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Premixed insulin aspart 30 vs. premixed human insulin 30/70 twice daily: a randomized trial in Type 1 and Type 2 diabetic patients

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Accepted 21 November 2001

Abstract

Aim To compare the efficacy and safety of premixed insulin aspart (30% free and 70% protamine-bound, BIAsp 30) with human insulin premix (BHI 30) used in a twice-daily injection regimen in people with Type 1 and Type 2 diabetes.

Methods People with Type 1 and Type 2 diabetes (n = 294) using twice-daily insulin were randomized to a 12-week open-label comparison of BIAsp 30 and BHI 30. Efficacy was assessed by analysis of variance of 12-week data, adjusted for baseline level.

Results BIAsp 30 was as effective as BHI 30 based on the primary efficacy measure, HbA_{1c}, mean difference –0.01 (90% confidence interval (CI) –0.14; 0.12) %Hb. Meal-time self-measured blood glucose increment averaged over the three main meals was significantly lower in the BIAsp 30 group than in the BHI 30 group (–0.68 (–1.20; –0.16) mmol/l; $P < 0.02$). Significant improvements were observed after breakfast, before lunch, after dinner and at bedtime ($P < 0.02$–0.05), with blood glucose around 1.0 mmol/l lower in the BIAsp 30 group. The number of major hypoglycaemic episodes with BIAsp 30 was half that with BHI 30. However, the overall risk of both minor and major hypoglycaemia did not differ significantly between treatments.

Conclusion Post-prandial glycaemic control was significantly improved, without increasing the risk of hypoglycaemia, and overall control was similar when people with Type 1 and Type 2 diabetes were treated on a twice-daily regimen with immediate premeal injections of BIAsp 30 compared with BHI 30.

Diabet. Med. 19, 393–399 (2002)

Keywords insulin analogue, insulin aspart, premixed insulin, glycaemic control, twice-daily regimen

Abbreviations IAsp, insulin aspart; BIAsp 30, biphasic insulin aspart 30; BHI 30, biphasic human insulin 30/70; BG, blood glucose; ANOVA, analysis of variance; QoL, quality of life; ITT, intention-to-treat; CI, confidence interval; HI, human insulin

Introduction

Meal-time glycaemic control is not optimal in most people using human insulin, even where it is recommended that injections are given approximately 30 min before meals [1,2]. Insulin analogues with improved absorption characteristics were developed to overcome the shortcomings of conventional native insulin treatment in matching more closely meal-time physiological insulin secretion [3]. One such analogue is insulin aspart (IAsp). Insulin aspart is homologous to human insulin, with the exception of the substitution of proline with aspartic acid at position B28 in the insulin molecule, resulting in it being predominantly monomeric in the subcutaneous injection site [4]. This leads to abolition of the injection–

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absorption lag-phase and faster absorption, leading to a more physiological time-action profile, even when insulin aspart is administered immediately before the meal [4–8].

A number of recent studies, most prominently the Diabetes Control and Complications Trial (DCCT) and the United Kingdom Prospective Diabetes Study, have confirmed that more intensive management of blood glucose control reduces the incidence and delays the progression of late diabetic complications associated with Type 1 and Type 2 diabetes [9–12]. However, in some people with insulin-requiring diabetes, multiple-injection regimens may not be desirable. Indeed, premixed insulin formulations are commonly prescribed for insulin-requiring Type 2 diabetes, and thus, improvement of the properties of such premixed regimens may be of clinical importance.

Biphasic insulin aspart 30 (BIAsp 30) is a premixed formulation containing 30% free IAsp and 70% protamine-bound IAsp. Previous pharmacodynamic studies in healthy subjects and people with Type 2 diabetes demonstrated that the faster onset and greater peak action of IAsp compared with human insulin (HI) are preserved in BIAsp 30 [13,14]. BIAsp 30 therefore provides the possibility of immediate premeal injection as well as the potential to improve post-prandial blood glucose control compared with the equivalent premixed formulation of human insulin (BHI 30). The objective of the present trial was to compare the efficacy and safety profiles of BIAsp 30 and BHI 30 when used in a twice-daily injection regimen.

