

Switch from biphasic human insulin 30 to biphasic insulin aspart 30 in Pakistani subjects

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Abstract

Objective: To determine the safety and effectiveness of biphasic insulin aspart 30 (BIAsp 30) in type 2 diabetes subjects switched from biphasic human insulin 30 (BHI 30) in the Pakistani subgroup of the multinational, prospective, non-interventional A1chieve study.

Methods: Subjects who switched therapy from BHI 30 to BIAsp 30 were included in this analysis. Serious adverse drug reactions (SADRs, including major hypoglycaemia) and effectiveness parameters (glycated haemoglobin [HbA1c], fasting plasma glucose [FPG], postprandial plasma glucose [PPPG], systolic blood pressure [SBP]) and body weight were evaluated at the end of 24 weeks.

Results: A total of 152 subjects (79 males, 73 females; mean age, 53.4±10.3 years; BMI, 28.4±5.8 kg/m²) with an average diabetes duration of 11.2±4.8 years switched therapy from BHI 30 to BIAsp 30. The mean pre-study BHI 30 dose was 0.66±0.25 IU/kg and the mean starting BIAsp 30 dose was 0.65±0.23 U/kg, titrated up to 0.77±0.22 U/kg after 24 weeks. No SADRs were reported. From baseline to Week 24, overall hypoglycaemia did not change and no major hypoglycaemia was reported at Week 24. HbA1c levels decreased significantly from 9.1±1.1% at baseline to 7.4±0.7% (57±8 mmol/mol) at Week 24 ($p < 0.001$). Significant improvements in FPG, post-breakfast PPPG and SBP were reported ($p < 0.001$).

Conclusion: Switching from BHI 30 to BIAsp 30 was well tolerated and improved glucose control without an increased incidence of hypoglycaemia in this Pakistani cohort.

Keywords: BIAsp 30, BHI 30, A1chieve, Pakistan. (JPMA 63: 1290; 2013)

Introduction

The prevalence of type 2 diabetes (T2D) has now reached epidemic proportions worldwide. It has been estimated that 552 million people would be living with diabetes by the year 2030.¹ Pakistan ranks second among the top 10 countries by diabetes cases in the Middle East-North Africa region. Currently, the prevalence of diabetes is 6.6 million people and the projected prevalence by 2030 is 11.4 million.¹ Pakistan faces multifaceted socioeconomic crises that prevent adequate clinical care from reaching the masses in a timely manner. Some identified areas include lack of infrastructure for diagnosis and consultation, limited centers specializing in diabetes care, cost of healthcare, lack of government support, and limited patient as well as HCP awareness.²

Despite the increasing importance of early and active intensification of insulin therapy, sales data from the IMS health sales analyzer estimate that only 320,000 people in Pakistan are currently treated with insulin.³ The progressive nature of T2D results in continually declining β -cell function that ultimately mandates the use of insulin in all patients. However, resistance to insulin therapy is often ascribed to factors such as fear of hypoglycaemia and weight gain.⁴ Furthermore, the variability in the pharmacological profile of human insulin preparations, such as biphasic human insulin 30 (BHI 30), often results in unpredictable effects on glycaemic control.⁵ Hence, the insulin analogue, biphasic insulin aspart 30 (BIAsp 30), was designed with an aim to overcome these limitations and provide adequate glycaemic control by regulating fasting plasma glucose (FPG) and post-prandial plasma glucose (PPPG) levels.⁶

BIAsp 30 is a dual release formulation, containing 30% soluble and 70% protamine-crystallized insulin aspart.⁷ Previously, the pharmacodynamics of BIAsp 30 in healthy individuals have indicated that the fast onset of action seen with insulin aspart is retained in this biphasic formulation, whereas the duration of action correlates with that of BHI 30 thus providing both prandial and basal coverage.⁸ Due to the rapid absorption of insulin aspart into the blood stream, BIAsp 30 can achieve higher

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maximum plasma concentration more rapidly compared with BHI 30.^{8,9} As a result, BIAsp 30 therapy is proven to establish superior glycaemic control compared to BHI 30.¹⁰⁻¹² The safety and efficacy of BIAsp 30 has been well-documented in randomized controlled trials as well as observational studies.¹³

So far, there is a sufficient body of evidence validating the efficacy and safety of premix insulin analogues over premix human insulin. However, knowledge regarding the implementation of premix insulin analogue therapy in routine clinical practice is scarce. The A1chieve study was conducted in 28 countries to determine the safety and effectiveness of insulin analogues in local clinical settings in less well-resourced countries.¹⁴ In this sub-analysis, data is analyzed from a Pakistani cohort that switched therapy from BHI 30 to BIAsp 30.

