Contents available at ScienceDirect

Diabetes Research and Clinical Practice

journal homepage: www.elsevier.com/locate/diabres

Efficacy and safety of three-times-daily versus twice-daily biphasic insulin aspart 30 in patients with type 2 diabetes mellitus inadequately controlled with basal insulin combined with oral antidiabetic drugs

Wenying Yang [a,*], *Canan Ersoy* [b], *Guixia Wang* [c], *Shandong Ye* [d,e], *Jun Liu* [f], *Heng Miao* [g], *Arthur Asirvatham* [h], *Shanti Werther* [i], *Priti Kadu* [i], *Francis Chow* [j]

[a] *China–Japan Friendship Hospital, East Yinghuayuan Street, Hepingli, Beijing 100029, China*
[b] *Division of Endocrinology and Metabolism, School of Medicine, Uludag University, Bursa, Turkey*
[c] *Department of Endocrinology and Metabolism, The First Hospital of Jilin University, Changchun, Jilin Province 130021, China*
[d] *School of Medicine, Shandong University, Jinan, Shandong, China*
[e] *Department of Endocrinology, Anhui Provincial Hospital Affiliated to Anhui Medical University, Hefei, China*
[f] *Department of Endocrinology, Shanghai Fifth People's Hospital Affiliated to Fudan University, 801 Heqing Road, Minhang District, Shanghai 200240, China*
[g] *The Second Affiliated Hospital of Nanjing Medical University, Nanjing, China*
[h] *Department of Medicine, Government Medical College, Madurai, Tamil Nadu, India*
[i] *Novo Nordisk A/S, Søborg, Denmark*
[j] *Department of Medicine & Therapeutics, Prince of Wales Hospital, The Chinese University of Hong Kong, Hong Kong, China*

ARTICLE INFO

Article history:
Received 30 May 2018
Received in revised form
23 December 2018
Accepted 25 February 2019
Available online 11 March 2019

Keywords:
Type 2 diabetes mellitus
Primary care
Insulin
Premixed

ABSTRACT

Aims: To compare the efficacy and safety of biphasic insulin aspart 30 (BIAsp 30) administered three times daily (TID) vs. twice daily (BID), plus metformin, in patients with type 2 diabetes mellitus (T2DM) inadequately controlled on basal insulin ± 1 oral antidiabetic drug (OAD).

Methods: Randomised, multinational, open-label, treat-to-target trial. Subjects inadequately controlled (HbA1c 7.5–10.0%) on basal insulin and metformin ± 1 OAD were randomised to BIAsp 30 TID ($n = 220$) or BIAsp 30 BID ($n = 217$). Primary endpoint was change from baseline in HbA1c after 24 weeks of treatment.

Results: Most (400/437, 91.5%) subjects completed the trial. The majority (276/400 [69.0%]) were from the China region. After 24 weeks, HbA1c decreased comparably in both BIAsp 30 groups (−1.7% vs. −1.6% [−19 vs. −18 mmol/mol], for TID and BID dosing, respectively; estimated treatment difference: −0.09% $[-0.23; 0.06]_{95\%\ CI}$, −1 mmol/mol [−3; 1], $p = 0.26$). Safety profiles, including number of subjects experiencing hypoglycaemia, were similar.

Conclusions: BIAsp 30 administered either TID or BID with metformin was a safe and effective option when intensifying treatment after failure of basal insulin and OADs in patients with T2DM. Adding a third injection at lunchtime may be preferable if HbA1c

* Corresponding author.
E-mail addresses: ywying_1010@163.com (W. Yang), ecanan@uludag.edu.tr (C. Ersoy), gwang168@jlu.edu.cn (G. Wang), miaoheng@njmu.edu.cn (H. Miao), scw@novonordisk.com (S. Werther), b410773@mailserv.cuhk.edu.hk (F. Chow).
https://doi.org/10.1016/j.diabres.2019.02.023

remains above target, if the lunchtime meal is the largest meal of the day, or if persistent postprandial hyperglycaemia after lunch is observed.

Trial registration number: ClinicalTrials.gov, NCT02582242.

1. Introduction

Type 2 diabetes mellitus (T2DM) is a progressive disorder characterised by a combination of insulin resistance and relative deficiency of first-phase insulin secretion due to declining beta-cell function [1,2]. American Diabetes Association (ADA) and Chinese Diabetes Society (CDS) guidelines recommend a glycaemic target of HbA1c < 7.0% in most patients with T2DM [3–5]. Achieving this target requires controlling both fasting plasma glucose (FPG) and postprandial plasma glucose (PPG) [6]. Furthermore, when treatment intensification is necessary, it is recommended that it is done in a timely manner in order to achieve and maintain glycaemic control and reduce the risk of diabetes-related complications [3,4,7,8]. Indeed, it has been demonstrated that patients with T2DM and HbA1c ≥7.0% who did not intensify treatment within 1 year had a significantly increased risk of myocardial infarction, stroke and heart failure compared with those who intensified treatment [9].

Basal insulin, such as the long-acting insulin analogues insulin detemir, insulin glargine, and insulin degludec, dosed once daily is recommended by the ADA and CDS as initial insulin therapy [3–5]. However, for patients who fail to reach glycaemic targets using a basal insulin alone, studies have demonstrated that biphasic insulin aspart 30 (BIAsp 30), a premixed insulin containing both rapid-acting soluble insulin aspart (30%) and intermediate-acting protaminated insulin aspart (70%) in one formulation, administered twice daily (BID) can be used to improve glycaemic control [10,11].

