ABSTRACT

Background: Insulin is recommended as a second-line treatment after diet and metformin fail to reach and/or maintain glycemic targets considered to minimize the risk for long-term diabetic complications. Hypoglycemia and the fear of developing hypoglycemia, however, remain substantial barriers to the initiation and optimal use of insulin.

Objective: The aim of this study was to compare biphasic insulin aspart 30 (BIAsp 30) with biphasic human insulin 30 (BHI 30) with respect to glycemic control and the risk for hypoglycemia using a meta-analysis of clinical trials comparing these insulins in patients with type 2 diabetes mellitus (T2DM).

Methods: We included all published and unpublished, randomized, controlled trials in adult patients with T2DM (treatment duration ≥12 weeks) for which individual patient data were available. All clinical databases and local trial registries of Novo Nordisk A/S (Soeborg, Denmark) were searched to identify clinical trials comparing the 2 products. The predefined primary end point of the study was the overall rate of nocturnal hypoglycemia (major, minor, and symptoms-only hypoglycemia occurring from 6:01 am–11:59 pm). Hypoglycemia was analyzed using a negative binomial distribution model, accounting for exposure time. Glycemic end points were analyzed at 12 to 16 weeks of treatment using ANCOVA, adjusting for baseline. Secondary safety end points were the rates of major hypoglycemia (hypoglycemia requiring third-party assistance), minor hypoglycemia (symptoms confirmed by plasma glucose [PG] <3.1 mmol/L), daytime hypoglycemia (major, minor, and symptoms-only hypoglycemia occurring from 6:01 am–11:59 pm), overall hypoglycemia (the sum of all major, minor, and symptoms-only episodes), and change in weight from baseline to 12 to 16 weeks of treatment. Secondary efficacy end points were changes in glycosylated hemoglobin (HbA1c), fasting PG (FPG), postprandial PG increment (averaged over breakfast, lunch, and dinner), and insulin dose.

Results: Nine randomized, parallel or crossover trials were included (N = 1674; male sex, 57%; mean [SD] age, 61.0 [10.6] years; body mass index, 26.7 [4.6] kg/m²; HbA1c, 8.1% [1.4%]; duration of diabetes, 10.9 [7.9] years). Rates of overall hypoglycemia were not significantly different (rate ratio [RR] = 1.08; 95% CI, 0.94–1.24; P = NS) between treatments. BIAsp 30 had a 50% lower rate of nocturnal hypoglycemia than BHI 30 (RR = 0.50; 95% CI, 0.38–0.67; P < 0.01), whereas the rate of daytime hypoglycemia was 24% lower for BHI 30 (RR = 1.24; 95% CI, 1.08–1.43; P < 0.01). The likelihood of major hypoglycemia was significantly lower with BIAsp 30 compared with BHI 30 (RR = 0.50; 95% CI, 0.38–0.67; P < 0.01).
pared with BHI 30 (odds ratio = 0.45; 95% CI, 0.22–0.93; P < 0.05). BIAsp 30 was associated with reduced PPG increment (averaged over breakfast, lunch and dinner) compared with BHI 30 (treatment difference, –0.31; 95% CI, –0.49 to –0.07; P < 0.01). There was a significantly larger reduction in FPG associated with BHI 30 (treatment difference, 0.63; 95% CI, 0.31–0.95; P < 0.01). However, no significant treatment difference was found for HbA1c (treatment difference, 0.04; 95% CI, –0.02 to 0.10; P = NS).

**Conclusion:** This meta-analysis found BIAsp 30 to be associated with a significantly lower rate of nocturnal and major hypoglycemia, but a significantly increased risk for daytime hypoglycemia, compared with BHI 30 at a similar level of HbA1c in patients with T2DM. (*Clin. Ther.* 2009;31:1641–1651) © 2009 Excerpta Medica Inc.

