglycaemic episodes were few in all three treatment arms but were more frequent in the BIAsp 70:70:70(30) arm (5.6% of subjects) than in either of the other two treatment arms (≤1.0%). Except for two episodes (one with BIAsp 30:30 and one with BIAsp 50:50:50(30)), all major hypoglycaemic episodes were experienced during daytime (06:00–24:00 hours). The rate of minor episodes was higher in the 70:70:70(30) arm (13.3 episodes/year) than in either of the other two arms (BIAsp 30:30: 7.9 episodes/year and BIAsp 50:50:50(30): 9.3 episodes/year) (table 3), and the relative risk was significantly higher with BIAsp 70:70:70(30) than with BIAsp 30:30 (table 4). The incidence of episodes was higher in the initial 12-week titration period (all three arms), particularly in the BIAsp 70:70:70(30) arm. This was seen in both high-mix treatment arms whether or not they switched to BIAsp 30 at dinner; however, the rate was consistently higher in subjects who needed to switch the dinner dose (data not shown). The rate of minor nocturnal episodes (occurring from 00:00 to 06:00 hours) was similar in the three treatment arms (1.3–1.6 episodes/year) (table 3), and the relative risks were not significantly different (table 4). During daytime, the rate of hypoglycaemia tended to be higher after breakfast with the BIAsp 30 regimen and highest after lunch and dinner with the high-mix regimens (data not shown). Overall, the rate of hypoglycaemia remained low through the trial period in all treatment arms and only few major episodes were recorded.

Insulin Dose

Insulin doses doubled in the high-mix arms and almost doubled in the BIAsp 30:30 arm during the initial intense 12-week titration period. After 36 weeks, the mean daily dose had increased a further 10% and remained significantly higher in the two high-mix arms than in the BIAsp 30 arm: with BIAsp 30:30 mean dose = 1.07 U/kg; BIAsp 50:50:50(30) mean dose = 1.18 U/kg and BIAsp 70:70:70(30) mean dose = 1.16 U/kg. Total daily insulin dose was significantly higher with BIAsp 50:50:50(30) and BIAsp 70:70:70(30) than with BIAsp 30:30 (mean difference of 0.11 and 0.08 units/kg/day respectively; $p < 0.05$ for both comparisons; data not shown). Total daily insulin dose did not differ significantly between the two

Table 3 Hypoglycaemic episodes by classification

	BIAsp 30:30			BIAsp 50:50:50(30)			BIAsp 70:70:70(30)		
	N (%)	E	Rate	N (%)	E	Rate	N (%)	E	Rate
Over 24 h									
Major	2 (1.0)	4	0.0	1 (0.5)	1	0.0	11 (5.6)	14	0.1
Minor	128 (64.0)	987	7.9	159 (79.1)	1213	9.3	148 (74.7)	1619	13.3
Nocturnal									
Major	1 (0.5)	1	0.0	1 (0.5)	1	0.0	0 (0.0)	0	0.0
Minor	66 (33.0)	196	1.6	77 (38.3)	169	1.3	73 (36.9)	189	1.6

BIAsp, biphasic insulin aspart.

Table 4 Risk of minor episodes – pairwise comparisons after 36 weeks

	BIAsp	BIAsp	RR (95% CI)	p Value
24 h	50:50:50(30)	30:30	1.208 (0.894–1.630)	0.2185
	70:70:-70(30)	30:30	1.714 (1.289–2.980)	0.0002
Nocturnal	50:50:50(30)	30:30	0.848 (0.578–1.243)	0.3979
	70:70:70(30)	30:30	1.045 (0.720–1.518)	0.8162

Nocturnal episodes are defined as episodes occurring between 00:00 and 06:00 hours, both inclusive. BIAsp, biphasic insulin aspart; RR, relative risk high-mix/BIAsp 30.

high-mix treatment arms. When mealtime dose was estimated as a proportion of total, there was a slight reduction in the dinner dose at 12 weeks, which was maintained until end of trial in the high-mix groups. Percentages of the total daily dose at breakfast:lunch:dinner were 26:25:49 (week 1), 27:31:42 (week 12) and 27:30:43 (week 36) in the 50:50:50(30) group and 25:25:49 (week 1), 28:29:43 (week 12) and 27:29:44 (week 36) in the 70:70:70(30) group.

Body Weight

Body weight increased similarly in all three arms. Although the baseline-adjusted increase in body weight was slightly higher at the end of the trial with BIAsp 50:50:50(30) and BIAsp 70:70:70(30) (approximately 4 kg) than with BIAsp 30:30 (approximately 3.5 kg), the increase was not significantly different in the three arms.

Adverse Events

The AE profiles were similar in the high-mix treatment arms and in the BIAsp 30 arm: in the BIAsp 30:30 arm, 102 (51%) of subjects reported an AE compared with 110 (55%) treated with BIAsp 50:50:50(30) and 105 (53%) with BIAsp 70:70:70(30). Serious AEs were reported by 18 (9%), 14 (7%) and 22 (11%) subjects, respectively. AEs considered to be possibly or probably related to trial medication were reported for 5 subjects in the BIAsp 30:30 arm, 4 subjects in the BIAsp 50:50:50(30) arm and 13 subjects in the BIAsp 70:70:70(30) arm. The majority of possibly/probably related AEs in the BIAsp 70:70:70(30) arm were hypoglycaemic episodes (six subjects) and hypokalaemia (six subjects). All other possibly/probably related AEs in the trial were sporadic events, occurring in no more than one or two individuals. Of these, two events were reported as serious in the BIAsp 30:30 arm (Brugada syndrome and weight increase) and nine were reported as serious in the BIAsp 70:70:70(30) arm (seven episodes of hypoglycaemia and two episodes of hypoglycaemic coma). There were no clinically relevant differences in physical examination, vital signs or clinical laboratory (haematological and biochemistry) evaluations at the end of the trial.

