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Biphasic insulin aspart 30 treatment improves glycaemic control in patients with type 2 diabetes in a clinical practice setting: Chinese PRESENT study

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Aim: PRESENT (Physicians' Routine Evaluation of Safety and Efficacy of NovoMix® 30 Therapy) is the largest, multinational, open-labelled, uncontrolled and completed observational study of the efficacy and safety of biphasic insulin aspart 30 (BIAsp 30) treatment in clinical practice. We present results of 3 months of treatment in Chinese patients with type 2 diabetes mellitus who were inadequately controlled on current treatment.
Methods: Patients received BIAsp 30 treatment with or without oral antidiabetic drugs (OADs). Patients were categorized according to their treatment prior to entering the study: drug-naive (n = 3697), OAD (n = 4754), insulin (n = 2392) or OAD + insulin (n = 817).
Results: At 3 months, significant reductions from baseline were observed in the mean haemoglobin A_{1c} (HbA_{1c}) (-2.24 ± 1.67, -2.04 ± 1.57, -1.82 ± 1.49 and -1.86 ± 1.61%), fasting plasma glucose (-3.93 ± 3.12, -3.51 ± 2.55, -2.99 ± 2.93 and -3.38 ± 3.16 mmol/l) and postprandial plasma glucose (-7.09 ± 4.92, -6.51 ± 4.02, -5.20 ± 4.31 and -5.50 ± 4.32 mmol/l) in the drug-naive, OAD, insulin and insulin + OAD groups respectively ($p < 0.001$). The proportions of patients in each group achieving target HbA_{1c} of less than 7% were higher at 3 months (49.5, 51.8, 51.0 and 48.3%) compared with baseline (3.2, 4.2, 7.1 and 8.3%). The rates of hypoglycaemic episodes (events per patient-year) were lower at the end of the study in all the groups compared with baseline. Hypoglycaemic episodes were mostly minor and diurnal in nature. A total of 151 adverse drug reactions were reported, of which five were serious adverse drug reaction (SADRs). These SADRs were all symptoms of local hypersensitivity.
Conclusions: The use of BIAsp 30 monotherapy or in combination with OADs in clinical practice was efficacious and safe in Chinese patients with poorly controlled type 2 diabetes.

Keywords: biphasic insulin aspart 30, clinical practice, insulin analogue, observational study, PRESENT study, type 2 diabetes mellitus
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Introduction

China has one of the largest populations of patients with diabetes mellitus in the world [1]. Within China, there is an upward trend in the prevalence of diabetes. There are currently approximately 40 million patients with diabetes in China, of which over 90% are type 2 diabetics [2]. Furthermore, two of three patients remain undiagnosed [3]. This trend is believed to be associated with economic advancement, urbanization, change of

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lifestyle and change of diagnostic criteria over the past decade [3–6]. Overall, this increase in the prevalence of diabetes will result in a substantial rise in healthcare costs in treatment, hospitalization and management of complications associated with diabetes [7,8].

The current status of glycaemic control among patients in China is believed to be poor. In a survey of over 2000 patients across five regions in China, only 25.9% of patients had a haemoglobin A_{1c} (HbA_{1c}) of less than 6.5% [9]. In the same survey, 36% of the patients reported having neuropathy, while 23% reported having retinopathy. Because of associated complications, patients with diabetes have a higher mortality and morbidity compared with healthy persons. These complications can be reduced or delayed through proper glycaemic control using intensive treatment with insulin [10]. Although insulin is the most effective diabetic medication in lowering hyperglycaemia, it is also associated with hypoglycaemia [11]. However, biphasic insulin aspart 30 (BIAsp 30) has shown efficacious glycaemic control, with a lower risk of hypoglycaemia compared with other insulins [12–21]. BIAsp 30 is a premixed insulin analogue containing 30% soluble rapid-acting insulin aspart and 70% protaminated insulin aspart. The pharmacokinetic profile of BIAsp 30 closely mimics the physiological profile of insulin, allowing BIAsp 30 to control both fasting blood glucose and postprandial blood glucose [17]. This results in greater overall glycaemic control with low risks of hypoglycaemia.