**Key words:** biphasic insulin, meta-analysis, hypoglycemia, type 2 diabetes mellitus.

**INTRODUCTION**

Type 2 diabetes mellitus (T2DM) is a progressive disease characterized by insulin resistance and a gradual decline in β-cell function that eventually necessitates the use of exogenous insulin by most patients. Although traditionally used as a final treatment option, insulin has been recently recommended by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) as a second-line treatment after diet and metformin fail to reach and/or maintain glycemic targets considered to minimize the risk for long-term diabetic complications.¹ To attain these targets, an earlier introduction of insulin treatment has also been advocated by the American College of Endocrinology and the American Association of Clinical Endocrinologists.²

Hypoglycemia and the fear of developing hypoglycemia, however, remain substantial barriers to the initiation and optimal use of insulin.³ For some patients, another potential obstacle is the number of daily injections required by basal-bolus regimens. Because of this, premixed insulins containing varying proportions of rapid- and intermediate-acting insulin were developed to limit the number of daily injections for patients who require both prandial and basal insulin.⁴ The earliest insulin premixes contained neutral protein Hagedorn (NPH) insulin as the basal component and regular human insulin as the prandial component. More recently, premixed insulin analogues have been developed that more accurately mimic the mealtime components of endogenous insulin secretion, providing significantly better postprandial plasma glucose (PPG) control than conventional premixed human insulins.⁴ However, the relative rates of hypoglycemia associated with conventional and insulin analogue premixes are less clear.

Biphasic insulin aspart 30 (BIAsp 30) is a premixed insulin analogue comprising 30% soluble rapid-acting insulin aspart and 70% intermediate-acting protamine-crystallized insulin aspart.⁵,⁶ Although some studies have shown BIAsp 30 to be associated with a significantly reduced rate of major⁷ and nocturnal hypoglycemia⁸ compared with biphasic human insulin 30 (BHI 30) (comprising 30% regular human insulin and 70% NPH insulin), other studies have been inconclusive.⁹–¹² A possible reason for these different findings is that, apart from 1 study,⁸ none were designed to have the statistical power to detect a difference in rates of hypoglycemia between BIAsp 30 and BHI 30.

Therefore, we conducted a meta-analysis of all published and unpublished, randomized, controlled trials for which individual patient data were available to compare the rate of hypoglycemia associated with BIAsp 30 and BHI 30 in patients with T2DM. Because there is a correlation between the degree of glycemic control and the risk for hypoglycemia,¹³ treatments were also compared with respect to specific glycemic end points.

**SUBJECTS AND METHODS**

A retrospective meta-analysis of individual patient data was performed based on the guidelines of Whitehead¹⁴ and *The Cochrane Policy Manual.*¹⁵

**Study Selection Criteria and Search Strategy**

All clinical databases and local trial registries of Novo Nordisk A/S, the manufacturer of BIAsp 30 (NovoLog® Mix 70/30 in the US and NovoMix® 30 elsewhere) and BHI 30 (Novolin® 70/30 in the US and Mixtard® 30 elsewhere), were searched to identify clinical trials comparing these 2 products. Predefined selection criteria were that the trial must be randomized and controlled, have a treatment duration of ≥12 weeks, individual patient data must be available, and the trial must have been conducted in accordance with the Declaration of Helsinki and the Guideline for Good Clinical Practice.¹⁶ Both published and unpublished studies were included. Short-term clinical phar-
reason a 12- to 16-week window was chosen for this comparison was that not all trials included in the meta-analysis collected weight, insulin dose, and glycemic data at week 12; three trials collected these data at week 13 (trial 03819) or week 16 (trials 1394 and 14668). For all other trials, week-12 data were collected and used for the meta-analysis of weight, insulin dose, and glycemic end points.

Hypoglycemic episodes were included in the analyses if they had an onset on or between the date of the first and the last dose of trial product. All analyses of hypoglycemia were based on self-reported episodes (symptoms-only or confirmed using standard blood glucose meters). For this meta-analysis, we decided to focus on confirmed hypoglycemia. Therefore, symptoms-only hypoglycemia was not a predefined end point of the study. It was not analyzed separately but was included in the meta-analysis of overall hypoglycemia (a combination of major, minor, and symptoms-only hypoglycemia).