Methods

The A1chieve study¹⁴ was a 24-week, international, prospective, multicentre, non-interventional study to evaluate the safety and effectiveness of BIAsp 30 (Novomix 30[®], Novo Nordisk, Denmark), insulin detemir (Levemir[®], Novo Nordisk, Denmark) and insulin aspart (NovoRapid[®], Novo Nordisk, Denmark), alone or in combination with oral glucose-lowering drugs (OGLDs) in people with T2D in regular clinical practice. This sub-analysis focuses on T2D subjects from Pakistan that switched therapy from BHI 30 to BIAsp 30. These subjects were recruited between August 1, 2009 and February 1, 2010 at 57 centers in Pakistan. The switch from BHI 30 to BIAsp 30, dosing and frequency of administration was mutually agreed upon by the subjects and their consulting physicians. The study drug was commercially available and used in accordance with local regulatory standards. Due to the observational approach of this trial, there were no defined study procedures and all assessments were made by physicians during routine clinical visits. Data for analysis from the physicians' clinical notes and subjects' recall and self-monitoring diary/ blood glucose meter was collected at baseline, Week 12 and Week 24 and transferred to a standard case report form (CRF).

Any patient switching from BHI 30 to BIAsp 30 therapy at the discretion of the physician was included in the sub-analysis. The concurrent use of oral glucose-lowering drugs (OGLDs) was permitted throughout the study at the discretion of the physician. Subjects who had received any of the study insulin analogues (alone or in combination) for more than 4 weeks prior to enrollment were not eligible. Pregnant women and women who were breast-feeding or had the intention of becoming pregnant were excluded. All subjects signed informed consent to participate in this study and the study was

approved by the local ethics committee of Pakistan.

The primary objective of this study was to evaluate the clinical safety of BIAsp 30 in subjects previously treated with BHI 30. The primary safety assessment was the incidence of serious adverse drug reactions (SADRs), including major hypoglycaemia related to BIAsp 30 from baseline to final visit. Secondary safety assessments included changes in number of hypoglycaemic events in the last 4 weeks prior to baseline and final visit, changes in nocturnal hypoglycaemia during this period and the number of adverse drug reactions.

Glucose control was evaluated using changes in HbA1c levels, FPG and post-breakfast PPPG from baseline to Week 24. The changes in systolic blood pressure (SBP) and body weight were also reported. Laboratory parameters were measured in local laboratories and were subject to local standardization and quality control procedures.

Statistical Analyses

Continuous and discrete variables were summarized using continuous variables and frequency tables (n [%]), respectively. The paired t-test was used to analyse the changes in HbA1c, FPG and PPPG from baseline to Week 24. McNemar's test was used to analyse the change in the proportion of subjects reporting at least one hypoglycaemic event from baseline to Week 24. All data were analysed by Novo Nordisk using SAS (Version 9.1.3).

Results

A total of 152 subjects (79 males and 73 females) enrolled in Pakistan switched from BHI 30 to BIAsp 30. Demographic and baseline characteristics for the entire cohort are reported in Table-1. The average duration of

Table-1: Baseline demographics and characteristics.

