Biphasic insulin aspart 30 three times daily is more effective than a twice-daily regimen, without increasing hypoglycemia, in Chinese subjects with type 2 diabetes inadequately controlled on OADs

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Running Title: TID BIAsp 30 in Chinese type 2 diabetes subjects

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ABSTRACT

Objective: To assess efficacy and safety of twice- (BID) and three-times daily (TID) biphasic insulin aspart 30 (BIAsp 30) in Chinese subjects with type 2 diabetes inadequately controlled with oral antidiabetic drugs (OADs).

Research Design and Methods: In this 24-week, multicenter, parallel-group, randomized, treat-to-target study, 321 Chinese insulin-naïve subjects with poorly-controlled type 2 diabetes (fasting blood glucose [FBG] ≥7.8 mmol/l; HbA1c ≥7.5%) were randomized (1:1) to BID or TID BIAsp 30 without OADs. Initial insulin doses were based on FBG at randomization. Insulin dose was adjusted with algorithm-controlled titration to achieve pre-meal BG of 4.4–6.1 mmol/L.

Results: HbA1c decreased significantly in both groups (BID: −2.48±0.07%; TID: −2.81±0.07%). TID BIAsp 30 showed superiority in HbA1c improvement (−0.33%, 95% CI (−0.53; −0.13), P<0.01) and helped more subjects achieve HbA1c targets <7% (BID: 51.3% vs. TID: 65.8%, P<0.01). TID BIAsp 30 was more effective in subjects with HbA1c baseline ≥9% (<7%: BID: 41.5% vs. TID: 58.3%, P<0.01). There was no significant difference in rates of overall and nocturnal major and minor hypoglycemia per subject year between groups. No significant differences in weight gain (BID: 3.87±0.28 kg; TID: 4.09±0.27 kg) and mean daily insulin doses (BID: 0.82±0.28 U/kg; TID: 0.86±0.34 U/kg) were observed.

Conclusions: BID and TID BIAsp 30 were effective in Chinese insulin-naïve subjects with poorly controlled type 2 diabetes. TID BIAsp 30 offered greater reduction in HbA1c without increasing risk of hypoglycemia, insulin dose and weight gain, especially in subjects with HbA1c ≥9%.
In subjects with type 2 diabetes inadequately controlled with OADs, insulin therapy could be used to improve glycemic control (1). The modern premixed insulins, such as NovoMix®30 (BIAsp 30), were regularly prescribed twice-daily in the clinical practice: the ACTION study showed superior HbA1c improvement in the subjects with the treatment of BID BIAsp 30 plus optimized metformin and pioglitazone than those with OADs only (2). More subjects could achieve HbA1c targets when the optimized OADs were added with BID BIAsp 30. Furthermore, in the INITIATE study (3), BID BIAsp 30 plus OADs could help the patients with a higher HbA1c baseline (more than 9.5%) significantly improve glycemic levels more than the patients treated with a once-daily basal insulin plus OADs. The 1-2-3 study is a stepwise comparison among once-, twice- and thrice-daily BIAsp 30 with OADs treatment in Western patients with type 2 diabetes (4). Patients could achieve more glycemic improvement by increasing BIAsp 30 from twice-daily to thrice-daily injection. From the studies mentioned above, no results on twice-daily or thrice-daily BIAsp 30 without OADs were reported.

In this study, we designed a head-to-head comparison to show the efficacy and safety of BID and TID BIAsp 30 in Chinese insulin-naïve subjects with type 2 diabetes after at least six months of inadequately controlled OAD treatment. We proposed that adding an injection before lunch in BID BIAsp 30 could provide superior HbA1c improvement to BID BIAsp 30, especially in those subjects with higher HbA1c baselines.

**RESEARCH DESIGN AND METHODS**

The study protocol was approved by the Independent Ethics Committees for each participating center, and was performed in accordance with the Declaration of Helsinki and Guidelines on Good Clinical Practice.

This was a 24-week, parallel-group, randomized, treat-to-target study comparing the efficacy and safety of BID and TID BIAsp 30. After a 2-week screening period, a total of 321 eligible insulin-naïve subjects from clinics at 8 hospitals in China were randomized in 1:1 ratio to receive BID (immediately before breakfast and dinner) or TID BIAsp 30 (immediately before breakfast, lunch and dinner) treatment. All subjects discontinued their previous OADs at randomization and no wash-out period of OADs was used. This study was designed as an open-labeled trial due to different numbers of daily subcutaneous administration with trial drugs. Randomization codes were stratified by center. Block randomization method was used in this study to minimize bias between the two treatment groups.