Discussion

An optimal insulin regimen should provide adequate interprandial, postprandial and nocturnal glycaemic control. In patients with type 2 diabetes, BIAsp 30 has been shown to provide improved postprandal glycaemic control compared with BHI 30, neutral protein hagedorn (NPH) or insulin glargine (Hamili *et al.*, 2005) [6]. BIAsp 30 b.i.d. has been shown to provide superior overall glycaemic control (HbA_{1c}) compared with NPH insulin b.i.d. and with equivalent safety profiles with both regimens [7]. Earlier data [8] have indicated that high-mix regimens provide improved daytime control but less nocturnal control compared with BHI 30, and clinical data have indicated that nocturnal control might be improved by substitution with BIAsp 30 at dinner [9]. In the current trial with the use of an intense insulin titration, overall control (HbA_{1c}), daytime control (eight-point PG) and nightly control (FPG) improved substantially with all regimens and more than seen in a previous trial [10], probably because of a more intense insulin titration and because of supplementary oral medication. However, the higher FPG with BIAsp 70 t.i.d. compared with BIAsp 30 (refer figure 3) is a clear illustration of the variation within the population as to nightly PG control and emphasize the importance of individual dose titration for treatment optimization. A difference between the two high-mix regimens was expected because of the lower fraction of basal insulin in BIAsp 70, but it is worth noticing that a large fraction of subjects in both high-mix regimens could meet the FPG targets at 12 weeks without a dose switch at dinner.

Subjects and staff were blinded as to the two high-mix regimens (BIAsp 50 or BIAsp 70) but not to whether the regimens were b.i.d. or t.i.d. However, as all hypoglycaemia analyses were based on either biochemical measurements (minor episodes) or well-defined clinical criteria, bias related to lack of blinding is considered minimal. Overall, the rate of hypoglycaemia remained low through the trial period in all treatment arms and the majority of the episodes were minor. The relative daytime risk of minor hypoglycaemia was slightly but significantly higher with the high-mix regimens. This was to be expected with an intensified treatment with more injections and a higher total daily dose and should be

weighed against the long-term glycaemic benefits. Less than 1% of the episodes were evaluated as major. The rate of minor episodes was approximately 50% higher than previously reported with a high-mix regimen [9], probably a reflection of the more aggressive insulin titration and more substantial HbA_{1c} reduction achieved in the current trial. With the high relative content of soluble IAsp in BIAsp 70, the timing of insulin injection relative to mealtime and the adjustment of dose relative to meal size and physical activity is more critical than with the other BIAsp mixtures. In a clinical setting, it might be easier for patient and investigator to make such adaptations and manage both to improve glycaemic control and avoid hypoglycaemic episodes. Insulin dose increased with all treatment regimens. With the BIAsp 30 regimen, breakfast and dinner dose ratio remained close to 1:1 throughout the trial, whereas with the high-mix regimens, the dinner doses changed slightly from the ratios of 26:25:49 (percentage of total daily dose at breakfast, lunch and dinner) at initiation to approximately 27:30:43 at end of trial. This shift might be explained as an adaptation to actual meal sizes and might also reflect that approximately 50% of the subjects switched to a formulation with a higher content of basal insulin after 12 weeks of treatment.

Weight gain is one of the main expected side effects of initiation of insulin therapy. An initial increase in body weight with intensive insulin therapy of about 4 kg is often observed over a period of 6 years [11]. The weight gain tended to lessen when insulin titration became less intense. Although the high-mix regimens resulted in a higher total insulin dose than BIAsp 30 b.i.d., the increase in body weight was not significantly different between the treatment regimens.

Glycaemic control may be substantially improved with a t.i.d. high-mix regimen with BIAsp 50 without risk of a higher incidence of major or nocturnal hypoglycaemia compared with BIAsp 30 b.i.d. and without higher weight gain. Subjects insufficiently controlled at night with BIAsp 50 alone improved after substitution of dinner treatment with BIAsp 30. A t.i.d. regimen with BIAsp 70 provided improved prandial glycaemic control but not overall control compared with BIAsp 30, and this regimen was associated with a higher risk of hypoglycaemia. The high-mix regimens showed similar characteristics to BIAsp 30 regarding frequency and severity of AEs; no other safety differences between regimens were recorded. A t.i.d. therapy with BIAsp 50 and 70 may provide beneficial effects on glycaemic control without major safety issues compared with BIAsp 30 b.i.d. The nocturnal glycaemic control of a high-mix t.i.d. regimen may be improved by switching the dinner dose to BIAsp 30 thus providing efficient nocturnal, diurnal and prandial PG control. This regimen may be adapted to the needs for basal insulin coverage in a broad range of patients with type 2 diabetes.

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