Parameters	Entire cohort
n	152
Sex, M/F (%)	52.0/48.0
Age (years)*	53.4±10.3
Body weight (kg)*	76.2±14.2
BMI (kg/m ²)*	28.4±5.8
Diabetes duration (years)*	11.2±4.8
Duration on prior insulin therapy*	2.7±1.8
HbA1c (%)*	9.1±1.1
Prior OGLDs, n (%)	
Metformin	131 (95.6%)
Sulfonylureas	34 (24.8%)
Thiazolidinediones	36 (26.3%)
One/two/>two	71 (51.8)/53 (38.7)/13 (9.5)

BHI, biphasic human insulin; BIAsp 30, biphasic insulin aspart 30; BMI, body mass index; F, female; HbA1c, glycated haemoglobin A1c; M, male; OGLD, oral glucose lowering drug.

*Data are mean (SD).

T2D was 11.2 ± 4.8 years and the average duration on insulin therapy was 2.7 ± 1.8 years. The majority of subjects (95.6%, $n=131$) were on metformin at pre-study. At baseline, mean HbA1c was $9.1 \pm 1.1\%$. Physicians reported that in 146 (96.1%) subjects, BIAsp 30 was initiated to improve glucose control. Unstable diabetes 74 (48.7%) subjects, patient dissatisfaction with current therapy 64 (44.1%) subjects, and reduction in plasma glucose variability 67 (44.1%) subjects, were among the other major reasons for insulin initiation.

At Week 24, no SADR or serious adverse events (SAEs) were reported in subjects included in this sub-analysis.

There was a 1.6 ± 3.8 kg increase in body weight from

76.2 ± 14.2 kg at baseline to 77.9 ± 13.4 kg at Week 24 ($p < 0.001$).

Overall hypoglycaemia did not increase following the switch from BHI 30 to BIAsp 30. No major hypoglycaemia was observed in the entire cohort. The proportion of subjects reporting nocturnal and minor hypoglycaemia was not significantly different between baseline and Week 24. (Table-2).

The insulin dose and frequency of administration are reported in Table 3. The mean insulin dose at baseline was 0.65 ± 0.23 U/kg titrated up to 0.77 ± 0.22 U/kg by Week 24. The majority of subjects received insulin twice-daily at pre-study (97.4%, $n=148$), baseline (88.2%, $n = 134$) and Week 24 (82.6%, $n=123$).