Results from other studies comparing premixed insulin regimens with optimised once-daily basal insulin ± oral antidiabetic drugs (OADs) have demonstrated greater reductions in HbA1c with premixed insulin and a greater proportion of patients achieving HbA1c < 7.0% [12], greater reductions in HbA1c with premixed insulin but no significant difference in the proportion of patients achieving HbA1c < 7.0% [13], or demonstrated non-inferiority in glycaemic control and no significant difference in the proportion of patients achieving HbA1c < 7.0% [14,15].

In addition to these studies, CDS guidelines state that a premixed insulin administered BID can be used either to initiate or intensify insulin treatment [4,5]. An extension of this recommendation from the CDS is that more poorly controlled (HbA1c > 9.0%) insulin-naïve patients can initiate treatment with premixed insulin administered three times daily (TID) [4,5]. Evidence supports this recommendation: a study conducted in insulin-naïve patients with T2DM from China with mean HbA1c of 9.5% reported that BIAsp 30 TID offered a greater reduction in HbA1c without increasing hypoglycaemia, insulin dose or weight gain, compared with BIAsp 30 BID [16].

With regard to insulin intensification in patients failing basal insulin ± OADs, both TID and BID premixed insulin regimens are effective and safe [11,17,18]. However, head-to-head data are lacking, and it is possible that splitting the dose across three meals may be of further benefit to some patients in terms of lower risk of hypoglycaemia [19]. Therefore, the aim of the current trial was to compare the efficacy and safety of BIAsp 30 TID vs. BIAsp 30 BID, both in combination with metformin, in subjects with T2DM inadequately controlled on basal insulin.

2. Subjects, materials and methods

2.1. Design

This was a 24-week, randomised, open-label, parallel-group, treat-to-target, multinational trial in patients with T2DM aged ≥ 18 years (≥19 years in Algeria) and BMI ≤ 35.0 kg/m^2 who were inadequately controlled (HbA1c 7.5–10.0% [58–86 mmol/mol]) on basal insulin (analogue or neutral protamine Hagedorn [NPH]) and treated with metformin ± 1 OAD for ≥ 90 days prior to screening. Furthermore, the dose of metformin (at least 1500 mg daily or maximum tolerated dose) was required to be stable for at least 60 days prior to screening. The study was conducted at 48 sites (28 sites in mainland China, Hong Kong and Taiwan, as well as 20 sites in Algeria, India, Turkey and the Ukraine), from October 2015 to April 2017. The trial consisted of a screening visit (visit 1), a randomisation visit (visit 2), a 24-week treatment period (six clinic visits and 17 phone contacts), an end-of-treatment visit (visit 26) and a follow-up phone contact (visit 27).

Key exclusion criteria were previous insulin intensification for more than 14 days (i.e. premixed insulin TID, basal–bolus regimen, or continuous subcutaneous insulin infusion); anticipated initiation or change in concomitant medications known to affect weight or glucose metabolism; and impaired liver function. Use of non-herbal Chinese medicine or other non-herbal local medicine with unknown/unspecified content within 90 days prior to the day of screening (visit 1) was prohibited. Herbal traditional Chinese medicine or other local herbal medicines could, at the investigator's discretion, be continued throughout the trial.

2.2. Randomisation, treatment and titration

Eligible patients (n = 437) were randomised (1:1) into one of two treatment arms: BIAsp 30 administered TID (n = 220) or

BIAsp 30 administered BID ($n = 217$). Randomisation was stratified by glycaemic control (HbA1c 7.5–8.5% and 8.6–10.0%) and prior OAD use (metformin alone and metformin ± 1 OAD). BIAsp 30 was titrated weekly using an algorithm (Supplementary Table 1) to achieve a pre-meal self-measured blood glucose (SMBG) of 4.4–6.1 mmol/L (80–110 mg/dL). All subjects were requested to measure SMBG three times daily (pre-breakfast, pre-lunch, and before the main evening meal on three random days before each scheduled visit or phone contact). For those randomised to BIAsp 30 BID, the lowest of three pre-breakfast SMBG values measured on the previous day was used to adjust the dose of BIAsp 30 before the main evening meal dose. The lowest of three before main evening meal SMBG values measured on the previous day was used to adjust the pre-breakfast dose. For subjects randomised to BIAsp 30 TID, the lowest of three pre-breakfast SMBG values measured on the previous day was used to adjust the dose of BIAsp 30 before the main evening meal dose, the lowest of three pre-lunch SMBG values was used to adjust the pre-breakfast dose, and the lowest of three before main evening meal SMBG values was used to adjust the pre-lunch dose.

Within each participating country, it was aimed to include a maximum of 20% of randomised subjects on treatment with NPH insulin prior to screening (visit 1). Subjects continued metformin during the trial, but other OADs were discontinued. BIAsp 30 (100 U/mL) was administered using a 3 mL FlexPen®. The total daily insulin dose of pre-trial basal insulin was transferred unit-to-unit to BIAsp 30. Subjects randomised to the BIAsp 30 TID arm received BIAsp 30 before breakfast, lunch and the main evening meal, whereas those randomised to the BIAsp 30 BID arm received BIAsp 30 before breakfast and the main evening meal.

The trial period consisted of a screening period (up to 2 weeks before randomisation) and a 24-week treatment period followed by a 30-day follow-up period. The investigator assessed treatment compliance of the subject at each visit/-phone contact by evaluating glycaemic control, the SMBG profiles and all relevant data in the subject's diary. The study was conducted in accordance with the Declaration of Helsinki and good clinical practice, including ethics review board approval. Written consent was obtained from all subjects before any study-related procedures were initiated.