A recent randomized controlled study of type 2 diabetic patients from seven Western Pacific countries, including China, has found that the addition of BIAsp 30 treatment in patients inadequately controlled on oral antidiabetic drug (OAD) therapy was more efficacious than optimizing OAD treatment. However, the results of a recent observational study involving 928 Chinese, 56 Japanese and 48 Polish patients (the IMPROVE™ study) found that the mean HbA_{1c} of patients starting BIAsp 30 was 9.4%, suggesting that many patients initiated insulin treatment late in the progression of the disease [22]. These findings have implications for patients poorly controlled on OADs to initiate BIAsp 30 treatment.

BIAsp 30 has been available in China since 2005, but information on its effects in the Chinese population is limited to a few published studies [22–25]. The Physicians' Routine Evaluation of Safety and Efficacy of NovoMix® 30 Therapy (PRESENT) study is the largest, multinational and observational study on BIAsp 30 carried out in a routine clinical setting completed to date. The aim of the study was to collect data on the safety and efficacy of BIAsp 30 treatment in a large number of patients with type 2 diabetes in routine clinical practice to support clinical data from smaller randomized clinical trials. In this article, we present results from the Chinese cohort. Our study could provide valuable data on the efficacy and safety of BIAsp 30 treatment, with practical implications for this growing patient population in China.

Methods

Study Design and Treatment

This observational study was designed to evaluate the efficacy and safety of using BIAsp 30, as a monotherapy or in combination with OADs, for type 2 diabetes management in routine clinical practice. This was a 6-month, multinational, multicentre, prospective, open-labelled and uncontrolled clinical experience evaluation study. However, data were collected from the Chinese cohort only at 3 months. Addition of BIAsp 30 treatment to existing OAD treatment and discontinuation of OADs were entirely at the discretion of the attending physicians. No special investigational procedures outside the normal clinical practice were planned. A total of 311 centres participated in the Chinese study. As this was an observational study, the selection criteria were that patients had type 2 diabetes mellitus, were inadequately controlled on their current therapy and were prescribed BIAsp 30, as a monotherapy or in combination with OADs, in accordance with the approved labelling.

Data Collection and Study End-points

The efficacy and safety end-points were evaluated at 3 months of BIAsp 30 treatment. The efficacy end-points were the changes in HbA_{1c}, fasting plasma glucose (FPG) and postprandial plasma glucose (PPPG) at 3 months compared with baseline. The safety end-points were the occurrence of hypoglycaemic episodes and adverse drug reactions (ADRs). Patients' data were collected during clinic visits at baseline and at 3 months using standardized forms. Data collected included patient demographic data at baseline (such as weight, duration of diabetes and current diabetes therapy), HbA_{1c} measurements within 1 month prior to the visits, FPG and PPPG measurements within 1 week prior to the visits, number of hypoglycaemic episodes and ADRs. The number of hypoglycaemic episodes and ADRs at baseline was based on patient recollection and clinical records from 3 months prior to the baseline visit. For the 3-month visit, the number of hypoglycaemic episodes was similarly based on patient recollection and clinical records. Major hypoglycaemic episodes were defined as those

where the patient needed third-party assistance to be treated.

Statistical Analyses

The patients were categorized into four groups based on their treatment before entering the study: drug-naive, OAD, insulin and OAD + insulin. The safety analysis set consisted of enrolled patients, with a minimum of baseline data. Baseline demographic information, diabetes therapy and efficacy and safety outcomes were presented as descriptive statistics (%, mean ± s.d. or 95% confidence interval). Changes in HbA_{1c}, FPG and PPPG from baseline were analysed using the paired *t*-test. The proportion of patients achieving American Diabetes Association target HbA_{1c} of less than 7% was presented. Hypoglycaemic episodes and ADRs were presented according to category and severity using summary statistics and event rates. All the statistical analyses were performed using SAS® version 9.1.3 (SAS Institute, Cary, NC, USA).

Results

Baseline Characteristics and Types of Prior Insulin Therapy

Of the 11 724 patients enrolled, 11 662 patients had baseline data and hence constituted the safety analysis cohort. The majority (99.3%) completed the study at 3 months. The four groups based on their prior treatment were drug-naive (n = 3697), OAD (n = 4754), insulin (n = 2392) and insulin + OAD (n = 817) (two patients were not included in this analysis because data on their prior treatment were incomplete). The baseline characteristics are presented in table 1. Patients previously on insulin treatment, either alone or in combination with OADs, had a longer duration of diabetes compared with the OAD and drug-naive groups. These groups had a slightly better baseline HbA_{1c} compared with the OAD and drug-naive groups. The mean body mass index (BMI) was comparable among the groups.

