

# Efficacy, Safety and Acceptability of Biphasic Insulin Aspart 30 in Indian Patients with Type 2 Diabetes: Results from the PRESENT Study

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## Abstract

**Aim:** The Physicians' Routine Evaluation of Safety and Efficacy of NovoMix® 30 Therapy (PRESENT) study was done to assess the safety and effectiveness of biphasic insulin aspart 30 (BIAsp 30) in patients with type 2 diabetes mellitus in routine clinical practice.

**Materials and Methods:** This was a prospective, multicentric, multinational, observational study in type 2 diabetes patients. The patients were transferred to BIAsp 30 with or without oral antidiabetic drugs (OADs). We present the results of 6 months of treatment in the Indian cohort (n=3559) with type 2 diabetes mellitus who were inadequately controlled on current treatment.

**Results:** At three and six months, significant reductions from baseline were observed in the mean glycated haemoglobin (HbA<sub>1c</sub>) (-1.32% and -1.94%), fasting plasma glucose (-56.16 mg/dl and -75.24 mg/dl) and post-prandial plasma glucose (-88.74 mg/dl and -119.16 mg/dl) (p<0.001). A significantly greater proportion of patients achieved target HbA<sub>1c</sub> of less than 7% at six months (31.1%), compared with baseline (3.1%), of which 70.4% did not report hypoglycaemia. The rate of total hypoglycaemia was reduced from 3.1 events per patient-year at baseline to 1.5 events per patient-year at end of the study. Episodes were mostly minor and diurnal. Except for two serious adverse drug reactions (ADRs) reported by one patient at 3 months, there were no reports of ADRs during the treatment period. More than 95% of patients and doctors were "very satisfied" or "satisfied" with BIAsp 30 treatment, compared to previous treatment.

**Conclusions:** The use of BIAsp 30 monotherapy or in combination with OADs in clinical practice was effective and safe in poorly controlled Indian type 2 diabetes patients. Both patients and doctors showed a high degree of treatment satisfaction. ©

## INTRODUCTION

India leads the world today in the prevalence of diabetes.<sup>1</sup> Genetic factors, changing dietary preferences, sedentary lifestyle and psychological stress are all important contributors to the burden of diabetes in India.<sup>2</sup>

Biphasic insulin aspart 30 (BIAsp 30) has been available in India since November 2003. It is emerging as the premixed

insulin of choice because its soluble fraction demonstrates a faster onset and shorter duration of action compared to conventional premixed human insulin. These properties allow a flexible mealtime dosing, superior postprandial glycaemic control and a lower risk of hypoglycaemia.<sup>3-8</sup>

Till date, there is little published data exploring the use of BIAsp 30 in routine clinical practice in India.<sup>9-11</sup> The Physicians' Routine Evaluation of Safety and Efficacy of NovoMix® 30 Therapy (PRESENT) study is a large, clinical experience study conducted to collect data on the use of BIAsp 30 among type 2 diabetes patients from 15 countries worldwide, including India. In this article, we present the efficacy, safety and acceptability of BIAsp 30 in Indian subjects with type 2 diabetes.

## MATERIALS AND METHODS

The study was a prospective, open-label clinical experience study carried out at 151 centres in India between

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November 2004 and December 2005. The research protocol was approved by independent ethics committees. The patients recruited at each centre were enrolled in the study for six months. Eligible patients had type 2 diabetes, were inadequately controlled on existing therapy and were prescribed BIAsp 30 either as monotherapy or in combination with other oral antidiabetic drugs (OADs), in accordance with approved labelling. BIAsp 30 treatment (dosing and injection regimen) or discontinuation was entirely at the physicians' discretion. Adequacy of treatment was determined by the treating physician, and was not necessarily in terms of objective criteria. No study-specific interventions were involved except for the collection of data.

Data were collected on individual data collection forms (DCFs) at baseline and after 3 and 6 months of treatment. These included patient's medical history, demography, antidiabetic treatment, blood glucose measurements, number of hypoglycaemic episodes and adverse drug reactions (ADRs). Treatment satisfaction, as judged by the patient as well as the physician, was also recorded in the DCFs.

A total of 3560 patients were enrolled, of which 3559 had baseline data and were included in the analysis set. Of the data collected, baseline characteristics of patients, diabetes treatment and blood glucose measurements were summarized by descriptive statistics (mean  $\pm$  standard deviation [SD]). Changes in fasting plasma glucose (FPG), post-prandial plasma glucose (PPPG), glycated haemoglobin (HbA<sub>1c</sub>) levels and change of weight from

baseline were tested using the paired t-test. Changes in the proportion of target HbA<sub>1c</sub> (<7%) achievers from baseline were compared using McNemar's test. Hypoglycaemic episodes were presented as event rates per patient-year. All statistical analyses were performed using SAS® version 9.1.3 (SAS Institute, NC, USA).