Male and female subjects were aged 18–75 years old, BMI ≤32 kg/m² and were poorly controlled on OAD therapy (FBG ≥7.8mmol/L, HbA1c ≥7.5%), having received one or more OADs for at least six months before this research. Subjects had not used insulin therapy preceding the study, and were otherwise healthy. No subject was receiving treatments that interfered with glucose metabolism or had any condition that would interfere with study participation or evaluation of results. All subjects were provided with the standard meals on office visits to compare 2 hour post-breakfast plasma glucose (2hr PPG) between the treatments. During the trial, the subjects received food intake and lifestyle suggestions from investigators. Female subjects who were pregnant, breast-feeding or not using adequate contraceptive measures were excluded from the study.

All OADs were discontinued upon initiation of BIAsp 30, and BIAsp 30 was administered subcutaneously using NovoMix®30 FlexPen®, a prefilled disposable pen device provided by Novo Nordisk (China) Pharmaceuticals Co., Ltd. The starting doses for BIAsp 30 were based on FBG at randomization. In the BID BIAsp 30 group, the initial total daily dose was equally divided into the pre-breakfast and
In the TID BIAsp 30 group, the initial dose distribution ratio for breakfast, lunch and dinner doses was 25%:25%:50%. Insulin dose was adjusted based on the mean pre-meal self-monitored blood glucose (SMBG) to achieve pre-meal blood glucose targets of 4.4–6.1 mmol/l. All subjects performed pre-meal SMBGs on three consecutive days prior to each of the 19 patient contacts during the 24-week trial. For the BID BIAsp 30 group, the pre-breakfast SMBG was used to adjust the dose at the next dinner; pre-lunch SMBG was used to adjust the dose at the next day’s breakfast; and pre-dinner SMBG was used to adjust the dose at the next day’s lunch. The extent of the dose titration was based on the following guidelines: decrease by two units if pre-meal BG is <4.4 mmol/l, no change if BG is 4.4–6.1 mmol/l, increase by two units if BG is 6.2–7.7 mmol/l, increase by four units if BG is 7.8–10.0 mmol/l and increase by six units if BG is >10.0 mmol/l (10). Dose adjustment was only performed at visits and no more than two daily doses were adjusted at the same visit. At each lab visit, pre-breakfast plasma glucose and 2hr post-breakfast plasma glucose testing was performed. Patients were required to fast prior to each lab visit.

**Efficacy parameters.** The change in HbA1c after 24 weeks’ treatment was the primary endpoint. Change in HbA1c after 12 weeks, pre-breakfast plasma glucose, 2hr PPG and percentages of subjects who achieved HbA1c targets (ADA <7% [5]; IDF ≤6.5% [6]) at the end of treatment were also recorded in the two treatment groups.

**Safety parameters.** Episodes of hypoglycemia (including major, minor and nocturnal hypoglycemia) were recorded during the study. Major hypoglycemia was defined as an episode with neurological symptoms consistent with hypoglycemia that could not be self-treated by the patient. Minor hypoglycemia were episodes that were self-treated and with a confirmed BG reading <2.8mmol/l. Adverse events were reported throughout the whole study. Standard laboratory parameters, weight and vital signs were assessed at the beginning and the end of the study.

**Statistical analyses.** A total of 321 subjects were randomized assuming a drop-out rate of 20%, allowing a power of 80% to detect that TID BIAsp 30 was non-inferior to BID BIAsp 30 (α=0.025, β=0.2). Analyses for primary and secondary endpoints were performed on the intent-to-treat population.

The estimated treatment difference (TID group minus BID group) in HbA1c, the 95% confidence interval and the P-value were obtained from an analysis of covariance (ANCOVA) model, with treatment and center as factors and HbA1c at baseline (visit 1) as a covariate. If non-inferiority could be demonstrated, the superiority of TID BIAsp 30 would be assessed. Percentages of subjects who achieved HbA1c targets at the end of the study were analyzed by a logistic regression approach with treatment, center and baseline HbA1c as explanatory variables. The changes in 2hr post-breakfast BG and pre-breakfast BG were analyzed for treatment difference using the ANCOVA model, with treatment and center as factors and the value of HbA1c at baseline (visit 1) as a covariate. The Poisson regression model was used for the analysis of hypoglycemia. Effects for sex and ethnicity were also investigated.