2.3. *Efficacy and safety endpoints*

The primary endpoint was change from baseline in HbA1c after 24 weeks of treatment. Supportive secondary efficacy endpoints (also after 24 weeks of treatment) included change from baseline in fasting plasma glucose (FPG), mean 7-point SMBG profiles, change from baseline in 2-h PPG and PPG increment after individual meals, and change from baseline in mean 2-h PPG and PPG increment over the three main meals.

Subjects were instructed to self-measure their blood glucose (BG) as described above, and the 7-point SMBG profile was performed on the day just prior to week 0, week 12 and week 24. All laboratory analyses reported here were performed at a central laboratory.

Dichotomous efficacy endpoints included the proportion of patients achieving HbA1c < 7.0% [53 mmol/mol] (without severe hypoglycaemia and without severe or BG-confirmed hypoglycaemia) after 24 weeks of treatment. BG was measured and recorded when a hypoglycaemic episode was suspected, and all BG values $\leq$ 3.9 mmol/L (70 mg/dL), or >3.9 mmol/L (70 mg/dL), if accompanied by hypoglycaemic symptoms, were to be recorded by the subject.

Finally, patient-reported treatment satisfaction was assessed via change from baseline in Diabetes Treatment Satisfaction Questionnaire (DTSQ) score. The DTSQ contained eight questions, of which six were related to the overall treatment satisfaction and two were related to glycaemic control (i.e. perceived frequency of hypoglycaemia and hyperglycaemia). The DTSQ items were scored on a scale from 0 to 6. For the overall treatment satisfaction, a higher score (0–36) was related to a better perception of treatment satisfaction. For questions related to perceived frequency of hypoglycaemia and hyperglycaemia, a lower score (0–6) was related to better BG control.

Supportive secondary safety endpoints included the number of treatment-emergent hypoglycaemic episodes, change in body weight from baseline, incidence of adverse events (AEs), change in clinical safety parameters (physical examination, vital signs, laboratory parameters), and total daily insulin dose.

2.4. *Statistical analysis*

The sample size was determined under the assumption of a two-sided test for mean treatment difference for change in HbA1c (BIAsp 30 TID minus BIAsp 30 BID) = 0% and a significance level of 5%. Assuming a treatment difference of 0.3 ± 1.1% for HbA1c, a total of 213 subjects per group in the full analysis set (included all randomised subjects who had been dosed and had any post-randomisation data) would have an 80% statistical power for detecting a statistically significant difference in change from baseline in HbA1c after 24 weeks.

Change from baseline in HbA1c at 4, 8, 12, 16, 20 and 24 weeks was analysed using a mixed model for repeated measurements (MMRM), with treatment, combination of the two stratification factors (HbA1c value and previous OAD treatment) and region (China/non-China) as fixed factors and baseline HbA1c as a covariate, with all variables nested within visit as a factor. Missing data were assumed to be missing at random. To compare the 7-point SMBG profiles of the two treatments after 24 weeks, a mixed effect model was fitted to the data. The model included treatment, time, interaction between treatment and time, combination of the two stratification factors and region as fixed effects. All other continuous endpoints described above, including change from baseline in FPG and the endpoints derived from the 7-point SMBG profile, were analysed using a method similar to that used for the primary endpoint, where the relevant baseline value replaced the baseline HbA1c in the model. The dichotomous endpoints were analysed by a logistic regression model. Effects in the model were treatment, combination of the two stratification factors and region as factors, and baseline HbA1c as a covariate. For the dichotomous

endpoint of HbA1c < 7.0% at week 24 (yes/no), missing HbA1c values at week 24 were imputed using the predicted value from an MMRM analysis. For the other two dichotomous endpoints, as a conservative approach, subjects withdrawn before 24 weeks were handled as non-responders.

A treatment-emergent adverse event (TEAE) was defined as an event that had onset date (or increase in severity) on or after the first day of exposure to trial product and no later than 7 days after the last day on trial product. Hypoglycaemic episodes were to be defined as treatment-emergent if the onset of the episode occurred on or after the first day of trial product administration, and no later than 7 days after the last day on trial product. Nocturnal hypoglycaemic episodes were episodes with time of onset between 00:01 and 05:59 (both inclusive). TEAEs were summarised descriptively.

Novo Nordisk, the trial sponsor, uses the following classification for describing hypoglycaemia: (1) severe hypoglycaemia according to the ADA classification; (2) BG-confirmed hypoglycaemia: an episode that is BG-confirmed by a PG value < 3.1 mmol/L (56 mg/dL) with or without symptoms consistent with hypoglycaemia; (3) severe or BG-confirmed hypoglycaemia: an episode that is severe according to the ADA classification or BG-confirmed by a PG value < 3.1 mmol/L (56 mg/dL) with or without symptoms consistent with hypoglycaemia.

All safety endpoints were summarised and analysed using the safety analysis set. Unless otherwise specified, safety endpoints were analysed by descriptive statistics only.

3. Results

3.1. Subjects

A total of 599 patients were screened, with 437 being randomised: 306 from the China region (i.e. China, Hong Kong, Taiwan) and 131 from the non-China region (i.e. Algeria, India, Turkey, Ukraine). There were 37 withdrawals: 20 in patients randomised to BIAsp 30 TID and 17 in patients randomised to BIAsp 30 BID. The subject disposition by country is reported in Supplementary Table 2. Baseline characteristics of the two treatment groups, including prevalence of diabetes complications, were comparable (Table 1).

With respect to diabetes-specific medications at screening, most patients were using insulin glargine (77.7 and 77.9%, for BIAsp 30 TID and BID, respectively). Other medications used at screening are listed in Table 1. The mean duration of basal insulin treatment prior to screening was 1.84 and 1.96 years, for BIAsp 30 TID and BID, respectively. The types of concomitant illnesses and concurrent medications were comparable between the two treatment arms.