Safety End Points

The predefined primary end point was the overall rate of nocturnal hypoglycemia (all major, minor, and symptoms-only hypoglycemia occurring from 12:00–6:00 AM). Secondary safety end points were the rates of major hypoglycemia (hypoglycemia requiring third-party assistance), minor hypoglycemia (symptoms confirmed by PG <3.1 mmol/L), daytime hypoglycemia (all major, minor and symptoms-only hypoglycemia occurring from 6:01 AM–11:59 PM), overall hypoglycemia (the sum of all major, minor, and symptoms-only episodes), and change in weight from baseline to 12 to 16 weeks of treatment. This was the treatment duration chosen to compare treatments with respect to glycemic end points and weight. The trials in the meta-analysis differed in length from 12 to 48 weeks (Table I). The reason a 12- to 16-week window was chosen for this comparison was that not all trials included in the meta-analysis collected weight, insulin dose, and glycemic data at week 12; three trials collected these data at week 13 (trial 03819) or week 16 (trials 1394 and 14668).

Table I. Summary of randomized, controlled clinical trials comparing biphasic insulin aspart 30 (BIAsp 30) with biphasic human insulin 30 (BHI 30) included in the meta-analysis.*

<table>
<thead>
<tr>
<th>Trial ID</th>
<th>Trial Design</th>
<th>Duration, Wk †</th>
<th>BIAsp 30, Mean (SD), Daily Dose, U/kg</th>
<th>BHI 30, Mean (SD), Daily Dose, U/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>03819</td>
<td>Open, parallel</td>
<td>13</td>
<td>0.56 (0.24)</td>
<td>0.58 (0.21)</td>
</tr>
<tr>
<td>108812</td>
<td>Double-blind, parallel</td>
<td>14</td>
<td>0.15 (0.04)</td>
<td>0.14 (0.03)</td>
</tr>
<tr>
<td>1234‡</td>
<td>Double-blind, crossover</td>
<td>12</td>
<td>0.75 (0.28)</td>
<td>0.74 (0.30)</td>
</tr>
<tr>
<td>1353§</td>
<td>Open, parallel</td>
<td>48</td>
<td>0.41 (0.19)</td>
<td>0.40 (0.18)</td>
</tr>
<tr>
<td>1394§</td>
<td>Open, parallel</td>
<td>16</td>
<td>0.64 (0.31)</td>
<td>0.64 (0.33)</td>
</tr>
<tr>
<td>14668†</td>
<td>Double-blind, crossover</td>
<td>16</td>
<td>0.66 (0.28)</td>
<td>0.64 (0.30)</td>
</tr>
<tr>
<td>1536‡</td>
<td>Open, parallel</td>
<td>12</td>
<td>0.54 (0.15)</td>
<td>0.56 (0.20)</td>
</tr>
<tr>
<td>3002‡</td>
<td>Double-blind, parallel</td>
<td>12</td>
<td>0.80 (0.21)</td>
<td>0.81 (0.22)</td>
</tr>
<tr>
<td>3006‡</td>
<td>Double-blind, parallel</td>
<td>12</td>
<td>0.69 (0.29)</td>
<td>0.78 (0.31)</td>
</tr>
</tbody>
</table>

*All trials were multicenter (6–55 centers), with 4 trials conducted in >1 country; all trials compared a twice-daily dosing regimen (before breakfast and dinner) of BIAsp 30 with BHI 30 except for trial 108812 that compared a once-daily (before dinner) regimen; none of the trials were treat-to-target (ie, insulin doses were not titrated according to any treatment algorithm); various inclusion criteria, such as certain glycosylated hemoglobin levels, age, and body mass index ranges and prestudy treatment requirements, were specified by the individual trials; with the exception of trial 1088,12 all patients were treated with insulin prior to trial entry.
† Treatment duration for each period for crossover studies.
‡ Unpublished.
Efficacy End Points
Secondary efficacy end points were changes from baseline to weeks 12 to 16 of treatment in glycosylated hemoglobin (HbA1c), fasting PG (FPG), PPG increment (averaged over breakfast, lunch, and dinner), and insulin dose. Data for FPG and PPG increment were derived from self-measured 8-point blood glucose profiles. PPG increment was defined as the PG concentration measured 90 minutes after a meal (120 minutes after a meal for trials 3002 and 3006) minus the PG concentration immediately prior to a meal.