Patients and methods

Setting

A total of 294 adult male and female Type 1 and Type 2 diabetic patients (body mass index (BMI) ≤ 35.0 kg/m^2 and $HbA_{1c} \leq 11.0\%$) already using a twice-daily insulin regimen were enrolled and randomized according to an open-label, parallel-group design. Patients were recruited from 36 centres in England, Northern Ireland, Germany, and Austria. The trial was conducted in accordance with the Helsinki Declaration [15] and with Good Clinical Practice [16]. Approval from health authorities and local Ethics Committees was obtained prior to commencement of trial-related activities. All patients gave written informed consent.

Patient population

Of the 143 patients randomized to BIAsp 30, 140 were exposed to trial insulin and 126 (90%) completed the trial. Fourteen did not complete the study due to four adverse events (diarrhoea, arterial thrombosis, rash, and hyperthyroidism), inadequate blood glucose control in one, five who could not keep to the protocol, and four due to other reasons (primarily personal). All the 151 patients randomized to BHI 30 were exposed to the insulin and 142 (96%) completed the trial. Among the nine who dropped out there were three who experienced adverse events (abdominal pain, neuropathy, and rash), three who could not keep to the protocol, and three due to other reasons (primarily personal).

In both treatment groups, 96% of those exposed were included in the intention-to-treat (ITT) analysis. Baseline characteristics for patients exposed to trial insulin are given in Table 1, split by diabetes type.

Following a screening visit to assess eligibility to participate, patients were randomized to a 12-week treatment period on a trial therapy, attending for assessments at 2, 4, 8, and 12 weeks after randomization. Changes in HbA_{1c} and self-measured eight-point blood glucose profiles (before and 90 min after main meals, at bed-time and at 02:00 h) from randomization to 12 weeks were analysed.

Treatment regimens

Both biphasic insulin aspart 30, 100 U/ml, and biphasic human insulin 30/70, 100 IU/ml, were contained in 1.5 ml Penfill cartridges (Novo Nordisk, Bagsvaerd, Denmark) and administered subcutaneously as a twice-daily injection regimen (before breakfast and dinner), using the NovoPen 1.5 device (Novo Nordisk).

BIAsp 30 was recommended to be injected within 10 min before meals and BHI 30 approximately 30 min before meals. Doses were adjusted according to self blood glucose measurements.

Table 1 Baseline characteristics of patients exposed to trial insulins, split by diabetes type

	Type 1 diabetes		Type 2 diabetes	
	BIAsp 30	BHI 30	BIAsp 30	BHI 30
n	55	49	85	102
Age (years)	43.2 ± 13.4	46.3 ± 12.8	62.7 ± 8.8	63.8 ± 8.4
Body weight (kg)	76.1 ± 14.2	79.7 ± 14.5	80.9 ± 13.9	78.0 ± 12.1
BMI (kg/m^2)	26.1 ± 3.7	26.4 ± 3.1	28.1 ± 3.5	28.0 ± 3.9
Duration of diabetes (years)	14.9 ± 11.0	17.0 ± 13.0	15.0 ± 9.1	14.4 ± 7.4
HbA_{1c} (%)	8.37 ± 1.24	8.38 ± 1.14	8.09 ± 1.20	8.18 ± 1.32
Sex (M/F (%))	64/36	69/31	54/46	45/55

Mean ± SD, number, or percentage.
HbA_{1c} normal range 4.0–6.0%.

Laboratory methods

HbA_{1c} was assayed by Clinical Research Laboratories (CRL; Zaventem, Belgium) using a method in agreement with that used in the DCCT: an ion-exchange High Performance Liquid Chromatography method on a BioRad DIAMAT (Hercules, CA, USA), normal range 4.0–6.0%. Basic haematology and biochemistry measurements were made by CRL using standard methods. Eight-point blood glucose profiles were measured by patients using OneTouch II meters (LifeScan, Milpitas, CA, USA) after training.

Adverse events

Patients recorded hypoglycaemic episodes in a diary. Hypoglycaemic episodes were classified as minor (symptoms of hypoglycaemia managed without assistance, confirmed if possible by a BG reading) or major A (requiring third-party assistance) or major B (receiving IV glucose or glucagon). Other adverse events were recorded at each visit and classified according to standard pharmaceutical industry guidelines.