3.2. Efficacy endpoints

After 24 weeks of treatment, there was no statistically significant difference between the treatment arms in change in HbA1c from baseline (−1.7% vs. − 1.6% [–19 vs. 18 mmol/mol], for BIAsp 30 TID and BIAsp 30 BID, respectively; estimated treatment difference [ETD]: –0.09% $[-0.23; 0.06]_{95\%\ CI}$, –1 mmol/mol [–3; 1], $p = 0.26$) (Fig. 1).

After 24 weeks of treatment, a numerically greater proportion of subjects using BIAsp 30 TID achieved glycaemic targets (HbA1c < 7.0% [53 mmol/mol]: 54.5 vs. 47.5%; HbA1c < 7.0% without severe hypoglycaemia: 50.0 vs. 44.7%; HbA1c < 7.0% without severe hypoglycaemia or BG-confirmed hypoglycaemia: 27.3 vs. 21.7%), for BIAsp 30 TID and BIAsp 30 BID, respectively. However, the odds were not statistically significantly different for the two treatments (Table 2).

The observed mean FPG appeared similar for BIAsp 30 TID and BIAsp 30 BID, both at baseline (8.68 mmol/L and 8.72 mmol/L, respectively) and at week 24 (7.27 mmol/L and 7.54 mmol/L, respectively); the estimated change from baseline for FPG was not statistically significantly different (ETD, BIAsp 30 TID – BIAsp 30 BID: –0.25 mmol/L $[-0.67; 0.16]_{95\%\ CI}$; $p = 0.23$) (Supplementary Fig. 1).

The observed 7-point SMBG profiles for the two treatment arms, both at baseline and at week 24, are shown in Supplementary Fig. 2. Statistical analysis showed that the time-by-treatment interaction at week 24 was not statistically significant ($p = 0.18$), which implies that the profiles of the two treatment groups were parallel over the 7 points. The observed means of the 7-point SMBG profile were nearly identical for BIAsp 30 TID and BIAsp 30 BID, at baseline and at week 24, and the ETD at week 24 was not statistically significantly different (Fig. 2; Supplementary Table 3). Similarly, the estimated treatment difference in mean change from baseline at week 24 for 2-h PPG and PPG increment was not statistically significantly different between the two treatment arms over all three meals or for individual meals.

3.3. Treatment satisfaction

The overall (median [range]) DTSQ scores were 26 [6; 36] and 26 [4; 36] at baseline, versus scores of 30 [6; 36] and 31 [9; 36] at week 24, for BIAsp 30 TID and BIAsp 30 BID, respectively. A marginal increase from baseline to week 24 was observed in total treatment satisfaction as measured by overall median DTSQ score, and this was slightly higher for BIAsp 30 BID compared with BIAsp 30 TID (5 [−21; 29] vs. 2 [−29; 24], respectively). The perceived frequency of hypoglycaemia was identical at baseline and at week 24 (median [range] DTSQ score 1 [0; 6] for both treatments and time periods). The perceived frequency of hyperglycaemia was observed to improve slightly from baseline to week 24, and the improvement was similar for both treatments arms (median change in DTSQ score −1 [−6; 4] and −1 [−6; 5]) for BIAsp 30 TID and BIAsp 30 BID, respectively.

3.4. Safety endpoints

The number of hypoglycaemic episodes according to the ADA classification was 1157 and 1235, and the hypoglycaemia event rate was 1209.8 and 1299.5 per 100 person-years of exposure (PYE), for BIAsp 30 TID and BIAsp 30 BID, respectively. The number of severe hypoglycaemic episodes was low: three events were reported by two subjects using BIAsp 30 TID and three events were reported by three subjects using BIAsp 30 BID. The observed percentage of subjects reporting

Table 1 – Baseline characteristics by treatment group.

Characteristic	BIAsp 30 TID (n = 220)	BIAsp 30 BID (n = 217)	All subjects (n = 437)
Male, n (%)	108 (49.1)	109 (50.2)	217 (49.7)
Age, years	57.0 ± 9.8	56.6 ± 9.3	56.8 ± 9.5
Body weight, kg	71.6 ± 13.4	72.2 ± 13.0	71.9 ± 13.2
BMI, kg/m^2	26.6 ± 3.5	26.9 ± 3.7	26.7 ± 3.6
Diabetes duration, years	11.1 ± 6.4	10.6 ± 5.8	10.9 ± 6.1
HbA1c, %	8.7 ± 0.69	8.7 ± 0.69	8.7 ± 0.69
HbA1c, mmol/mol	72 ± 8	72 ± 8	72 ± 8
FPG, mmol/L	8.7 ± 2.7	8.7 ± 2.4	8.7 ± 2.5
Strata, n (%)			
7.5% ≤ HbA1c ≤ 8.5% [58 mmol/mol ≤ HbA1c ≤ 69 mmol/mol] + MET + one OAD	54 (24.5)	53 (24.4)	107 (24.5)
7.5% ≤ HbA1c ≤ 8.5% [58 mmol/mol ≤ HbA1c ≤ 69 mmol/mol] + MET monotherapy	29 (13.2)	27 (12.4)	56 (12.8)
8.6% ≤ HbA1c ≤ 10% [70 mmol/mol ≤ HbA1c ≤ 86 mmol/mol] + MET + one OAD	91 (41.4)	90 (41.5)	181 (41.4)
8.6% ≤ HbA1c ≤ 10% [70 mmol/mol ≤ HbA1c ≤ 86 mmol/mol] + MET monotherapy	46 (20.9)	47 (21.7)	93 (21.3)
All diabetes complications, n (% yes)	116 (52.7)	112 (51.6)	228 (52.2)
Diabetic retinopathy	73 (33.2)	61 (28.1)	134 (30.7)
Diabetic neuropathy	55 (25.0)	48 (22.1)	103 (23.6)
Diabetic nephropathy	40 (18.2)	26 (12.0)	66 (15.1)
Macroangiopathy	42 (19.1)	39 (18.0)	81 (18.5)
Usage of diabetes-specific medications, n (% yes)			
Biguanides	217 (98.6)	214 (98.6)	431 (98.6)
Combinations of oral blood glucose-lowering drugs	3 (1.4)	4 (1.8)	7 (1.6)
Insulins and analogues for injection			
Long-acting (~88% of long-acting were glargine U100)	194 (88.2)	194 (89.4)	388 (88.8)
Intermediate-acting	25 (11.4)	23 (10.6)	48 (11.0)
Fast-acting[†]	1 (0.5)	0	1 (0.2)
Sulfonylureas	76 (34.5)	71 (32.7)	147 (33.6)
Alpha-glucosidase inhibitors	36 (16.4)	31 (14.3)	67 (15.3)
Other blood glucose-lowering drugs, excluding insulins	21 (9.5)	23 (10.6)	44 (10.1)
DPP-4 inhibitors	9 (4.1)	12 (5.5)	21 (4.8)
Thiazolidinediones	0	1 (0.5)	1 (0.2)