Statistical Methods
The intent-to-treat population, defined as all randomized patients exposed to ≥1 dose of trial treatment,20 was used for the meta-analysis of all end points. For assessments that measured a change from baseline (weight and all efficacy end points), the last available measurement between 12 and 16 weeks was used. Missing values were imputed by the last-observation-carried-forward method. To combine results from crossover and parallel-group trials in the meta-analysis, estimates of the treatment effect were obtained separately for each study and then combined using the inverse variance method,14 whereby weight is assigned to the individual estimates according to their precision.

The predefined primary objective of the meta-analysis was to compare BIAsp 30 and BHI 30 with respect to the rate of nocturnal hypoglycemia. Hypoglycemia was analyzed using a negative binomial distribution model, with the number of episodes as the dependent variable, log-transformed exposure time as an offset variable, baseline HbA1c as a continuous covariate, and treatment as fixed effect. The rate ratio (RR) of nocturnal hypoglycemia (BIAsp 30/BHI 30) was calculated together with 95% CI. Minor, daytime, and overall hypoglycemia was analyzed as described for nocturnal hypoglycemia. Due to the low number of events, the frequency of patients experiencing ≥1 episode of major hypoglycemia was compared between treatments using the Mantel-Haenszel method.14 An odds ratio (BIAsp 30/BHI 30) together with 95% CI was calculated.

All outcomes that assessed a change from baseline to weeks 12 to 16 of treatment (weight, insulin dose, and all glycemic end points) were analyzed using ANCOVA, adjusting for appropriate baseline covariates (for crossover studies, patients were included as random effects). An estimate of the treatment difference (BIAsp 30 – BHI 30) with corresponding 95% CI was calculated for each end point.

Heterogeneity was assessed for each end point by calculating I², the percentage of total variation across the studies that is due to heterogeneity rather than chance.21 Values >75% were considered to indicate high heterogeneity. If heterogeneity was observed for a particular end point, data were analyzed by a random-effects meta-analysis model in addition to the fixed-effects model. An additional sensitivity analysis was conducted to explore the influence of blinding on conclusions for the primary end point, nocturnal hypoglycemia.

RESULTS
Nine randomized, controlled trials were identified that met the selection criteria for the meta-analysis (Table I). The meta-analysis population comprised 1674 patients with T2DM (48.3% white, 49.6% Asian/Pacific islander; male sex, 57.4%; mean [SD] age, 61.0 [10.6] years; body mass index, 26.7 [4.6] kg/m²; HbA1c, 8.1% [1.4%]; duration of diabetes, 10.9 [7.9] years) of which 810 were exposed to BIAsp 30, 524 to BHI 30, and 340 to both treatments (in crossover studies). The 2 treatment groups were closely matched with respect to demographic and baseline characteristics. Demographic characteristics are summarized on an individual trial basis in Table II.

Hypoglycemia
Hypoglycemic episodes were reported in all 9 trials. The definition of major hypoglycemia was consistent across trials. For one trial (trial 13539), minor hypoglycemia was defined (and included in the meta-analysis) based on symptoms without a confirmatory measurement of PG concentration. The frequency of hypoglycemia in the meta-analysis population is summarized in Table III. No significant difference was found between treatments with respect to the rate of overall hypoglycemia (RR = 1.08; 95% CI, 0.94–1.24; P = NS; Table IV). However, BIAsp 30 had a significantly lower rate of nocturnal hypoglycemia than did BHI 30 (RR = 0.50; 95% CI, 0.38–0.67; P < 0.01; Figure 1), whereas BHI 30 was associated with a significantly lower rate of daytime hypoglycemia (RR = 1.24; 95% CI, 1.08–1.43; P < 0.01; Table IV). Significantly fewer patients experienced a major hypoglycemic episode with BIAsp 30 compared with BHI 30 (P < 0.05; Figure 2), while rates of minor hypoglycemia were not significantly different between treatments (Table IV).
Table II. Demographic information for the randomized, controlled clinical trials included in the meta-analysis.