Statistical analysis

The comparison of the primary endpoint, HbA_{1c} at 12 weeks, was based on a non-inferiority criterion in accordance with normal regulatory practice (corresponding to a one-sided test, upper 90% confidence interval (CI) limit for the treatment comparison required to be < 0.6% absolute). Using this criterion, a SD of HbA_{1c} of 1.2–1.5%, a 5% significance level and 80% power, 254 patients were required for analysis. With an expected drop-out rate of 15%, and in accordance with the numbers needed for adverse event monitoring [17], it was planned to randomize 300 patients. All efficacy analyses were based on the ITT population [18], defined as all patients exposed to trial drug and with any efficacy data. The safety population in analyses of hypoglycaemia was based on actual exposure (n = 138 for BIAsp 30 and n = 153 for BHI 30; discrepancy due to pharmacy dispensing error).

Randomization was carried out using an electronic drug request system (a voice response system that allocates treatment based on the subject number given at screening). Randomization was stratified within each centre in blocks of eight.

For the primary endpoint, HbA_{1c} at 12 weeks, the main ana-lysis of variance (ANOVA) model included the fixed effects of treatment, centre, and HbA_{1c} at baseline as covariates. HbA_{1c} at 12 weeks was also analysed, adjusted for rate of hypoglycaemic episodes (minor and major, separately) in the whole treatment period and adjusted for insulin dosing.

Secondary endpoints, except as discussed below, were analysed with an ANOVA including the fixed effects of treatment and centre and with data at baseline as a covariate. Cox regression analysis of time to first major hypoglycaemic episode [19] was used to estimate the relative risk of having a major hypoglycaemic episode for BIAsp 30 relative to BHI 30. The number of minor hypoglycaemic episodes was analysed using a generalized linear model based on the Poisson distribution [20]. The Mantel–Haenszel method was used to estimate the relative risk of nocturnal and daily hypoglycaemic episodes. Type 1/Type 2 subset analyses were not performed for major hypoglycaemia due to the low number of episodes. Haematology, biochemistry, lipids, and vital signs were compared by a two-sample Student's t-test with the change at 12 weeks as endpoints. Analyses of all secondary endpoints are two-tailed.

Stratification of the randomization according to type of diabetes was not performed, as the aim of the protocol was to evaluate the effect of the two treatments in any person with diabetes eligible for a twice-daily premixed regimen. Subset analyses by diabetes type are presented as supportive to the overall analyses.

Statistical programming was performed using SAS v6.11 (SAS Institute, Raleigh, NC, USA) on a UNIX platform or S-plus v4.0 Release 3 for Windows (MathSoft, Cambridge, MA, USA).

Results

Insulin dose

A small increase in the total daily biphasic insulin dose was observed with BIAsp 30 compared with BHI 30 (mean difference at 12 weeks 0.03 (95% CI 0.01; 0.05) U/kg; P < 0.01; Table 2).

Blood glucose control

The mean treatment difference in HbA_{1c} after 12 weeks was –0.01 (90% CI –0.14; 0.12)% (NS; Table 2).

Meal-time blood glucose increment averaged over the three main meals (including lunch) was significantly lower in the BIAsp 30 group than in the BHI 30 group: –0.68 (95% CI –1.20; –0.16) mmol/l (P < 0.02; Table 2). The eight-point blood glucose profiles showed significant treatment differences in favour of BIAsp 30 after breakfast, before lunch, after dinner and at bedtime, with blood glucose values around 1.0 mmol/l lower in the BIAsp 30 group at each of these time-points (Table 2, Fig. 1).

Analyses adjusted for hypoglycaemia rate and insulin dosage are in agreement with the primary analysis, as are subset analyses by diabetes type (Table 2).

Hypoglycaemia

With BIAsp 30, 20 major and 362 minor hypoglycaemic episodes were reported, compared with 42 major and 361 minor episodes with BHI 30. Thus, half as many major episodes were reported with BIAsp 30 and risk estimates for major episodes were lower with BIAsp 30, but not significantly so. The lack of statistical significance arises in part because three patients on BHI 30 accounted for 19 of the 42 major episodes. A tendency for a lower risk of minor nocturnal episodes with BIAsp 30 was observed (P = 0.06; Table 3). Approximately 85% of minor episodes were accompanied by a home BG reading.