Values are mean ± SD unless otherwise specified.

BIAsp 30, biphasic insulin aspart 30; BID, twice daily; BMI, body mass index; DPP-4, dipeptidyl peptidase-4; FPG, fasting plasma glucose; MET, metformin; n, number of patients; OAD, oral antidiabetic drug; TID, three times daily.

[†] Subject was withdrawn from trial as this was a violation of inclusion criteria.

Table 2 – HbA1c responders at week 24, by treatment group and responder category.

Classification of responder type	Number of patients (%)		Estimated odds ratio BIAsp 30 TID/BIAsp 30 BID [95% CI]
	BIAsp 30 TID	BIAsp 30 BID	
HbA1c < 7.0% [53 mmol/mol]			
Yes	120 (54.5)	103 (47.5)	1.36 [0.92; 2.01]
No	100 (45.5)	114 (52.5)	$p = 0.1248$
HbA1c < 7.0% [53 mmol/mol] without severe hypoglycaemia			
Yes	110 (50.0)	97 (44.7)	1.26 [0.86; 1.85]
No	110 (50.0)	120 (55.3)	$p = 0.2387$
HbA1c < 7.0% [53 mmol/mol] without severe or BG-confirmed hypoglycaemia			
Yes	60 (27.3)	47 (21.7)	1.37 [0.88; 2.14]
No	160 (72.7)	170 (78.3)	$p = 0.1679$

Full analysis set. The analysis is based on a logistic regression model including randomised treatment, strata and region as factors; baseline HbA1c (%) is used as a covariate.
BIAsp 30, biphasic insulin aspart 30; BG, blood glucose; BID, twice daily; CI, confidence interval; TID, three times daily.

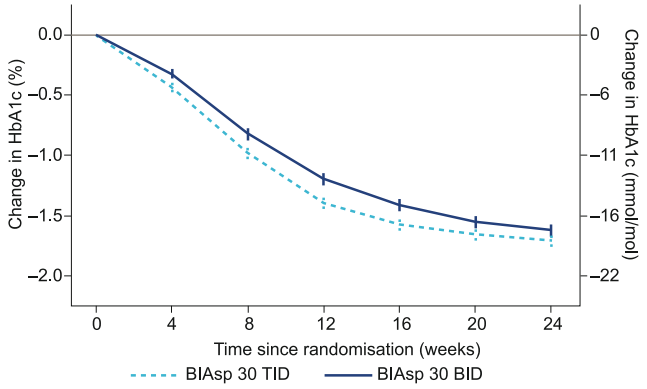

Fig. 1 – Estimated mean change from baseline in HbA1c during 24 weeks of treatment with BIAsp 30 administered BID or TID. Full analysis set. Error bars are ± SEM. BIAsp 30, biphasic insulin aspart 30; BID, twice daily; CI, confidence interval; SEM, standard error of the mean; TID, three times daily.

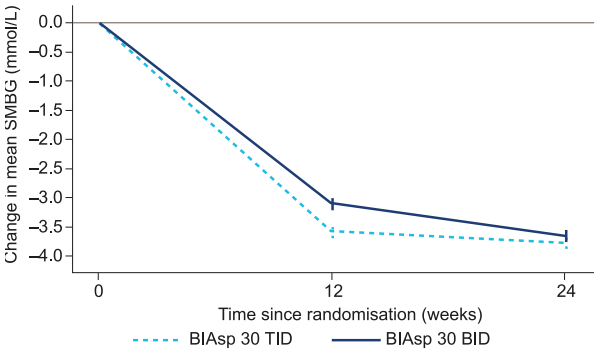

Fig. 2 – Estimated mean change from baseline of 7-point SMBG profile during 24 weeks of treatment with BIAsp 30 administered BID or TID. Full analysis set. Error bars are ± SEM. BIAsp 30, biphasic insulin aspart 30; BID, twice daily; CI, confidence interval; SEM, standard error of the mean; SMBG, self-measured blood glucose; TID, three times daily.

severe or BG-confirmed hypoglycaemic episodes (45.5% and 45.6%, respectively) and the corresponding event rate (263.5 and 265.2 per 100 PYE, respectively) appeared similar between BIAsp 30 TID and BIAsp 30 BID (Supplementary Table 4). Using the Novo Nordisk classification of hypoglycaemia, the estimated rate ratio of overall severe or BG-confirmed hypoglycaemic episodes was not significantly different for BIAsp 30 TID (estimated treatment ratio: 0.98 [0.72; 1.33]$_{95\%CI}$, $p = 0.89$).

