

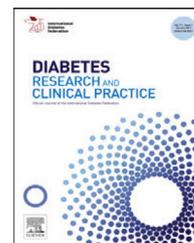


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Diabetes Research and Clinical Practice

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

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Safety and effectiveness of biphasic insulin aspart 30 in a Bangladeshi subgroup of type 2 diabetic patients switched from biphasic human insulin 30: A sub-analysis of the A₁chieve study

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ARTICLE INFO

Keywords:

Bangladesh
Type 2 diabetes mellitus
Biphasic insulin aspart 30
Biphasic human insulin 30
A₁chieve

ABSTRACT

Aim: To determine the safety and effectiveness of biphasic insulin aspart 30 (BIAsp 30) therapy in Bangladeshi type 2 diabetes (T2D) patients switched from biphasic human insulin (BHI) as a sub-analysis of the A₁chieve study.

Methods: Bangladeshi patients switched from BHI to BIAsp 30 at the discretion of their physicians were included. The primary outcome was the incidence of serious adverse drug reactions (SADRs), including major hypoglycaemia. Secondary outcomes comprised changes from baseline to Week 24 in the number of hypoglycaemic events, glycated haemoglobin A_{1c} (HbA_{1c}), fasting plasma glucose (FPG), postprandial plasma glucose (PPPG), systolic blood pressure and body weight. Quality of life (QoL) was evaluated at baseline and Week 24 using the EQ-5D questionnaire.

Results: A total of 82 patients (mean age \pm SD: 52.3 \pm 12.2 years; body mass index: 25.6 \pm 3.3 kg/m²) with a mean diabetes duration of 9.5 \pm 5.5 years and mean duration on insulin of 2.5 \pm 2.4 years were included. The mean BIAsp 30 dose was 0.49 \pm 0.20 U/kg at baseline and 0.47 \pm 0.17 U/kg at Week 24. No SADRs were reported. No events of hypoglycaemia (overall, major, minor or nocturnal) were reported at Week 24. Mean HbA_{1c}, FPG and PPPG levels improved by $-2.5\pm 1.3\%$, -65.0 ± 31.8 mg/dL and -119.3 ± 48.7 mg/dL, respectively, over 24 weeks. QoL also improved (mean change from baseline: +28.5 \pm 12.9 points).

Conclusion: Switching from BHI to BIAsp 30 therapy improved blood glucose control and was well-tolerated in this Bangladeshi subgroup.

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1. Introduction

Low-income countries such as Bangladesh are witnessing an increased incidence of type 2 diabetes (T2D) resulting from rapid urbanization and the associated lifestyle and dietary changes [1,2]. According to an estimate by the International Diabetes Federation (IDF), Bangladesh had a diabetes prevalence of 10.5% in 2011 that is expected to rise to 13.7% by the year 2030. In fact, the number of diabetic Bangladeshi

adults (aged between 20 and 79 years) is projected to double in the next 20 years, from 8.4 million in 2011 to 16.8 million in 2030, making it the fifth highest diabetic populous country in the world [3]. This will impose a heavy burden on the already strained healthcare resources [4], thus making it critical that appropriate measures are used for the management of T2D.

Studies have shown that the progressive deterioration of insulin-producing β -cells and the resultant hyperglycaemia associated with T2D need to be counteracted by prompt and

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effective treatment intensification [5,6]. Prolonged periods of high blood glucose levels can increase the risk of diabetic complications. Regular testing of the glycaemic parameters, glycated haemoglobin A_{1c} (HbA_{1c}), fasting plasma glucose (FPG) and postprandial plasma glucose (PPPG), is indispensable to monitor disease progression and is highly recommended by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes [7]. However, in the 2008 DiabCare Bangladesh study, 77% of patients were found to have HbA_{1c} levels $\geq 7.0\%$ (≥ 53 mmol/mol), pointing to inadequate monitoring and sub-optimal treatment intensification [8].