Type 1 diabetes and longer duration of diabetes were significant risk factors for major hypoglycaemia. Patients in

Table 2 Treatment comparisons of changes in HbA_{1c}, blood glucose endpoints, insulin dosing, and body mass index (BMI) after 12 weeks of trial insulin therapies

	BIAsp 30, mean (SEM)	BHI 30, mean (SEM)	BIAsp 30–BHI 30 mean [CI]	*P*-value
HbA_{1c} (%Hb)				
Primary analysis	8.14 (0.06)	8.15 (0.06)	–0.01 [–0.14; 0.12]	NS
Adj. for insulin dose			–0.03 [–0.16; 0.10]	NS
Adj. for hypoglycaemia			Maj: 0.02 [–0.12; 0.15]	NS
			Min: 0.02 [–0.11; 0.15]	NS
Blood glucose (mmol/l)				
Prandial increment	1.66 (0.20)	2.34 (0.19)	–0.68 [–1.20; –0.16]	< 0.02
Adj. for insulin dose			–0.69 [–1.10; –0.26]	< 0.01
Eight-point profile				
Before breakfast	8.92 (0.28)	8.24 (0.27)	0.67 [–0.05; 1.40]	NS
Breakfast + 90 min	10.40 (0.37)	11.40 (0.36)	–1.01 [–1.97; –0.05]	< 0.05
Before lunch	6.64 (0.28)	7.57 (0.27)	–0.93 [–1.66; –0.20]	< 0.02
Lunch + 90 min	9.57 (0.28)	9.97 (0.27)	–0.40 [–1.13; 0.33]	NS
Before dinner	8.91 (0.30)	8.72 (0.29)	0.19 [–0.60; 0.98]	NS
Dinner + 90 min	9.22 (0.33)	10.20 (0.32)	–1.03 [–1.89; –0.18]	< 0.02
Bed-time	8.22 (0.31)	9.10 (0.30)	–0.88 [–1.69; –0.07]	< 0.05
02:00 h	8.12 (0.25)	8.12 (0.25)	–0.00 [–0.65; 0.65]	NS
Insulin dose (U/kg)	0.65 (0.01)	0.62 (0.01)	0.03 [0.01; 0.05]	< 0.01
BMI (kg/m^2)	–0.17 (0.07)	–0.00 (0.07)	–0.17 [–0.37; 0.03]	NS

90% CI for HbA_{1c} (one-sided test; non-inferiority criterion) and 95% CI for all other endpoints. HbA_{1c} normal range 4.0–6.0%. Means, SEMs, confidence intervals and *P*-values are based on an ANOVA with adjustment for centre and baseline values. BMI is two-sample *t*-test on change from baseline.

Point estimate, CI and P*-value for subset analyses by diabetes type:*

HbA_{1c}: Type 1: 0.19 [–0.05; 0.43], NS Type 2: –0.13 [–0.28; 0.03], NS.

Prandial incr.: Type 1: –1.08 [–2.25; 0.09], 0.06 Type 2: –0.29 [–0.88; 0.29], NS.

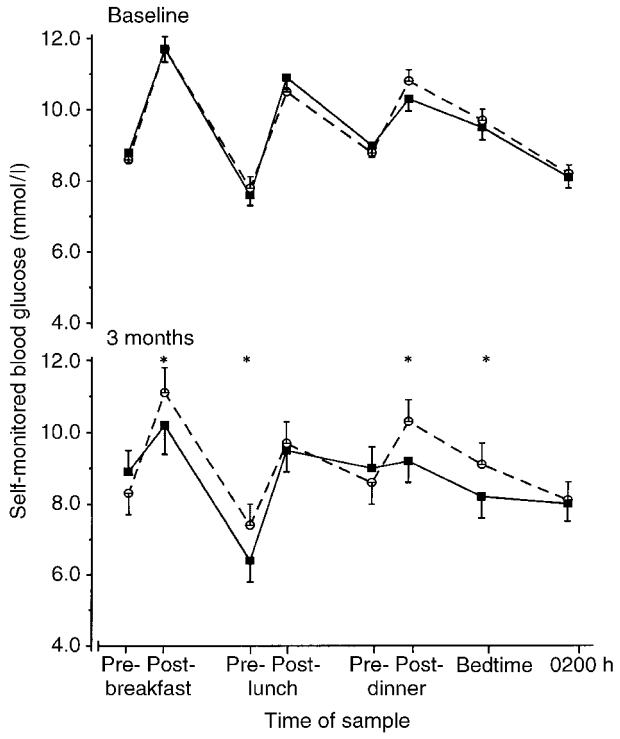

Figure 1 Mean self-measured eight-point blood glucose profiles at baseline and 3 months in people with diabetes treated with BIAsp 30 (■) or BHI 30 (○). *Significant difference ($P < 0.05$).

the BIAsp 30 group did not report more hypoglycaemic episodes during the initial phase of treatment than patients in the BHI 30 group (major four vs. 14; minor 117 vs. 101 episodes).