The number of nocturnal hypoglycaemic episodes (97 and 115) and the nocturnal hypoglycaemia event rates (101.4 and 121.0 per 100 PYE), for BIAsp 30 TID and BIAsp 30 BID, respectively, were numerically lower with BIAsp 30 TID compared with BIAsp 30 BID (Supplementary Table 4). There was no severe nocturnal hypoglycaemic episode in either treatment arm. Although the estimated rate of nocturnal severe or BG-confirmed hypoglycaemic episodes was numerically higher for BIAsp 30 BID, the estimated rate ratio was not statistically significantly different (26.17 episodes/100 PYE compared with 36.80 episodes/100 PYE, for BIAsp 30 TID and BIAsp 30 BID, respectively; estimated rate ratio: 0.71 [0.35; 1.46]$_{95\%\ CI}$, $p = 0.35$).

The mean daily insulin dose increased in both treatments over the 24-week period and was slightly higher for BIAsp 30 TID throughout the trial (0.347 U/kg [24.5 U] to 0.970 U/kg [69.8 U] for BIAsp 30 TID at baseline and 24 weeks, respectively, compared with 0.337 U/kg [24.2 U] to 0.899 U/kg [64.8 U] for BIAsp 30 BID). For BIAsp 30 TID, both the mean lunch dose and the mean main evening meal dose increased throughout the trial whereas the mean breakfast dose was stable from around week 10. For BIAsp 30 BID, both the mean breakfast dose and the mean main evening meal dose increased throughout the trial, with the mean breakfast dose being higher than the mean main evening meal dose (Fig. 3).

Estimated increase in mean body weight from baseline to week 24 was 1.53 kg for BIAsp 30 TID and 1.74 kg for BIAsp 30 BID (ETD, –0.21 kg [–0.79; 0.37]$_{95\%\ CI}$, $p = 0.48$) (Supplementary Fig. 3).

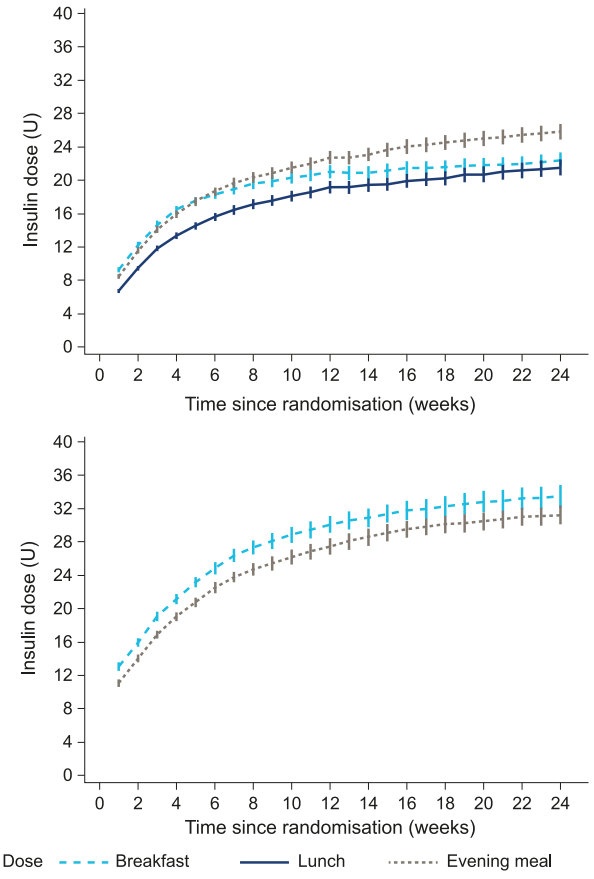

Fig. 3 – Actual daily insulin dose (U) by meal and treatment week, for BIAsp 30 TID (top) and BIAsp 30 BID (bottom). Safety set, observed data. Error bars +/– standard error (mean). The breakfast and main evening meal doses are the latest available doses of the 3 days collected prior to a visit.

Overall, both treatments were safe and well-tolerated. The proportion of subjects with AEs and the number of AEs were similar between BIAsp 30 TID and BIAsp 30 BID: 54.5% of subjects using BIAsp 30 TID reported 275 events and 55.3% of subjects using BIAsp 30 BID reported 251 events. The majority of AEs were mild or moderate in both treatment arms: there were three severe AEs reported by three subjects using BIAsp 30 TID and two severe AEs reported by two subjects using BIAsp 30 BID (Table 3). There were 13 serious AEs in both the BIAsp 30 TID and BIAsp 30 BID treatment arms. The number of treatment-emergent AEs considered 'probably related' to trial product by the investigators was higher with BIAsp 30 TID than with BIAsp 30 BID (8 vs. 0 events, respectively). Fourteen events were considered 'possibly related' to trial product in both treatment arms. The most frequently reported AEs in either of the treatment arms were upper respiratory tract infection, headache and diabetic retinopathy. No deaths were reported.