In patients who had previously received insulin treatment, the majorities were treated with premix insulin: 82.7% in insulin-only group and 66.8% in insulin + OAD group.

BIAsp 30 Dosage

The majority of patients in all groups received a twice-daily injection regimen of BIAsp 30 at baseline and at 3 months (97.3 and 96.7% in the drug-naive group, 95.8 and 94.0% in the OAD group, 94.8 and 92.3% in the insulin group and 94.1 and 92.5% in the insulin + OAD group). The mean total daily dosage of BIAsp 30 by body weight (BW) increased in all groups (table 2). The OAD and drug-naive groups, having had no experience with insulin use, were prescribed the lowest doses of BIAsp 30.

Glycaemic Control and BW

Significant reductions from baseline were observed in HbA_{1c}, FPG and PPPG in all groups at the end of treatment

Table 1 Baseline characteristics and types of prior insulin therapy

	Drug-naive	OAD	Insulin	Insulin + OAD
Safety population	3697	4754	2392	817
Characteristics				
Gender (% males)	56.5	55.1	58.2	55.9
Asian or Pacific Islander	100.0	100.0	100.0	100.0
Mean age (years) ± s.d.	50.0 ± 11.2	54.6 ± 10.9	55.7 ± 11.7	57.8 ± 10.9
Mean diabetes duration (years) ± s.d.	2.9 ± 3.7	5.5 ± 4.2	6.4 ± 4.9	7.3 ± 4.9
Mean BMI (kg/m^2) ± s.d.	24.3 ± 2.6	24.3 ± 2.7	24.1 ± 2.7	24.8 ± 2.8
Mean HbA_{1c} (%) ± s.d.	9.3 ± 1.8	9.1 ± 1.7	8.8 ± 1.7	8.9 ± 1.8
Types of prior insulin therapy				
Intermediate only	NA	NA	42 (1.8%)	148 (18.1%)
Intermediate + short acting	NA	NA	157 (6.6%)	48 (5.9%)
Premix only	NA	NA	1977 (82.7%)	546 (66.8%)
Short acting only	NA	NA	123 (5.1%)	51 (6.2%)
Other combinations	NA	NA	93 (3.8%)	24 (2.9%)
Total daily insulin dose				
U/IU	NA	NA	34.19 ± 10.28	32.02 ± 14.95
U/IU per kg			0.52 ± 0.16	0.47 ± 0.22

BMI, body mass index; HbA_{1c}, haemoglobin A_{1c}; OAD, oral antidiabetic drug; NA, not applicable.

Table 2 Change in glucose parameters and BIAsp 30 dosage from baseline to 3 months

	Drug-naive	OAD	Insulin	Insulin + OAD
Safety population	3697	4754	2392	817
Total daily BIAsp 30 dose (U/kg BW)				
At treatment initiation	0.39 ± 0.15	0.43 ± 0.14	0.49 ± 0.15	0.49 ± 0.17
At 3 months	0.44 ± 0.15	0.48 ± 0.15	0.50 ± 0.15	0.51 ± 0.17
HbA_{1c}, % (95% CI)				
At baseline	9.27 ± 1.81	9.09 ± 1.70	8.82 ± 1.69	8.92 ± 1.78
At 3 months	7.04 ± 1.01	7.05 ± 0.97	7.00 ± 0.93	7.06 ± 1.04
Change at 3 months	−2.24 ± 1.67*	−2.04 ± 1.57*	−1.82 ± 1.49*	−1.86 ± 1.61*
	(−2.29 to −2.18)	(−2.08 to −1.99)	(−1.88 to −1.76)	(−1.97 to −1.75)
FPG, mmol/l (95% CI)				
At baseline	11.33 ± 3.17	10.69 ± 2.73	10.36 ± 3.19	10.85 ± 3.39
At 3 months	7.39 ± 1.64	7.18 ± 1.18	7.38 ± 1.29	7.48 ± 1.61
Change at 3 months	−3.93 ± 3.12*	−3.51 ± 2.55*	−2.99 ± 2.93*	−3.38 ± 3.16*
	(−4.03 to −3.83)	(−3.59 to −3.44)	(−3.11 to −2.87)	(−3.60 to −3.16)
PPPG, mmol/l (95% CI)				
At baseline	16.57 ± 4.87	15.75 ± 4.20	14.59 ± 4.50	15.14 ± 4.74
At 3 months	9.48 ± 2.02	9.25 ± 1.64	9.40 ± 1.86	9.62 ± 2.06
Change at 3 months	−7.09 ± 4.92*	−6.51 ± 4.02*	−5.20 ± 4.31*	−5.50 ± 4.32*
	(−7.25 to −6.93)	(−6.63 to −6.40)	(−5.37 to −5.03)	(−5.80 to −5.20)
BW, kg (95% CI)				
At baseline	67.63 ± 9.77	67.73 ± 10.18	67.3 ± 9.84	68.65 ± 10.17
At 3 months	67.01 ± 9.53	67.22 ± 9.62	66.70 ± 9.27	67.92 ± 9.85
Change at 3 months	−0.59 ± 3.60**	−0.51 ± 4.03**	−0.58 ± 3.16**	−0.71 ± 3.56**
	(−0.71 to −0.48)	(−0.62 to −0.39)	(−0.71 to −0.45)	(−0.96 to −0.47)