<table>
<thead>
<tr>
<th>Trial ID</th>
<th>038(^9) (n = 187)</th>
<th>1088(^{12}) (n = 93)</th>
<th>1234 (n = 180)</th>
<th>1353(^9) (n = 428)</th>
<th>1394 (n = 292)</th>
<th>1466(^8) (n = 160)</th>
<th>1536 (n = 195)</th>
<th>3002 (n = 36)</th>
<th>3006 (n = 103)</th>
<th>Total(^*) (N = 1674)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, no. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>95 (50.8)</td>
<td>39 (41.9)</td>
<td>79 (43.9)</td>
<td>177 (41.4)</td>
<td>125 (42.8)</td>
<td>48 (30.0)</td>
<td>98 (50.3)</td>
<td>16 (44.4)</td>
<td>46 (44.7)</td>
<td>713 (42.6)</td>
</tr>
<tr>
<td>Male</td>
<td>92 (49.2)</td>
<td>54 (58.1)</td>
<td>101 (56.1)</td>
<td>251 (58.6)</td>
<td>167 (57.2)</td>
<td>112 (70.0)</td>
<td>97 (49.7)</td>
<td>20 (55.6)</td>
<td>57 (55.3)</td>
<td>961 (57.4)</td>
</tr>
<tr>
<td>Race, no. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>185 (98.9)</td>
<td>68 (73.1)</td>
<td>112 (62.2)</td>
<td>–</td>
<td>290 (99.3)</td>
<td>154 (96.3)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>809 (48.3)</td>
</tr>
<tr>
<td>Black</td>
<td>1 (0.5)</td>
<td>10 (10.8)</td>
<td>–</td>
<td>–</td>
<td>1 (0.3)</td>
<td>5 (3.1)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>17 (1.0)</td>
</tr>
<tr>
<td>Asian/PI</td>
<td>1 (0.5)</td>
<td>1 (1.1)</td>
<td>64 (35.6)</td>
<td>428 (100)</td>
<td>1 (0.3)</td>
<td>1 (0.6)</td>
<td>195 (100)</td>
<td>36 (100)</td>
<td>103 (100)</td>
<td>830 (49.6)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>–</td>
<td>11 (11.8)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>11 (0.7)</td>
</tr>
<tr>
<td>Other</td>
<td>–</td>
<td>3 (3.2)</td>
<td>4 (2.2)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>7 (0.4)</td>
</tr>
<tr>
<td>Weight, mean (SD), kg</td>
<td>79.2 (13.0)</td>
<td>85.4 (13.3)</td>
<td>77.7 (15.7)</td>
<td>60.0 (9.8)</td>
<td>83.6 (14.6)</td>
<td>86.2 (14.5)</td>
<td>66.6 (10.0)</td>
<td>63.7 (10.0)</td>
<td>63.5 (10.0)</td>
<td>–</td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>63.2 (8.6)</td>
<td>56.9 (11.5)</td>
<td>60.3 (12.0)</td>
<td>60.9 (10.0)</td>
<td>65.8 (10.2)</td>
<td>62.9 (9.1)</td>
<td>57.8 (8.7)</td>
<td>53.5 (10.7)</td>
<td>53.8 (10.6)</td>
<td>61.0 (10.6)</td>
</tr>
</tbody>
</table>

PI = Pacific islander.

*Patients with type 2 diabetes mellitus randomized and exposed to treatment.
All 9 trials provided HbA1c data for the meta-analysis. Three trials (1353, 1466, and 1536) were excluded from the meta-analyses of PPG increment and FPG, as these data were not collected. Mean base-
line and end-of-treatment values for HbA1c, FPG, and PPG increment are presented in Table V. BIAsp 30 was associated with reduced PPG increment (averaged over breakfast, lunch, and dinner) by a significantly greater extent than was BHI 30 ($P < 0.01$; Table IV), whereas BHI 30 treatment was associated with a significantly larger reduction in FPG ($P < 0.01$). However, no significant treatment difference was found for HbA1c.