**RESULTS**

Of 321 randomized subjects, 160 subjects received BID BIAsp 30 and 161 received TID BIAsp 30. A total of 12 and 4 individuals withdrew from the study in the BID and TID BIAsp 30 groups, respectively. In the BID group, eight subjects withdrew due to noncompliance with the protocol; three due to adverse events and one due to ineffective therapy. In the TID group, two subjects withdrew due to adverse events, one for noncompliance and one for not wanting to inject insulin. Baseline characteristics were comparable
between two treatment groups (Table 1), with the mean baseline HbA1c being approximately 9.5% in both groups. Around half of subjects in the two groups received three or more OADs before the study. No effect of sex or ethnicity was found in this trial. The relatively low BMI at baseline is reflective of a typical patient with type 2 diabetes in China (7, 8).

**Efficacy.** HbA1c: HbA1c was significantly reduced by 2.48±0.07% (mean±SE) and 2.81±0.07% in the BID and TID BIAsp 30 group, respectively, after 24-weeks’ treatment (Figure 1). End of trial HbA 1c values were 7.01% and 6.68% in the BID and TID groups, respectively. Subjects receiving TID BIAsp 30 achieved a greater reduction in HbA 1c compared with BID BIAsp 30-treated subjects (difference: −0.33%, 95% CI (–0.53; –0.13), P<0.01). After only 12 weeks of treatment, subjects receiving TID BIAsp 30 achieved superior reduction in HbA 1c to the order of 0.3% (P<0.01) compared with those receiving BID BIAsp 30, and this was maintained until the end of the trial. In a sub-analysis, subjects with baseline HbA1c ≥9%, achieved greater reductions in HbA1c than was observed in the main cohort (BID: –3.16±1.50% and TID: −3.61±1.46%, the HbA1c difference: –0.45%, 95% CI (–0.76; –0.14), P<0.01).

**Achieving HbA1c targets.** At the end of treatment, significantly more subjects in the TID BIAsp 30 group reached HbA1c targets than in the BID BIAsp 30 group (Figure 2). In particular, in subjects with baseline HbA1c ≥9%, achieved greater reductions in HbA1c than was observed in the main cohort (BID: –3.43±1.50% and TID: –3.62±1.46%, the HbA1c difference: –0.19%, 95% CI (–0.56; 0.18), P<0.01).

**Hypoglycemia.** Major hypoglycemic episodes were experienced by one person (one event) in the BID BIAsp 30 group and three people (five events, one of which was nocturnal) in the TID BIAsp 30 group. Minor episodes were experienced by 23% of the BID group (a total of 91 events) and 19% of the TID group (65 events). The rates (episodes per subject year) of overall major and minor hypoglycemia were 1.28 in BID group and 0.96 in TID group. For minor hypoglycemia, rates of 1.27 episodes per subject year in the BID BIAsp 30 group, and 0.89 episodes per subject year in the TID BIAsp 30 group, were recorded. There was no significant difference in the rate of overall (Relative Risk [RR]=0.75, P=0.32) and nocturnal (RR=0.98, P=0.97) major and minor hypoglycemia between treatments. In subjects who achieved an HbA1c target <7.0%, 43.9% of subjects in the BID group and 47.2% of subjects in the TID group had no hypoglycemia. Furthermore, the TID BIAsp 30 showed a significantly lower risk of major and minor hypoglycemia compared with the BID BIAsp 30 group in this sub-population (RR=0.41; P<0.05).

**Insulin doses and weight gain.** There was no significant difference in the total daily insulin dose between the two treatments (0.82±0.28 U/kg for BID and 0.86±0.34 U/kg for TID groups, respectively; P=0.19). In the BID BIAsp 30 group, the 50:50 split of the total insulin daily dose initiated at the start of the trial was maintained by the end of the trial (pre-breakfast and pre-dinnertime doses were 0.40±0.15 and 0.41±0.15 U/kg), while those in the TID BIAsp 30 group were 0.29±0.15, 0.22±0.11 and 0.36±0.14 U/kg (pre-breakfast, pre-lunch and pre-dinner doses, respectively). The dose ratio at the end of trial in the TID treatment was similar to that at the start of trial.

Weight increased significantly in both treatment groups: in the BID group, the increase was 3.87±0.28 kg (95% C.I.: [3.323; 4.417]); for the TID group, the increase was 4.09±0.27 kg (95% C.I.: [3.549; 4.626]). There was no difference in weight gain between treatment groups.