Insulin is the single most effective treatment for T2D, yet negative connotations of body weight gain, hypoglycaemia, patient fear of needles, multiple injections and clinical apathy on the part of healthcare providers often lead to a delay in intensifying insulin therapy [9]. Premixed insulin regimens require a lower number of injections than classic basal-bolus therapy due to formulations that combine a short-acting insulin with a slower-acting version. Human premixed insulin, otherwise known as biphasic human insulin (BHI), has however been found to have unpredictable effects on the lowering of glycaemic levels due to variability in action that ties in with an increased risk of hypoglycaemic events [10].

Biphasic insulin aspart 30 (BIAsp 30) is a premixed insulin analogue that was developed to address the pharmacokinetic limitations of BHI. BIAsp 30 contains a mixture of 30% insulin aspart (IAsp) and 70% protaminated IAsp that provides bolus and basal insulin replacement, respectively [11]. A retrospective review of clinical trials comparing BIAsp 30 and BHI found that BIAsp 30 therapy has a lower risk of nocturnal hypoglycaemia and major hypoglycaemia [12]. Due to the rapid subcutaneous absorption properties of IAsp which are retained in this premixed formulation, BIAsp 30 is also associated with better PPPG control and can be injected either pre-meal or post-meal, offering greater ease of dosing compared to BHI [11]. The effects of switching from BHI to BIAsp 30 in routine clinical practice have previously been examined in several large observational studies [13–15].

This sub-analysis of the international, non-interventional A₁chieve study [16] was conducted with the aim of evaluating the clinical safety and effectiveness of BIAsp 30 in Bangladeshi T2D patients who were previously treated with BHI and also to report the current status of disease management in local healthcare settings in Bangladesh.

2. Materials and Methods

2.1. Study design, objectives and assessments

A₁chieve was a non-interventional, international, 24-week, open-label study of the clinical safety and effectiveness of BIAsp 30 (NovoMix[®] 30, Novo Nordisk A/S, Denmark), insulin detemir (Levemir[®], Novo Nordisk A/S, Denmark) and IAsp (NovoRapid[®], Novo Nordisk A/S, Denmark), as monotherapy or in combination, in the treatment of T2D

in non-Western economies [16]. Complete study results are now available online under www.A1chieve.com. This sub-analysis focused on the data of Bangladeshi patients who had started BIAsp 30 therapy after being switched from BHI. The study was designed to assess standard safety and efficacy parameters in local outpatient settings. No special investigational procedures were conducted; all measurements were carried out by the treating physicians and recorded in standard case report forms.

The study was approved by the local ethics committee in Bangladesh. The physicians supervised all aspects of the therapy change from BHI to BIAsp 30, including the starting dose of BIAsp 30, the subsequent titration of doses over 24 weeks, frequency of administration and any changes in the concomitant medications administered.

The primary objective was the assessment of safety based on the number of serious adverse drug reactions (SADRs), including major hypoglycaemic events, reported from baseline to Week 24. The secondary efficacy assessments comprised HbA_{1c}, FPG, PPPG, systolic blood pressure (SBP) and quality of life (QoL). The secondary safety assessments included the change in the number of hypoglycaemic events (overall, minor and nocturnal) in the last 4 weeks before the final visit and the last 4 weeks before baseline and the number of adverse drug reactions (ADRs) and serious adverse events (SAEs) after 24 weeks of treatment. All samples were evaluated by local laboratories and were subject to local quality control and standardization procedures. The change in QoL at Week 24 compared to baseline was determined using the visual analogue scale of the EQ-5D, a validated QoL questionnaire.

2.2. Patient eligibility

Any Bangladeshi patient with T2D who had not been previously treated with BIAsp 30, insuling detemir or IAsp and who had transferred therapy from BHI to BIAsp 30 within the last 4 weeks before inclusion into the study was eligible for participation. Patients were enrolled between 15 January 2010 and 15 September 2010 from 48 study centres in Bangladesh.

Patients who were hypersensitive to these analogues or to any of the excipients were excluded, as were women who were pregnant, breast-feeding or had the intention of becoming pregnant within the next 6 months. All patients provided written informed consent prior to study participation.