Adverse events

The adverse event profile with BIAsp 30, apart from hypoglycaemia, was similar to BHI 30. No specific problems were detected with BIAsp 30. Weight gain was not observed during the trial. Mean BMI changes were –0.2 kg/m^2 in the BIAsp 30 and –0.0 kg/m^2 in the BHI 30 group, and no treatment difference was observed at 12 weeks (Table 2).

Patient acceptability

All patients completing the 3-month treatment period were offered the opportunity to continue their randomized treatment in an extension trial. The proportion of patients continuing (72% in the BIAsp 30 group and 68% in the BHI 30 group) indicated excellent patient acceptability. In addition, all patients at the German-speaking centres completed The Diabetes-specific quality-of-life (QoL) scale for diabetic patients on conventional insulin treatment (DSQOLS-2) and Diabetes Treatment Satisfaction Questionnaire (DTSQ).

Table 3 Major and minor hypoglycaemic episodes reported during 12 weeks of exposure to the trial insulins

	BIAsp 30 (n = 138)	BHI 30 (n = 153)	P
Major episodes			
Patients (%)	8	12	
Episodes (n), total (Type 1/Type 2)	20 (14/6)	42 (30/12)	
Overall relative risk BIAsp 30/BHI 30[a]	0.66 [0.31; 1.41]		NS
06:00–24:00 h	0.72 [0.34; 1.54]		NS
00:00–06:00 h	0.62 [0.19; 2.04]		NS
Minor episodes			
Patients (%)	54	56	
Episodes (n), total (Type 1/Type 2)	362 (176/184)	361 (191/170)	
Overall relative risk BIAsp 30/BHI 30[b]	1.12 [0.80; 1.56]		NS
06:00–24:00 h	1.02 [0.82; 1.27][c]		NS
00:00–06:00 h	0.63 [0.37; 1.09][c]		0.06

Relative risk and 95% CI for all comparisons.
[a]Cox regression on time to first major episode; [b]Poisson regression on number of minor episodes; [c]58 events for BIAsp 30 vs. 39 events for BHI 30.
RR, CI and P-value for subset analyses of minor hypoglycaemia by diabetes type:
Type 1: RR = 0.92 [0.59; 1.43], NS. Type 2: RR = 1.32 [0.81; 2.13], NS.

These data are still being recorded as part of the extension trial.

Discussion

BIAsp 30 was developed to provide improved post-prandial blood glucose control while retaining the convenience of immediate premeal injection in a twice-daily regimen. The use of premixed insulins is increasing world-wide. Under normal out-patient conditions, overall blood glucose control attained with twice-daily regimens may in some patients be as good as with multiple injection therapy [21–23].

In the present study, BIAsp 30 was as effective as BHI 30 in controlling HbA_{1c}. However, meal-time blood glucose control, including lunch when no insulin was administered, was significantly better with BIAsp 30, even after adjusting for insulin dose. All the statistically significant treatment differences at individual time points (after breakfast, before lunch, after dinner, and at bedtime) were in favour of BIAsp 30. Thus, the well-described superior post-prandial blood glucose control with IAsp compared with HI [8,24–28] is preserved in the premixed 30/70 formulation. Furthermore, this did not occur at the expense of increased risk of hypoglycaemia. Post-lunch blood glucose control was similar with BIAsp 30 and BHI 30. Examination of the glucose profiles shows this to be because the improved blood glucose control after breakfast persists through to the prelunch level, with some convergence of glucose levels after lunch.

The discrepancy between the gains in post-breakfast and post-dinner blood glucose control, and the identical HbA_{1c} level, need explanation. It is possible that the long half-life of glycated haemoglobin means that it did not completely reflect blood glucose control at 12 weeks, as experience was gained with the new insulin. Indeed, the bias of prior experience giving possible advantage to the comparator insulin leaves the speculative possibility of future further advantage for BIAsp 30 unaddressed.

An alternative explanation of the similar HbA_{1c} results is that preprandial and overnight glucose levels are higher. Indeed, in the present study there was very little evidence of such an effect, with blood glucose levels being better with BIAsp 30 at lunch time and bed time, and essentially the same at 02:00 h and predinner.