Weight

Eight clinical trials provided weight data for the meta-analysis. One trial (14668) was excluded because data were only collected at baseline. For trial 1234, change in weight from baseline was determined separately for each period. Both BIAsp 30 and BHI 30 were associated with an increase in weight from baseline (mean [SD] change of 0.2 [2.3] and 0.7 [2.1] kg, respectively), but no significant treatment difference was found (Table IV).

Insulin Dose

All 9 trials provided total daily insulin dose data for the meta-analysis. A higher increase from baseline in total daily dose was observed for BIAsp 30 relative to BHI 30 ($P < 0.01$; Table IV). For BIAsp 30, total daily dose increased from 0.54 (0.28) U/kg at baseline to 0.61 (0.31) U/kg; for BHI 30, total daily dose increased from 0.58 (0.30) U/kg at baseline to 0.64 (0.32) U/kg.

Heterogeneity

In all cases where heterogeneity was found across trials for a particular end point (ie, $I^2 > 0\%$), similar
recognized as the most effective diabetes medication to lower glycemia. Moreover, cases have been reported where patients intentionally keep blood glucose levels above recommended targets to avoid hypoglycemia. It is important, therefore, to evaluate insulin products and/or treatment regimens that carry a lower risk of hypoglycemia and do not jeopardize glycemic efficacy.

In this study, we compared the rate of hypoglycemia associated with BIAsp 30 and BHI 30 using a meta-analysis of 9 published and unpublished randomized, controlled trials in adults with T2DM. Four of these trials also included patients with type 1 diabetes, but there was an insufficient number (151 patients) to conduct a meaningful meta-analysis on this patient population. Our results, based on individual data for 1674 patients with T2DM, suggested that, overall estimates and 95% CI were obtained when the meta-analysis was repeated using a random-effects model (data not shown).

**DISCUSSION**

Intensive insulin treatment, designed to reduce the risk of long-term diabetic complications, has been associated with an increased risk of hypoglycemia in patients with T2DM, with clinical consequences ranging from mild discomfort to coma and even death. Although considered less common in patients with T2DM, rates of hypoglycemia may approach those observed in patients with type 1 diabetes with increasing age, duration of diabetes, and length of insulin treatment. Fear of hypoglycemia can result in a reluctance to initiate insulin treatment, even though insulin is recognized as the most effective diabetes medication to lower glycemia. Moreover, cases have been reported where patients intentionally keep blood glucose levels above recommended targets to avoid hypoglycemia. It is important, therefore, to evaluate insulin products and/or treatment regimens that carry a lower risk of hypoglycemia and do not jeopardize glycemic efficacy.

In this study, we compared the rate of hypoglycemia associated with BIAsp 30 and BHI 30 using a meta-analysis of 9 published and unpublished randomized, controlled trials in adults with T2DM. Our results, based on individual data for 1674 patients with T2DM, suggested that,
although no statistically significant difference in the overall rate of hypoglycemia was found between treatments, BIAsp 30 was associated with a significantly lower rate of nocturnal hypoglycemia compared with BHI 30, but a significantly higher rate of daytime hypoglycemia. Hypoglycemia is unwelcome at any time of the day but may be a particular problem at night, because a sleeping patient may be unaware of symptoms that would have otherwise prompted corrective action.

Whereas no significant difference was found in the frequency of minor hypoglycemia associated with BIAsp 30 or BHI 30, significantly fewer patients on BIAsp 30 experienced a major hypoglycemic event. Because major hypoglycemia can be potentially life threatening (and incur high health care costs), reducing the risk for such events is essential for both the patient and health care industry.