4. Discussion

BIAsp 30 administered either TID or BID was found to be effective in decreasing HbA1c, FPG and PPG during the 24 weeks of treatment when administered in combination with metformin, in patients with T2DM inadequately controlled on basal insulin ± OADs. Compared with BIAsp 30 BID, a numerically greater proportion of subjects using BIAsp 30 TID achieved HbA1c < 7.0%, HbA1c < 7.0% without severe hypoglycaemic episodes, and HbA1c < 7.0% without severe or BG-confirmed hypoglycaemic episodes, after 24 weeks of treatment. This is in accordance with the 1-2-3 study [20]. In the current study, for any of the above endpoints, the estimated differences between BIAsp 30 TID and BIAsp 30 BID were not statistically significantly different. Total treatment satisfaction with BIAsp 30 BID was slightly better than with TID administration, likely due to the inconvenience of adding a third injection at lunchtime for the latter. Both treatments were safe and well-tolerated, with the vast majority of treatment-emergent AEs being mild or moderate in severity and considered unrelated to the trial product; there were few serious AEs and no unexpected safety issues.

The results of the current trial differed from those of Yang et al. [16] using a similar trial design, which showed a greater reduction in HbA1c with BIAsp 30 TID compared with BID administration, in insulin-naïve patients. Patients in the Yang et al. study also had poorer control at baseline than the insulin-experienced population in the present study (9.5% vs. 8.7%, respectively), and thus had the potential for a greater reduction in HbA1c. The hypoglycaemic advantage observed for BIAsp 30 TID in the Yang et al. study was not observed in the present study. However, there was a numerically greater number of hypoglycaemic episodes for BIAsp 30 BID before lunch, likely due to the higher morning dose required for BID administration.

In terms of clinical implications, given the similar glycaemic control and safety profile of the two treatments in the present study and the lower number of injections per day, BIAsp 30 BID may be the most convenient option for patients failing to achieve glycaemic targets on basal insulin who decide to intensify treatment using a premix regimen. This may be particularly true for patients whose HbA1c is already approaching the desired target. It was unexpected that splitting the insulin dose by adding a third injection did not result in statistically fewer episodes of hypoglycaemia compared with BID administration. Nevertheless, given the comparable safety profile with BID administration, adding a third injection at lunchtime does seem to be a safe and effective alternative for people further from desired targets at baseline and people who require still further intensification, including those with persistent hyperglycaemia after lunch.

The current trial included subjects from China and non-China regions. There are differences in insulin sensitivity, lifestyle and dietary habits between these regions. Consequently, TID administration of BIAsp 30 may be more appropriate for Chinese patients who tend to consume a larger meal at lunchtime. In future studies, it would be interesting to assess BG profiles and variability at baseline and end of treatment using continuous glucose monitoring.

In summary, a patient-centric approach should always be considered when prescribing diabetes treatment. These results indicate that BIAsp 30 administered TID has a similar safety profile to that of BIAsp 30 administered BID, and both regimens were effective in decreasing HbA1c during the 24 weeks of treatment when administered in combination

Table 3 – Treatment-emergent adverse events for 437 patients using BIAsp 30 for 24 weeks.

Event	BIAsp 30 TID (n = 220)			BIAsp 30 BID (n = 217)		
	N (%)	E	R	N (%)	E	R
Events	120 (54.5)	275	287.6	120 (55.3)	251	264.1
Serious AEs						
Yes	12 (5.5)	13	13.6	9 (4.1)	13	13.7
No	118 (53.6)	262	274.0	118 (54.4)	238	250.4
Severity						
Severe	3 (1.4)	3	3.1	2 (0.9)	2	2.1
Moderate	25 (11.4)	41	42.9	22 (10.1)	33	34.7
Mild	107 (48.6)	231	241.5	114 (52.5)	216	227.3
Relation to trial product						
Probable	5 (2.3)	8	8.4	0		
Possible	11 (5.0)	14	14.6	10 (4.6)	14	14.7
Unlikely	112 (50.9)	253	264.6	116 (53.5)	236	248.3
Missing	0			1 (0.5)	1	1.1
AEs leading to withdrawal	4 (1.8)	4	4.2	3 (1.4)	3	3.2

%, percentage of subjects; AE, adverse event; BID, twice daily; E, number of adverse events; N, number of subjects; R, event rate per 100 years of exposure; TID, three times daily.

with metformin in patients with T2DM inadequately controlled on basal insulin ± 1 additional OAD. The more physiological dosing profile of TID administration without any increased risk of hypoglycaemia may be another reason to consider TID dosing, especially if further titration with BID dosing would increase this risk. Although twice-daily administration may be the most convenient option when switching to a premixed regimen for intensification, BIAsp 30 offers the option to simply add a third injection at lunchtime if HbA1c remains above target, if the lunchtime meal is the largest meal of the day, or if there is persistent postprandial hyperglycaemia after lunch. Options for non-responders could include adding a high mix such as BIAsp 50 or a higher dose of only prandial insulin before lunch, or switching to a basal–bolus regimen.

Conflicts of interest

WY has attended advisory boards for Novo Nordisk, received investigator-initiated trial research funds from AstraZeneca, been a speaker for Novo Nordisk, Bayer, Sanofi Aventis, Merck Sharp & Dohme China, AstraZeneca, Eli Lilly, Boehringer-Ingelheim, and Servier, and received honorarium and travel support as an advisory board member from Merck & Co., Inc, outside the submitted work.

CE has received speaker honoraria from Novo Nordisk, Sanofi, AstraZeneca and Lilly; and served on advisory boards of Novo Nordisk, Sanofi and AstraZeneca.

GW, SY, JL, HM, and AA have no conflicts of interest to declare.

SW is an employee of Novo Nordisk.

PK is an employee of Novo Nordisk.