HbA_{1c} is usually the preferred primary efficacy measure for these studies, but will reflect both hyper- and hypoglycaemic episodes. However, the DCCT results show a non-linear relationship between control and complications, and it is possible that the higher levels of glucose seen after meals may be of greater pathological significance than the average levels over the rest of the day. This is supported by epidemiological observations, by experimental data from healthy subjects, and by the observation that HbA_{1c} itself is a better predictor of microvascular complications than fasting plasma glucose [29–31]. Insulin preparations which better control post-prandial blood glucose levels may therefore lead to fewer microvascular complications, even if HbA_{1c} is unchanged, a hypothesis that could only be tested in a long-term outcome study.

Another confounder of the usefulness of HbA_{1c} to predict microvascular complications will be hypoglycaemia. Although estimates for major events (and minor events at night) were lower for BIAsp 30 than BHI 30, the number of events in this study was too small for this to have statistical significance. In larger phase 3 studies with insulin aspart and insulin lispro, significantly less hypoglycaemia, in particular at night, has been a relatively consistent finding [27,28,32].

The analyses performed for Type 1 and Type 2 diabetes separately are all in agreement with the results of the overall analyses. Such comparisons have been limited by two considerations. First, they were not predefined. The aim of the protocol was to evaluate the effect of the two treatments in

any person with diabetes eligible for a twice-daily premixed regimen. Second, an unbalanced distribution of diabetes type between Germany and the UK complicates the interpretation of the covariates 'diabetes type' and 'country' in the ANOVA and regression analyses since the effects may reflect both the difference in diabetes type and a country difference in the diabetes care provided.

Other published studies on premixed insulin analogues are few. Data from one long-term treatment trial have been published. In a 6-month randomized, open-label cross-over study of 89 Type 1 diabetic patients, a premixed 25/75% formulation of insulin lispro (Humalog Mix25, Lilly) attained better meal-time blood glucose control compared with a human insulin 30/70 premix after the morning and evening meals before which the insulin was administered [33].

In the current study BIAsp 30 was recommended to be injected within 10 min before the meal and BHI 30 insulin 30 min before the meal. Surveys have shown that recommendations on the timing of human insulin injections vary substantially [34], and that up to two-thirds of people with diabetes ignore the advice [35,36]. Although some suggest that an injection meal interval is an obsolete dogma [37], a number of studies have confirmed that longer injection–meal intervals with human insulin give better post-prandial blood glucose control without increased risk of hypoglycaemia [2,24–26,37,38].

In conclusion, the present trial shows that HbA_{1c} is no different but post-prandial blood glucose control is significantly better when patients are treated in a twice-daily regimen with immediate premeal injections of BIAsp 30 than with BHI 30, without increasing the risk of hypoglycaemia. The potential of BIAsp 30 to reduce further HbA_{1c} and risk of hypoglycaemia compared with BHI 30 needs to be investigated in long-term studies.

Acknowledgements

We thank all the people with diabetes who took part in this study. The authors would like to acknowledge the other members of the 'European BIAsp 30 Study Group': UK, S. C. Bain, Birmingham; M. Clements, Watford; A. Collier, Ayr; R. Corrall, Bristol; J. Dean, Bolton; M. Fisher, Paisley; C. Fox, Northampton; R. S. Gray, Howden; K. Hardy, Whiston; G. Jones, Blackburn; P. McNally, Leicester; B. O'Malley, Kettering; S. Page, Nottingham; J. Reckless, Bath. Ireland, J. J. Nolan, Dublin; C. Thompson, Dublin; D. J. O'Halloran, Cork. Germany and Austria, G. Allolio, Wuerzburg; M. Frank, Saar; T. Hampel, Schwedt; R. Hampel, Rostock; H. R. Henrichs, Quakenbrueck; M. Jecht, Berlin; S. Krabbe, Anklam; J. Krug, Leipzig; H. P. Meissner, Berlin; U. A. Mueller, Jena; M. Pein, Hamburg; R. Prager, Wien; P. D. Laus-Peter, Erkner; E. Standl, Muenchen; H. Toplak, Graz; B. Wegner, Cottbus; H. Alawi, Saarlouis. This study was part of the clinical development programme for insulin aspart by Novo Nordisk. C.B., N.M.K. and A.L. are employees of the company. B.O.B. and P.D.H., on behalf of their institutions, have received research grants and/or provided consultancy to Novo Nordisk and other insulin manufacturers.

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