BIAsp 30, biphasic insulin aspart 30; BW, body weight; CI, confidence interval; FPG, fasting plasma glucose; HbA_{1c}, haemoglobin A_{1c}; OAD, oral antidiabetic drug; PPPG, postprandial plasma glucose.
Data presented as mean ± s.d.
*$p < 0.001$ (change from baseline).
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($p < 0.001$) (table 2). Although patients in the drug-naive and OAD groups showed a greater reduction in HbA_{1c}, FPG and PPPG compared with the insulin and insulin + OAD groups, the end-of-treatment glycaemic parameters were comparable among the groups (table 2). The proportion of patients achieving target HbA_{1c} of less than 7% at 3 months increased from baseline in all groups (figure 1).

BW was significantly reduced at the end of treatment in all groups ($p < 0.0001$) (table 2). The change in BW ranged from 0.51 to 0.71 kg in all groups.

Hypoglycaemia

The overall proportion of patients reporting hypoglycaemic episodes was higher at 3 months in the drug-naive group (17.7%) compared with baseline (14.9%) (baseline here refers to the period of 3 months before the start of the study when the patients were using their previous diabetes treatment). The overall proportions of patients reporting hypoglycaemic episodes were lower at 3 months in the OAD (28.2%), insulin (31.9%) and insulin + OAD (26.6%) groups compared with baseline (42.4, 53.1 and 46.8% respectively). The rates of hypoglycaemic episodes (events per patient-year) were lower at the end of the study in all the groups compared with baseline (figure 2). Hypoglycaemic episodes were mostly minor and diurnal in nature.

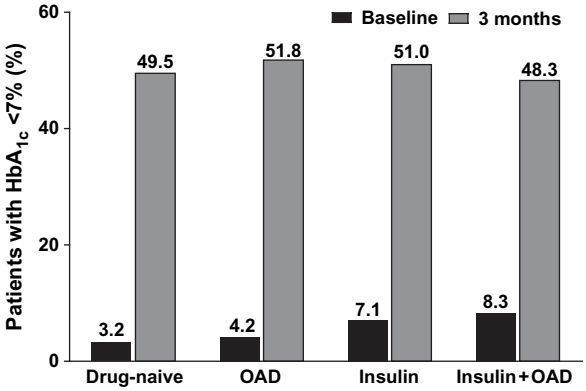

Fig. 1 Proportion of patients with a haemoglobin A_{1c} (HbA_{1c}) of less than 7% at baseline and at 3 months. OAD, oral antidiabetic drug.