FC has received research support from Boehringer Ingelheim, GlaxoSmithKline, Merck, Novartis, Novo Nordisk, Sanofi-Aventis, and Takeda, and has served on advisory boards for Boehringer Ingelheim, Eli Lilly, Merck, Novartis and Novo Nordisk.

Authorship contributions

All authors had full access to all of the study data and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors had final responsibility for the decision to submit for publication. Individual contributions were as follows:

- Acquisition, analysis, or interpretation of data: SW, PK.
- Writing and review of manuscript: WY, CE, GW, SY, LJ, HM, AA, SCW, PK, FC.

Role of the funding source

Novo Nordisk provided financial support for the conduct of the research and/or preparation of the article. Novo Nordisk contributed to the study design, statistical analyses, data interpretation, manuscript preparation and the decision to submit this manuscript for publication. Medical writing and submission support were provided by Gary Patronek and Erin Slobodian of Watermeadow Medical, an Ashfield company, part of UDG Healthcare plc, and funded by Novo Nordisk.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2019.02.023.

REFERENCES

[1] Polonsky KS, Given BD, Hirsch LJ, et al. Abnormal patterns of insulin secretion in non-insulin-dependent diabetes mellitus. N Engl J Med 1988;318:1231–9.

[2] Woerle HJ, Szoke E, Meyer C, et al. Mechanisms for abnormal postprandial glucose metabolism in type 2 diabetes. Am J Physiol Endocrinol Metab 2006;290:E67–77.
[3] American Diabetes Association. Standards of medical care in Diabetes – 2018. Diabetes Care 2018;41:S1–159.
[4] Chinese Diabetes Society. China T2DM prevention and treatment guideline (2013). Chin J Diabetes Mellitus 2014;6:447–98.
[5] Weng J, Linong J, Weiping J, Juming L, Zhou Z, Zou D, et al. Standards of care for type 2 diabetes in China. Diabetes Metab Res Rev 2016;32:442–58.
[6] Monnier L, Lapinski H, Colette C. Contributions of fasting and postprandial plasma glucose increments to the overall diurnal hyperglycemia of type 2 diabetic patients: variations with increasing levels of HbA1c. Diabetes Care 2003;26:881–5.
[7] Meneghini LF. Intensifying insulin therapy: what options are available to patients with type 2 diabetes? Am J Med 2013;126: S28–37.
[8] Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med 2008;359:1577–89.
[9] Khunti K, Millar-Jones D. Clinical inertia to insulin initiation and intensification in the UK: a focused literature review. Prim Care Diabetes 2017;11:3–12.
[10] Gao Y, Luquez C, Lynggaard H, Andersen H, Saboo B. The SimpleMix study with biphasic insulin aspart 30: a randomized controlled trial investigating patient-driven titration versus investigator-driven titration. Curr Med Res Opin 2014;30:2483–92.
[11] Liebl A, Prager R, Binz K, Kaiser M, Bergenstal R, Gallwitz B, et al. Comparison of insulin analogue regimens in people with type 2 diabetes mellitus in the PREFER study: a randomized controlled trial. Diabetes Obes Metab 2009;11:45–52.
[12] Aschner P, Sethi B, Gomez-Peralta F, Landgraf W, Loizeau V, Dain MP, et al. Insulin glargine compared with premixed insulin for management of insulin-naïve type 2 diabetes patients uncontrolled on oral antidiabetic drugs: the open-label, randomized GALAPAGOS study. J Diabetes Complic 2015;29:838–45.
[13] Tinahones FJ, Gross JL, Onaca A, Cleall S, Rodríguez A. Insulin lispro low mixture twice daily versus basal insulin glargine once daily and prandial insulin lispro once daily in patients with type 2 diabetes requiring insulin intensification: a randomized phase IV trial. Diabetes Obes Metab 2014;16:963–70.
[14] Vora J, Cohen N, Evans M, Hockey A, Speight J, Whately-Smith C. Intensifying insulin regimen after basal insulin optimization in adults with type 2 diabetes: a 24-week, randomized, open-label trial comparing insulin glargine plus insulin glulisine with biphasic insulin aspart (LanScape). Diabetes Obes Metab 2015;17:1133–41.
[15] Jin SM, Kim JH, Min KW, Lee JH, Ahn KJ, Park JH, et al. Basal-prandial versus premixed insulin in patients with type 2 diabetes requiring insulin intensification after basal insulin optimization: a 24-week randomized non-inferiority trial. J Diabetes 2016;8:405–13.
[16] Yang W, Ji Q, Zhu D, Yang J, Chan L, Liu Z, et al. 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 oral antidiabetes drugs. Diabetes Care 2008;31:852–6.
[17] Downie M, Kilov G, Wong J. Initiation and intensification strategies in type 2 diabetes management: a comparison of basal plus and premix regimens. Diabetes Ther 2016;7:641–57.
[18] Giugliano D, Chiodini P, Maiorino MI, Bellastella G, Esposito K. Intensification of insulin therapy with basal-bolus or premixed insulin regimens in type 2 diabetes: a systematic review and meta-analysis of randomized controlled trials. Endocrine 2016;51:417–28.
[19] Unnikrishnan AG, Tibaldi J, Hadley-Brown M, Krentz AJ, Ligthelm R, Damci T, et al. Practical guidance on intensification of insulin therapy with BIAsp 30: a consensus statement. Int J Clin Pract 2009;63:1571–7.
[20] Garber AJ, Wahlen J, Wahl T, Bressler P, Braceras R, Allen E, et al. Attainment of glycaemic goals in type 2 diabetes with once-, twice-, or thrice-daily dosing with biphasic insulin aspart 70/30 (the 1-2-3 study). Diabetes Obes Metab 2006;8:58–66.