**Other safety parameters.** All serious adverse events (BID group: three cases by three subjects; TID group: one case by one subject) were assessed as unlikely to be
related to the treatment. The end-of-treatment laboratory results in blood chemistry or hematology and the mean values for vital signs were similar to those at baseline in both groups.

CONCLUSIONS

As type 2 diabetes progresses, the need for insulin also increases and patients should receive adequate insulin therapy in order to improve glycemic control. But the consensus on how or when to initiate insulin treatment in type 2 diabetes is lacking and insulin regimens are known to vary among countries (6, 9). In China, diagnosis of diabetes and initiation of insulin therapy in patients with type 2 diabetes may be late due to lack of awareness. The UKPDS results showed β-cell function was reduced by 50% at the time of diagnosis of fasting hyperglycemia (10). In our study, subjects had a long duration of diabetes (around 8 years) and were in poor control (mean HbA1c at baseline was 9.5%) suggesting that the subjects in our trial would have very little β-cell function remaining. In addition, patients in China have relatively low BMI, so Chinese patients may have worse β-cell function compared to Caucasians when initiating insulin therapy, especially in those with a high HbA1c baseline. In this study, we aimed to compare, for the first time, the efficacy and safety of a BID and TID regimen of BIAsp 30 – without OADs – in a group of patients whose baseline characteristics were similar to those seen in day-to-day practice in our clinics.

In our study, both the BID and TID regimens were effective for insulin-naïve patients and resulted in significant HbA1c improvements. Insulin therapy with TID BIAsp 30 mediated a significantly greater reduction in HbA1c than BID BIAsp 30 (HbA1c difference of 0.33%). The mean HbA1c at the end of the trial in the TID group was about 6.68% lower than the HbA1c target (<7%). Clinically, more subjects achieved the ADA and IDF HbA1c targets with TID BIAsp 30 regimen than with a BID regimen. In subjects with HbA1c baseline ≥ 9%, the advantage of TID BIAsp 30 was more notable than BID treatment; HbA1c achieved greater reductions with TID BIAsp 30 compared to subjects in the main cohort. These improvements with a TID regimen were seen despite no significant difference in total daily dose. By spreading the dose equally between three meals rather than just two, the additional BIAsp 30 injection may be more suitable for Chinese patients who have a heavy lunch. The TID regimen provided prandial insulin coverage at lunch, in addition to breakfast and dinner, compared with BID BIAsp 30. TID BIAsp30 may be more physiological for Chinese patients with poor β-cell function and a heavy lunch. Both FPG and PPG contribute to HbA1c (11) though our study showed that there was no difference between treatment groups in FPG or PPG after breakfast. We propose, therefore, that the third lunchtime injection lowered PPG after lunch to such an extent that overall glycemia, as measured by HbA1c, was significantly reduced, though we do not have the data to verify this.

The extent of the improvement in glycemia was similar to that reported in the INITIATE study (3). In the INITIATE study, where a similar titration algorithm was used, HbA1c reduced by 2.8% with BID BIAsp 30. Twice-daily BIAsp 30 allowed 42% and 66% of subjects achieve the HbA1c targets ≤6.5% and <7% respectively, after 28 weeks’ treatment. It is worthy to note that the extent of glycemia achieved with our study was through insulin alone, since all OADs were discontinued at the start of the trial. A number of trials have shown that when used in combination with metformin, the effects of BIAsp 30 are far greater than when used alone (11, 12). One may wonder, therefore, if greater improvements in glycemia may have been achieved had metformin been used? A study investigating the most optimal treatment regimen using BIAsp 30 initiated in type 2 diabetes patients is still called for.

There was no difference in overall major and minor hypoglycemia between
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treatments. In subjects who achieved HbA1c<7%, the rate of major and minor hypoglycemia was significantly lower in the TID BIAsp 30 group than the BID BIAsp 30 group (P<0.05). This suggests that by spreading the dose more evenly throughout the day, with lower doses at each injection, there is less risk of hypoglycemia, without compromising glycemia. In addition, the rates of minor hypoglycemia observed in our study are lower than those reported for the BID BIAsp 30 regimen in the INITIATE study (3.4 episodes per patient per year), where similar reductions in HbA1c were achieved (3). However, there were different blood glucose hypoglycemia definitions between the two studies; for INITIATE, the BG level was <3.1 mmol/l, whereas our study was lower at 2.8 mmol/l. This may explain the apparent lower rate of hypoglycemia seen in our study. Moreover, the treatment of insulin combined with OADs may explain the higher rate of hypoglycemia in the INITIATE study compared with the use of insulin only in our study.