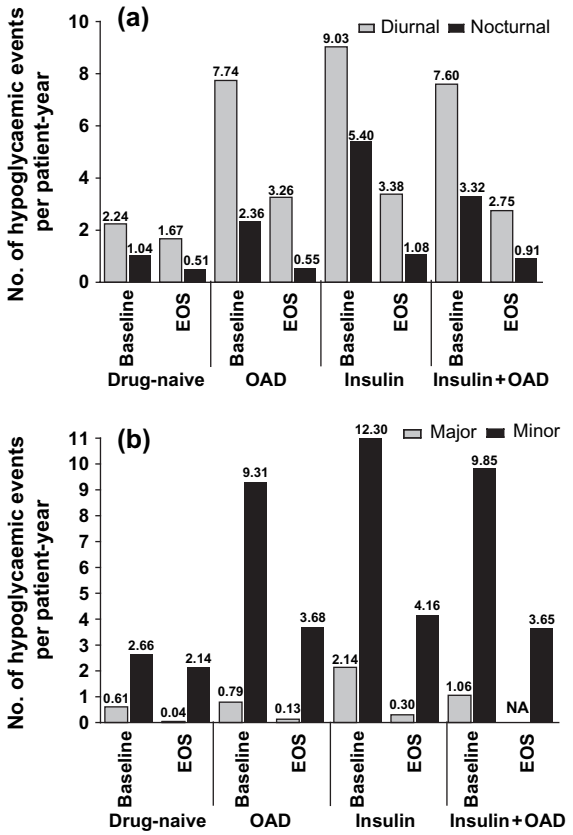

Fig. 2 Hypoglycaemia at baseline and end of study (EOS) classified according to (a) time of day and (b) severity. OAD, oral antidiabetic drug; NA, not applicable.

Adverse Drug Reactions

During the 3-month treatment period, a total of 151 ADRs were reported. Of these, five were serious adverse drug reactions (SADRs): two in the drug-naive group, one in the insulin group and two in the insulin + OAD group. All five SADRs were classified as local hypersensitivity reactions.

Discussion

In this Chinese cohort of over 11 000 patients with poor glucose control, BIAsp 30 treatment was observed to effectively improve parameters of glycaemic control while conferring a lowered risk of hypoglycaemia and other ADRs, regardless of their previous therapy. These results provide 'real-world' clinical support for the findings from clinical trials and clinical experience studies [13–23,26].

This Chinese study showed mean reductions in HbA_{1c} ranging from 1.9 to 2.2%, in FPG ranging from 3.0 to 3.9 mmol/l and in PPPG ranging from 5.2 to 7.1 mmol/l among the groups at the end of 3 months. The only other published study of BIAsp 30 treatment in an all-Chinese cohort was a randomized, parallel group study (BIAsp-1707) that compared 24 weeks of twice-daily treatment vs. thrice-daily treatment [23]. Compared with the present Chinese study, the BIAsp-1707 study showed a greater reduction in HbA_{1c} (by 2.2 and 2.8%) and fasting blood glucose (by 4.7 mmol/l). The final mean dosage of BIAsp 30 was also higher in that study (0.82 and 0.86 U/kg BW) compared with the present Chinese study (0.44–0.51 U/kg BW). Baseline HbA_{1c} was slightly higher in the BIAsp-1707 study (9.5 and 9.6%). The longer duration of treatment, difference in baseline glycaemic control and higher dosage of insulin could have contributed to the better improvements in that study. Other trials involving both BIAsp 30 monotherapy and BIAsp 30 + OAD combination therapy in other countries have shown reductions in HbA_{1c} comparable to those in the present study, by 1.6% (BIAsp 30 monotherapy) and 1.7% (BIAsp 30 + metformin) in a 16-week trial [27] and by 1.3% (BIAsp 30 + metformin) in a 12-week trial [13].

In type 2 diabetes, the development of obesity-related insulin resistance in combination with loss of beta-cell function over time is often the cause of secondary treatment failure. This cohort of Chinese diabetes patients had diabetes for approximately 6 years and was only slightly overweight (average BMI was 24 kg/m^2). They are thus more insulin sensitive to exogenous insulin, and continued improvement was observed after treatment with BIAsp. In addition, baseline demographic status is also a likely reason for this difference in the extent of improvements. Because the drug-naive and OAD groups had poorer glycaemic control at baseline, both treatment groups showed more pronounced reductions in the glucose parameters compared with the insulin and insulin + OAD groups. Also, frequent follow-up through telephone calls or home visits to enhance compliance improved glycaemic outcomes, as shown by a follow-up intervention study [28]. Regardless of the extent of improvement, the final glucose parameters at 3 months were comparable between groups. Indeed, the insulin and insulin + OAD groups continued to show improvements in glycaemic control with BIAsp 30 therapy compared with their previous insulin therapy.