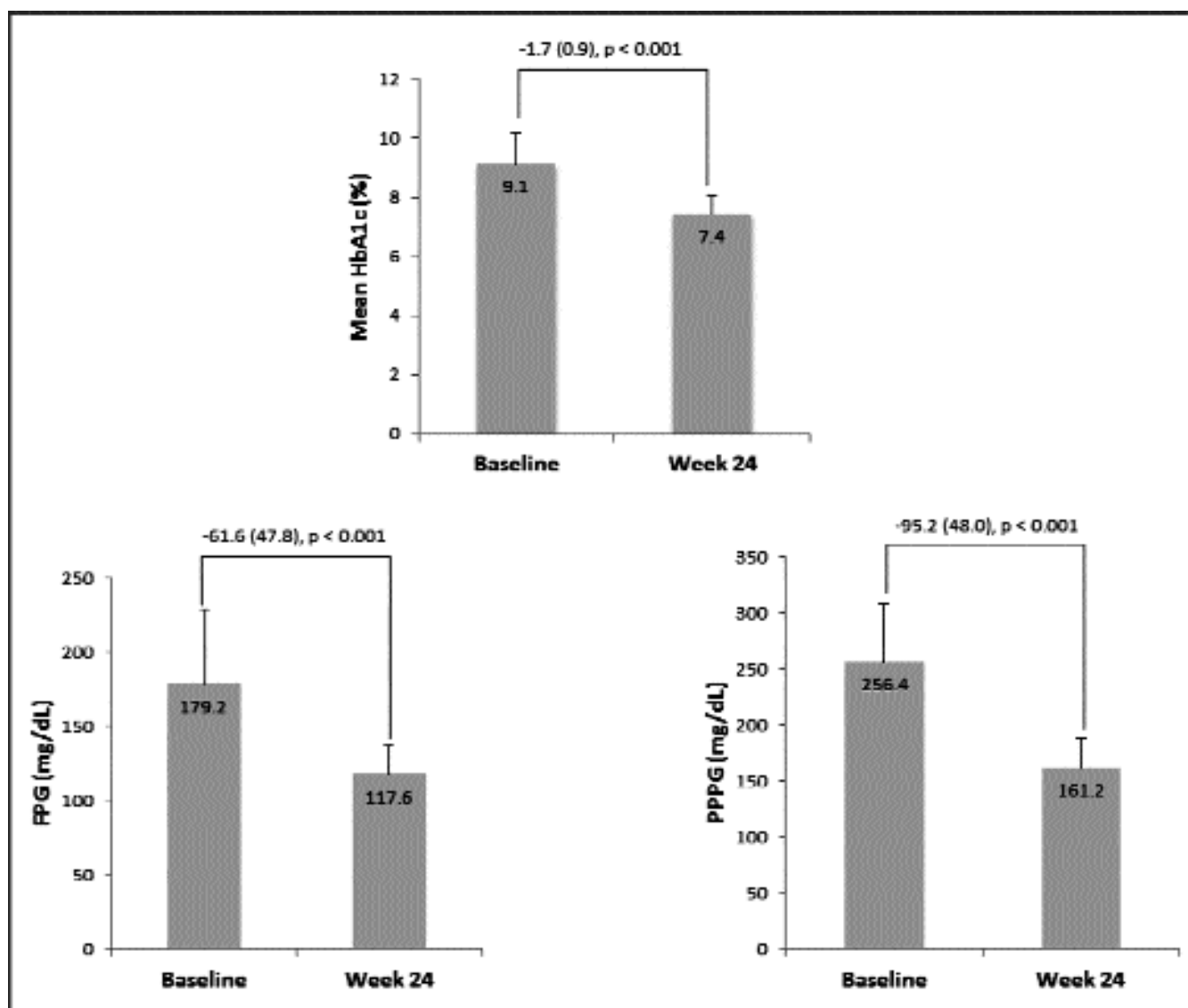


Figure: Change in glucose control parameters from baseline to week 24.

Table-2: Baseline and 24-week data for hypoglycaemia.

Event per patient-year/Percent with at least one event		
Overall	Baseline	3.25/11.2
	Week 24	3.05/10.7
	p*	NS
Minor	Baseline	3.25/11.2
	Week 24	3.05/10.7
	p*	NS
Nocturnal	Baseline	0.94/5.3
	Week 24	1.13/6.7
	p*	NS
Major	Baseline	0.0/0.0
	Week 24	0.0/0.0
	p*	--

*p-value is for difference in percent of subjects with at least one event evaluated using the McNemar's test.

Table-3: Insulin dose and frequency.

Parameters	Entire cohort	
Insulin dose per day	n	152
	Pre-study(IU/day)*#	49.1 (18.6)
	Baseline (IU/day)*	48.7 (17.0)
	Week 24 (IU/day)*	60.3 (17.6)
Insulin dose by body weight	n	145
	Pre-study (IU/kg) * #	0.66 (0.25)
	Baseline (U/kg)*	0.65 (0.23)
	Week 24 (U/kg)*	0.77 (0.22)
Dose frequency (daily)	Pre-study (n)	152
	Once/ Twice/Thrice**	2 (1.3)/148 (97.4)/2 (1.3)
	Baseline (n)	152
	Once/ Twice/Thrice**	0 (0)/134(88.2)/18 (11.8)
	Week 24 (n)	149
	Once/ Twice/Thrice**	0 (0)/123 (82.6)/26 (17.4)

*Data are represented as mean(SD).

** Data are represented as n (%).

#The unit of measurement for BHI 30 at pre-study was IU/day or IU/kg.

Following 24 weeks of BIAsp 30 therapy, significant improvements in HbA1c ($-1.7 \pm 0.9\%$, $p < 0.001$), FPG (-61.6 ± 47.8 mg/dL, $p < 0.001$) and PPPG (-95.2 ± 48.0 mg/dL, $p < 0.001$) were observed (Figure). Additionally, the number of subjects with HbA1c $< 7.0\%$ increased from 2 (1.4%) at baseline to 28 (24.3%) at Week 24. A significant decrease of 12.6 ± 15.2 mmHg ($p < 0.001$) in SBP was observed from baseline (141.3 ± 17.0 mmHg) to Week 24 (128.7 ± 9.9 mmHg). Additional effectiveness parameters were not included in this sub-analysis as the subject numbers were too small to indicate a statistical significance.