The total daily insulin dose in the two treatment groups was similar by the end of the study, suggesting that greater glycemic control can be achieved if the total daily dose is spread more evenly throughout the day. Once again, the BID BIAsp 30 group of the INITIATE study reported almost identical total daily insulin doses (0.82 ± 0.40U/kg). The proportion of total daily insulin dose of each injection (1:1 for BID BIAsp 30; 1:1:2 for TID BIAsp 30) is a recommendable regimen but which still needs further exploration.

Weight gain was similar between the two groups and indeed similar to that seen in patients receiving BID BIAsp 30 in the INITIATE study (3). Patients coming from such poor glycemic control often experience some weight gain when they achieve good control (12). We may expect greater improvements in glycemia and less weight gain if metformin had been added. Of course, it is still essential, therefore, to re-enforce diet and lifestyle advice when starting insulin to limit any weight gain.

In conclusion, as an insulin initiation regimen, both BID and TID BIAsp 30 regimens were efficacious and well tolerated in the treatment of insulin-naïve subjects with type 2 diabetes. Patients with very poor glycemic control (≥9% HbA1c) can achieve greater reductions in HbA1c and more patients achieved HbA1c targets with a TID versus BID BIAsp 30 regimen. Furthermore, by spreading the dose more evenly throughout the day with TID BIAsp 30, the risk of hypoglycemia was not increased with better glycemic control.

ACKNOWLEDGEMENTS

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REFERENCES

TABLE 1. Subject baseline characteristics of the intent-to-treat population

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<th>BID BIAsp 30</th>
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<tr>
<td>Number of subjects randomized, n</td>
<td>160</td>
<td>161</td>
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<td>Completers, n</td>
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<tr>
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<td>Sex, M/F</td>
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<td>Duration of diagnosed diabetes, years (mean±SD)</td>
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**Diabetic complications**

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<tr>
<td>Retinopathy, %</td>
<td>11.3</td>
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<td>Nephropathy, %</td>
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<td>Neuropathy, %</td>
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<td>Macroangiopathy, %</td>
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<td>Baseline HbA1c*, % (mean±SD)</td>
<td>9.52±1.4</td>
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**Prior treatments with OADs***

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**Discontinuation from study**

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<th>BID BIAsp 30</th>
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<tr>
<td>For adverse event</td>
<td>3 (2)</td>
<td>2 (1)</td>
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<tr>
<td>For noncompliance</td>
<td>8 (5)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>For ineffective therapy</td>
<td>1 (1)</td>
<td>0</td>
</tr>
<tr>
<td>For other reasons</td>
<td>0</td>
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Data are means ± SD or n (%) unless otherwise indicated. *BMI, body mass index; HbA1c, glycosylated hemoglobin 1C; OAD, oral anti-diabetic drug. #Adverse event withdrawals in the BID treatment were anaphylaxis appendicitis and pain of waist; adverse event withdrawals in the TID treatment were nausea and acute myocardial infarction. The one ‘other’ referred to refusal to inject insulin.
FIGURE LEGENDS

Figure 1. The changes in HbA₁c after treatment with BID or TID BIAsp30. **P value<0.01.

Figure 2. The percentages of subjects who achieved HbA₁c targets (≤6.5% and <7%). A) The percentages of subjects who achieved HbA₁c targets in the main cohort; B) The percentages of subjects who achieved HbA₁c targets in subjects with HbA₁c baseline ≥ 9%.
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-2.5%, P < 0.001**

-2.8%, P < 0.001**

-0.33%, P = 0.0015**
TID BIAsp 30 in Chinese type 2 diabetes subjects

(A) O.R. = 0.48, \textit{P} < 0.0046**

- BID BIAsp 30: 65.8%
- TID BIAsp 30: 51.3%

O.R. = 0.57, \textit{P} < 0.0220**

- BID BIAsp 30: 46.6%
- TID BIAsp 30: 34.4%

(B) O.R. = 1.69, \textit{P} < 0.0102**

- BID BIAsp 30: 58.3%
- TID BIAsp 30: 41.5%

O.R. = 2.19, \textit{P} < 0.0127**

- BID BIAsp 30: 42.7%
- TID BIAsp 30: 26.6%