2.3. Statistical analyses

All data were analyzed by Novo Nordisk using SAS[®] (Version 9.1.3). The mean change from baseline in HbA_{1c}, FPG, PPPG, SBP and QoL was assessed using a paired t-test with baseline and Week 24 values. The change from baseline to Week 24 in the proportion of patients reporting at least one hypoglycaemic event was analyzed using McNemar's paired test.

Only descriptive results are presented in this paper due to the small sample size (n = 82).

3. Results

3.1. General characteristics

A total of 82 Bangladeshi patients who switched treatment from BHI to BIAsp 30, as guided by their physicians, were included in this subgroup. Demographic and baseline data are presented in Table 1.

Table 1 – Baseline demographics and characteristics

Parameter	All patients (n = 82)
Gender (male/female), %	51.2/48.8
Age, years	52.3 (12.2)
Body weight, kg	65.6 (8.7)
BMI, kg/m ²	25.6 (3.3)
Diabetes duration, years	9.5 (5.5)
Duration on prior insulin therapy, years	2.5 (2.4)
HbA _{1c} , %	9.8 (1.4)
HbA _{1c} , mmol/mol	84 (15)
OGLDs, n (%)	
Metformin	36 (70.6)
Sulfonylureas	18 (35.3)
Thiazolidinediones	11 (21.6)
1 OGLD	36 (70.6)
2 OGLDs	14 (27.5)
>2 OGLDs	1 (2.0)

BMI, body mass index; HbA_{1c}, glycated haemoglobin A_{1c}; OGLD(s), oral glucose-lowering drug(s).
Data are presented as mean (SD) unless specified otherwise.

At baseline, these patients had an average age (mean±SD) of 52.3±12.2 years, while the mean age at diagnosis was 42.8±10.7 years. The mean body mass index in this subgroup was 25.6±3.3 kg/m² and the mean HbA_{1c} level was 9.8±1.4% (84±15 mmol/mol) at baseline.

3.2. OGLDs used

At baseline, metformin, sulfonylurea and thiazolidinedione use was reported in 70.6%, 35.3% and 21.6% of patients, respectively (Table 1), while at Week 24, 90.9% of patients were using 1 OGLD and the majority of patients were taking sulfonylurea (59.1%).

3.3. Reasons for therapy change

All physicians cited the need to improve glycaemic control as the major reason for switching therapy. The other commonly reported reasons were to try a new insulin (36.6% of patients) and unstable diabetes (17.1% of patients).

3.4. Insulin dose and dosing frequency

Insulin dose and dosing frequency pre-study, at baseline and at Week 24 are described in Table 2. The mean pre-study BHI dose by body weight was 0.46±0.16 IU/kg and the mean starting BIAsp 30 dose at baseline was 0.49±0.20 U/kg (n = 82). At the end of the study, the mean BIAsp 30 dose was 0.47±0.17 U/kg (n = 74).

Table 2 – Insulin dose and frequency

		All patients
Pre-study	n	82
	Insulin dose per day, IU/day ^a	30.0 (10.2)
	Insulin dose by weight, IU/kg ^a	0.46 (0.16)
	Dose frequency, n (%)	
	Once daily	1 (1.2)
	Twice daily	81 (98.8)
	Thrice daily	0 (0)
Baseline	n	82
	Insulin dose per day, U/day	31.7 (12.4)
	Insulin dose by weight, U/kg	0.49 (0.20)
	Dose frequency, n (%)	
	Once daily	5 (1.6)
	Twice daily	75 (91.5)
	Thrice daily	2 (2.4)
Week 24	n	74
	Insulin dose per day, U/day	30.1 (10.5)
	Insulin dose by weight, U/kg	0.47 (0.17)
	Dose frequency, n (%)	
	Once daily	0 (0)
	Twice daily	74 (100)
	Thrice daily	0 (0)

Data are presented as mean (SD).

^a The unit of measurement for biphasic human insulin pre-study was IU/day or IU/kg.

3.5. SADR, SAEs and hypoglycaemia

No SADR, SAEs or ADRs were reported in this subgroup.