Both PPPG control and a lower rate of hypoglycaemia would encourage the upward titration of BIAsp 30 and therefore improve glycaemic control. Because the pharmacokinetic profile of biphasic insulin aspart closely mimics physiological mealtime insulin profile compared with biphasic human insulin, postprandial hypoglycaemia

is less likely to occur when glycaemic control is improved. Also, given the observational nature of the study, insulin dose in patients was titrated based on individual needs. Therefore, gradual titration may have led to decrease in HbA_{1c} with a relatively low hypoglycaemic rate. With a reduction in the occurrence of hypoglycaemia, frequent snacking between meals to prevent hypoglycaemia can be avoided, which may explain why BW did not increase but decreased instead, although the magnitude of change over a 3-month period may not be clinically relevant in this short-term study.

The low rate of hypoglycaemic episodes in this study was consistent with the reported literature on BIAsp 30, which ranged from 0.04 to 3.4 events per patient-year [16,27]. The proportion of patients in this Chinese study who reported minor hypoglycaemia episodes also fell within the range reported in other studies (10–43%) [16,21,26,27]. The biggest reduction in hypoglycaemic episodes in this study was observed in the insulin-only group. This is evidence of the more physiological pharmacokinetic profile of BIAsp 30 and has practical implications for patients transferring to BIAsp 30 from other insulin treatments. In this study, even the insulin-naive groups (i.e. the drug-naive and OAD groups) reported a decrease in the rate of hypoglycaemia, implying that the initiation of BIAsp 30 treatment could be well tolerated by this group of patients.

The dosage of BIAsp 30 received by patients in this study was based on the routine clinical practice in China. Hence, the dosage was not as high as those observed in treat-to-target studies, such as the INITiation of Insulin to reach A1c TargEt (INITIATE) study [16]. In that study, patients were titrated to a final dosage of 0.82 ± 0.40 U/kg BW, with no occurrence of major hypoglycaemic episodes. Because the final dosage in the four groups in this Chinese study was much lower compared with that in the INITIATE study, and the rates of hypoglycaemic episodes were low, the potential exists for further titration of BIAsp 30 doses to achieve further improvements in glycaemic control.

The low incidence of ADRs in this study was consistent with the good safety profile of BIAsp 30 reported in the literature [12]. In this study, all the SADRs were symptoms of local hypersensitivity.

Study Limitations

As this was an observational study, there were only a few selection criteria. Hence, a small percentage of patients enrolled in the study were identified to have baseline HbA_{1c} of less than 7%, although they may have been judged by their physicians to have poor glycaemic control. The method of data collection for hypoglycaemic episodes and ADRs was based on patient recollection, which could have resulted in under-reporting. Furthermore, blood glucose measurements were not recorded during hypoglycaemic episodes that occurred prior to the start of the study or during the study. This could limit the comparability of the hypoglycaemia reported before and during the study. Of interest is the observation that drug-naive patients reported experiencing major hypoglycaemic episodes at baseline, which decreased after 3 months of treatment. In non-diabetic patients who presented with hypoglycaemia, co-morbid illnesses such as chronic renal failure, alcohol intoxication, liver failure and sepsis were identified as causes of hypoglycaemia [29], while in a Turkish study, endocrine deficiencies and malignancy were found to be the leading cause [30]. While data on these co-morbid illnesses were not collected in this study, neurological impairment such as neuropathy was found in 10.8% of the drug-naive patients (data not shown). This, together with the fact that some of these drug-naive patients, with average age of approximately 50 years, may have been elderly and was unable to self-manage when a hypoglycaemic episode occurred.

Because patients acted as their own control group, it is possible that the improvement in glycaemic control was a result of study effect. However, in an observational study, study effect should be minimized as the data collected mimic real-life settings compared with randomized clinical trials where patients make the effort to control their diabetes condition.

The study was conducted over a short period, and therefore, it was inadequate for capturing long-term trends and observations. Because of the above-stated limitations, the results should be viewed with some caution. However, the large number of patients enrolled in this study does serve as a counterbalance to the traditional shortcomings of an observational study, and the positive results from this study do confirm the results of randomized controlled trials.

Conclusions

The findings from this large observational study involving more than 11 000 Chinese patients concurred with those from clinical trials and showed that the use of BIAsp 30 treatment in clinical practice was both efficacious and safe in patients with type 2 diabetes mellitus who were poorly controlled on prior diabetes therapy.

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