## RESULTS

Out of the 3559 subjects, 62.2% were males, with a mean age of 53.44  $\pm$  10.60 years, mean BMI of 25.67  $\pm$  4.46 kg/m<sup>2</sup> and mean diabetes duration of 9.17  $\pm$  6.28 years. After BIAsp 30 treatment, all glycaemic parameters were significantly improved at 3 and 6 months (p<0.001 for both) (Table 1). Mean HbA<sub>1c</sub>, FPG and PPPG were reduced by 1.94  $\pm$  1.42%, 75.24  $\pm$  55.08 mg/dl and 119.16  $\pm$  72.9 mg/dl, respectively, after 6 months. In addition, the proportion of patients achieving target HbA<sub>1c</sub> of <7% increased from 3.1% at baseline to 31.1% at 6 months (p<0.001) (of which 70.4% did not report hypoglycaemia). Regardless of the number of BIAsp 30 injections (once, twice or thrice daily), HbA<sub>1c</sub> showed improvement from baseline (Table 1).

Throughout the study, changes in total BIAsp 30 dose and body weight from baseline were marginal (Table 1). Hypoglycaemia rate, however, declined from baseline to the end of the study and hypoglycaemic episodes were mostly minor and diurnal in nature (Table 1). There were no ADRs reported except for two serious adverse drug reactions (SADRs) – symptoms of generalized hypersensitivity and oedema which were reported by one patient after 3 months of therapy.

Table 1 : Glycaemic parameters and hypoglycaemia rates of the study population

	Baseline	3 months	6 months
Analysis Population (3559)			
Overall cohort			
HbA <sub>1c</sub> (%)	9.2 $\pm$ 1.5	8.0 $\pm$ 1.19*	7.3 $\pm$ 0.94*
FPG (mg/dl)	194 $\pm$ 56.2	137.9 $\pm$ 39.1*	118.8 $\pm$ 30.4*
PPPG (mg/dl)	285.5 $\pm$ 76	196.7 $\pm$ 52*	165.2 $\pm$ 40*
BIAsp 30 dose (U/kg)	0.36 $\pm$ 0.17	0.38 $\pm$ 0.18	0.38 $\pm$ 0.18
Weight (kg)	67.61 $\pm$ 12.38	67.91 $\pm$ 12.21	67.83 $\pm$ 11.97
Hypoglycaemia rate (episodes per patient year)			
Overall	3.136	—	1.458 <sup>†</sup>
Major	0.548	—	0.050 <sup>†</sup>
Minor	2.588	—	1.409 <sup>†</sup>
Diurnal	1.960	—	0.851 <sup>†</sup>
Nocturnal	1.176	—	0.607 <sup>†</sup>
Stratification by number of BIAsp 30 injection			
Once-daily (n=430), twice-daily (n=1768) and thrice-daily (n=24) <sup>§</sup>			
HbA <sub>1c</sub> (%)			
Once-daily	9.14 $\pm$ 1.50	7.90 $\pm$ 1.15*	7.06 $\pm$ 0.96*
Twice-daily	9.23 $\pm$ 1.43	7.98 $\pm$ 1.12*	7.33 $\pm$ 0.90*
Thrice-daily <sup>Q%</sup>	10.06 $\pm$ 1.19	7.80 $\pm$ 0.83	6.67 $\pm$ 0.61
% achieving target HbA <sub>1c</sub> (< 7%)			
Once-daily	4.2	10.8*	41.8*
Twice-daily	1.9	13.4*	30.0*
Thrice-daily <sup>Q%</sup>	0.0	17.4	55.6

All values are mean  $\pm$  SD unless otherwise stated. \*p < 0.001, p-values as compared to baseline. <sup>†</sup>Refers to hypoglycaemia rate at end of study. <sup>§</sup>This classification excludes patients who indicated changes to their injection regimens during the study. <sup>Q%</sup>Thrice-daily cannot be tested because n < 30.

The majority of patients (95.5% at 3 months and 97.2% at 6 months) and physicians (96.4% at 3 months and 97.1% at 6 months) were "very satisfied" or "satisfied" with BIAsp 30 treatment compared to the previous treatment regimen.