Discussion

This sub-analysis demonstrated the safety and effectiveness of BIAsp 30 in Pakistani T2D subjects switched

from BHI 30. Overall, BIAsp 30 therapy was well tolerated and no SAEs or SADR were reported. Although there was a slight reduction in the incidence of overall hypoglycaemia, the difference was not significant. As reported in Table-2, the overall hypoglycaemia rates were primarily attributed to the incidence of minor hypoglycaemia.

Previously, it has been reported that the risk of major hypoglycaemia is lower with BIAsp 30 when compared to BHI;^{15,16} however, in this study there were no major hypoglycaemic events reported at baseline and Week 24. From baseline to Week 24, minor hypoglycaemia decreased and nocturnal hypoglycaemia increased; however, these changes were not statistically significant. A significant reduction in overall hypoglycaemia in this cohort may have been masked due to the small sample size or the introduction of recall bias that we acknowledge as limitations of this study.

As evident in large observational studies such as PRESENT,¹⁰ IMPROVE¹¹ and A1chieve,¹⁴ poorly controlled diabetes (HbA1c, 9.1%) was also observed in this cohort at baseline. BIAsp 30 therapy resulted in marked improvements in glucose control parameters after 24 weeks. A significant decrease in HbA1c, FPG and PPPG ($p < 0.001$) was observed in this sub-analysis. These results are similar to the data from the observational studies- PRESENT, IMPROVE and global A1chieve as well as other studies involving a switch from BHI 30 to BIAsp 30.^{8,10,11,14,15} The American Diabetes Association and the European Association for the Study of Diabetes recommend HbA1c levels $< 7.0\%$ in order to prevent the onset and progression of chronic complications.¹¹ Following BIAsp 30 administration, the percentage of subjects achieving the HbA1c target $< 7.0\%$ increased from 1.4% to 24.3% in this cohort. The superior glucose control of BIAsp 30 compared to BHI 30 is often attributed to its pharmacological profile that provides both prandial and basal coverage. Notably, the improvements in glucose control were evident without a corresponding increase in the incidence of hypoglycaemia.

Ultimately, all patients on OGLDs alone require insulin therapy or intensification due to the disease progression. The United Kingdom Prospective Diabetes study demonstrated that 53% patients treated with sulphonylurea monotherapy required insulin over a period of 6 years.¹⁹ However, in this cohort despite the average diabetes duration being 11.2 years, subjects had been on insulin therapy for only 2.7 years. This suggests an urgent need to revisit the current standards of diabetes management in routine clinical practice in Pakistan.

The observational nature of this study has certain limitations such as the lack of standardization of measurements and

the absence of a control arm. However, all measurements were in accordance with local regulations and by methods that are NGSP-certified. The 24-week duration of this study, although short, could be reasonable to assess the effectiveness and safety of FDA and EMA approved drugs for chronic diseases such as T2D in which early and rapid responses are desired. Furthermore, this study provides an opportunity to explore the current status of diabetes care and potential therapy options in a heterogeneous group of subjects in local settings in Pakistan. Due to the significant healthcare challenges faced by this country, it is of utmost importance to educate the patients and physicians on effective and sustainable diabetes management.

Conclusion

The results from this study prove that switching therapy to insulin analogues such as BIAsp 30 would be beneficial to achieve target glycaemic control with a low incidence of hypoglycaemia.

Acknowledgements

The authors would like to thank the entire study group, their staff, clinical trial personnel and investigators involved in the A1chieve study. Special thanks to all the patients for their participation in this study.

The authors would like to thank Chunduo Shen of Novo Nordisk for providing statistical analysis. The authors would also like to thank Ruchita Kapoor from Cognizant Technology Solutions for writing and editorial assistance, funded by Novo Nordisk.

Financial Support

The trial design, data collection and analysis, manuscript preparation and publication were funded by Novo Nordisk.

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