In terms of glycemic control, the meta-analysis found that BIAsp 30 was associated with reduced PPG increment averaged over the 3 main meals to a significantly greater extent than was BHI 30, whereas a significantly larger reduction in FPG was found for BHI 30. However, overall metabolic control (as measured by HbA1c) did not differ significantly between treatment groups. Therefore, the reduced risk for nocturnal and major hypoglycemia associated with BIAsp 30 was not achieved at the expense of overall glycemic control. It is also noteworthy that the comparable overall glycemic control provided by BIAsp 30 and BHI 30 was obtained with similar total daily doses of insulin, and that both treatments resulted in similar weight gain. For both treatment groups, HbA1c following 12 to 16 weeks of treatment was ~7.9%, which is above ADA- and EASD-recommended HbA1c targets of <7%25 and may reflect the fact that none of the trials in the meta-analysis were of a treat-to-target design. Due to the relatively short treatment duration of the majority of clinical trials in the meta-analysis (12 to 16 weeks) and the low number of major hypoglycemic episodes reported in these studies, our findings for HbA1c and major hypoglycemia need to be

| Table V. Summary of glycemic end points in patients with type 2 diabetes mellitus treated with biphasic insulin aspart 30 (BIAsp 30) or biphasic human insulin 30 (BHI 30). |
|------------------------------------------|----------------|----------------|----------------|
|                                         | BIAsp 30       | BHI 30         |
| No. of Patients                         | Mean (SD)      | Mean (SD)      |
| HbA1c, %                                |                |                |
| Baseline                                | 965            | 690            |
| Change from baseline to weeks 12 to 16  | 929            | 647            |
| FPG, mmol/L                             |                |                |
| Baseline                                | 466            | 400            |
| Change from baseline to weeks 12 to 16  | 458            | 396            |
| PPG increment, mmol/L*                  |                |                |
| Baseline                                | 446            | 386            |
| Change from baseline to weeks 12 to 16  | 446            | 391            |

HbA1c = glycosylated hemoglobin; FPG = fasting plasma glucose; PPG = postprandial plasma glucose.
*Averaged over breakfast, lunch, and dinner.
confirmed by a larger, properly powered, randomized, controlled trial of sufficient length.

The meta-analysis confirmed previous findings that BIAsp 30 provides significantly better postprandial glycemic control than does BHI 30.8–11,17 The improved mealtime coverage has been attributed to the faster onset and higher plasma insulin levels attained by the soluble insulin aspart component of BIAsp 30 compared with the regular human insulin constituent of BHI 30.4 Short-acting human insulin has a longer pharmacodynamic action profile than does insulin aspart,26 with this characteristic likely to account, at least in part, for the significantly higher rate of nocturnal hypoglycemia with BHI 30 in this study. The observed peaking action of the intermediate-acting NPH insulin component of BHI 30 may also contribute to the higher rate of nocturnal hypoglycemia and lower FPG levels observed for this premixed insulin.27 As higher prandial plasma insulin levels are attained with BIAsp 30 than BHI 30,4 it could be speculated that the higher rate of daytime hypoglycemia associated with this insulin premix may be partially attributed to occasions in which there is inadequate carbohydrate intake with the mealtime dose.

Low to moderate heterogeneity was found across trials for some of the end points analyzed (weight, insulin dose, overall hypoglycemia, daytime hypoglycemia, and nocturnal hypoglycemia). However, in all cases, the same conclusions were reached for the end point regardless of whether a fixed- or random-effects model was used for the meta-analysis, thereby supporting the robustness of the results. To test for any potential bias in the reporting of hypoglycemic events for open-label trials, a sensitivity analysis was performed for the primary end point whereby only trials that were blinded to treatment allocation were included in the meta-analysis of nocturnal hypoglycemia. Near-identical results were found to those observed for the full meta-analysis dataset, indicating that reporting bias was unlikely.

CONCLUSION
This meta-analysis found BIAsp 30 to be associated with a significantly lower rate of nocturnal and major hypoglycemia, but a significantly increased risk for daytime hypoglycemia, compared with BHI 30 at a similar level of HbA1c in patients with T2DM.

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