## DISCUSSION

A recent systematic review of comparative trials in adults with type 2 diabetes has shown that premixed insulin analogues provide better post-prandial glycaemic control than that of premixed human insulin and may provide tighter glycaemic control than long-acting insulin analogues with oral antidiabetic agents.<sup>12</sup> Even in this study, which evaluated BIAsp 30 treatment in routine clinical practice, overall glycaemic control improved significantly with a trend towards a decline in the overall rate of hypoglycaemia. Our cohort showed a mean HbA<sub>1c</sub> reduction of 1.32% at 3 months and 1.94% at 6 months. Similar improvements in HbA<sub>1c</sub> (1.3-1.6% points) have been reported in clinical experience studies after 12 weeks of BIAsp 30 treatment.<sup>9-11</sup> Similarly, this reduction was comparable to that observed in the 1-2-3 study, in which type 2 diabetes patients who failed oral agents (with or without basal insulin) had basal insulin replaced with BIAsp 30 as a once, twice or thrice daily regimen.<sup>13</sup> According to the literature, type 2 diabetes patients were reported to be sub-optimally controlled for a period of 6 to 13 years on various antidiabetic treatments (OAD with or without insulin or insulin therapy) prior to transfer to BIAsp 30 treatment. In these instances, the addition of an analogue mix to existing OAD or the transfer of human insulin to an analogue mix provided significant improvements in glycaemic control.

The proportion of subjects reaching target HbA<sub>1c</sub> (<7%) with once daily BIAsp 30 in this study was again similar to 1-2-3 study (41%). Overall proportion of target HbA<sub>1c</sub> (<7%) achievers at the end of our study was lower compared to studies using more aggressive treat-to-target regimens.<sup>13,14</sup> Although the dose of biphasic insulin aspart was not rigorously titrated, as compared to clinical trials, approximately 31% of all patients were able to reach the target of HbA<sub>1c</sub> <7% after 6 months of therapy. In the INITIATE study,<sup>14</sup> a group of insulin-naïve patients inadequately controlled on OADs were additionally treated with twice-daily BIAsp 30. The dosage of BIAsp 30 was increased from a baseline of 0.1 U/kg/day to 0.8 U/kg/day at the end of 28 weeks. The mean HbA<sub>1c</sub> was lowered by 2.8%. The proportion of patients achieving target HbA<sub>1c</sub> of <7% was 66% and <6.5% was 42%. This was a much greater improvement in glycaemic control compared to our study and it suggested that a more aggressive titration regimen of BIAsp 30 could result in better glycaemic control.

The reports on hypoglycaemic episodes were based on patient-recall of the 3 months preceding the first, second and third visit. In studies to date, insulin analogues are associated with fewer episodes of hypoglycaemia compared with human insulin. Hypoglycaemic episodes reported in this study were mostly minor in severity and hypoglycaemia

rate declined during the course of study. This concurs with the results of a 2-year randomized controlled trial that showed that hypoglycaemia declined at the end of the trial as the patients understanding and confidence with insulin therapy improves over a period of time.<sup>8</sup> The frequency of SADR was low in our study and reflects the good safety profile of BIAsp 30, also reported in three other observational studies.<sup>9-11</sup>

Weight gain was negligible in our study. This was consistent with small weight increases seen in a short-term study<sup>10</sup> and a long-term study,<sup>8</sup> which recorded an increase of only 0.05 kg at the end of 24 months. Other studies have reported slightly higher weight increases of 0.7-5.4 kg.<sup>7,14,15</sup> In these studies, treatment was more aggressive and the insulin dosage was higher. It appears that weight increase could be dependent on BIAsp 30 dosage. However, in our study, weight gain and insulin dosage were not found to have a significant relationship. The study period of 6 months in our study was short, and the dosage of BIAsp 30 was based on routine clinical practice and not treat-to-target algorithms. It is possible that a longer duration of study (at least 2 years of observation) and higher doses of insulin would be necessary to estimate the weight-gain effect of insulin therapy.

Till date, two clinical studies<sup>16,17</sup> have also shown that patients achieve greater treatment satisfaction with BIAsp 30 compared to their previous treatment regimens. International guidelines on diabetes management recommend initiating insulin for type 2 diabetes patients when they are unable to maintain the target HbA<sub>1c</sub> on optimized doses of OADs. It seems, however, that these recommendations are seldom being followed. Often, both patients and health care professionals prefer to delay the initiation of insulin until it is absolutely essential. The Diabetes Attitudes Wishes and Needs program,<sup>18</sup> a study of health care professionals and people with diabetes, showed that 40% of health care professionals prefer to delay the initiation of insulin until it is absolutely necessary. In this scenario where both physicians and patients have some reluctance in initiating insulin therapy it is very important that the insulin therapy which is initiated in the patients should be convenient and provide sense of satisfaction over the previous treatment. In this study majority of patients and physicians were satisfied with BIAsp 30 treatment over previous treatment.

This study showed that BIAsp 30 was effective, safe and well-received among Indian patients with type 2 diabetes. Our study has some inherent limitations such as the observational design, short duration and lack of standardized laboratory measurements. Nevertheless, it provides a valuable and practical insight for the use of BIAsp 30 in routine clinical practice.

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### Announcement

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