At baseline, the incidence of overall hypoglycaemic events was 2.38 events/patient-year and 17.1% of patients had reported at least one event in the 4 weeks prior to the study (Table 3). Also, major, minor and nocturnal hypoglycaemic events were reported in 3.7%, 13.4% and 6.1% of patients, respectively, during the 4 weeks prior to the study. At Week 24, no hypoglycaemic events were reported in any of the categories (overall, major, minor and nocturnal) in this subgroup (Table 3).

Table 3 – Baseline and 24-week data for hypoglycaemia

Hypoglycaemia	Events per patient-year / percent with at least one event	
Overall	Baseline	2.38 / 17.1
	Week 24	0.0 / 0.0
Minor	Baseline	1.90 / 13.4
	Week 24	0.0 / 0.0
Nocturnal	Baseline	0.79 / 6.1
	Week 24	0.0 / 0.0
Major	Baseline	0.48 / 3.7
	Week 24	0.0 / 0.0

3.6. Glycaemic control, body weight and SBP

The mean HbA_{1c} level improved to 7.4±1.3% (57±14 mmol/mol) at Week 24 associated with a mean change from baseline of -2.5±1.3% (-27±14 mmol/mol) (Table 4). The number of patients who reached the target HbA_{1c} of <7.0%

Table 4 – Baseline and 24-week data for blood glucose control parameters

Parameter		All patients
HbA _{1c} , % / mmol/mol	n	71
	Baseline	9.8 (1.4) / 84 (15)
	Week 24	7.4 (1.3) / 57 (14)
	Change	–2.5 (1.3) / –27 (14)
FPG, mg/dL	n	74
	Baseline	185.2 (30.5)
	Week 24	120.2 (15.5)
	Change	–65.0 (31.8)
PPPG, mg/dL	n	74
	Baseline	278.2 (48.5)
	Week 24	158.8 (18.4)
	Change	–119.3 (48.7)

FPG, fasting plasma glucose; HbA_{1c}, glycated haemoglobin A_{1c}; PPPG, postprandial plasma glucose.
Baseline, Week-24 and change values are mean (SD).

(<53 mmol/mol) was 31 (43.1%) at Week 24 compared to 2 (2.5%) at baseline.

The mean FPG and post-breakfast PPPG levels also decreased by -65.0 ± 31.8 mg/dL and -119.3 ± 48.7 mg/dL, respectively, from baseline to Week 24 (Table 4).

The change in mean body weight after 24 weeks of BIAsp 30 therapy was -0.3 ± 1.3 kg. The mean SBP was 128.3 ± 11.1 mmHg at baseline and 122.7 ± 6.3 mmHg at Week 24 (mean change: -5.6 ± 13.8 mmHg).

3.7. Patient QoL

The mean patient QoL increased from 54.7 ± 12.8 points at baseline to 83.2 ± 4.8 points at Week 24 on the EQ-5D visual analogue scale (mean improvement: 28.5 ± 12.9 points).

4. Discussion

This subgroup analysis in Bangladeshi patients with T2D revealed poor baseline glycaemic control as was also observed in other non-interventional studies in routine clinical practice [13–15]. Switching from BHI to BIAsp 30 therapy resulted in improved levels of blood glucose and was associated with a decreased incidence of hypoglycaemia over 24 weeks. No SADR or SAE were reported in this sub-analysis.

An analysis of the Bangladesh Institute of Research and Rehabilitation for Diabetes, Endocrine, and Metabolic Disorders (BIRDEM) patient registry showed that the average age at diagnosis for T2D has significantly decreased from 1995 to 2005 [17]. In this Bangladeshi subgroup, the average age at baseline was 52.3 years and patients had been diagnosed approximately 9.5 years earlier.

In the 2008 DiabCare survey in Bangladesh, the average HbA_{1c} level was 8.6% (70 mmol/mol) among diabetic patients and the majority of insulin-treated patients were taking human insulin [8]. The baseline data from our study revealed that the patients were poorly controlled on BHI

with an average HbA_{1c} level of $9.8 \pm 1.4\%$ (84 ± 15 mmol/mol). Only 2 patients had an HbA_{1c} level that matched the ADA-recommended target of $<7.0\%$ (<53 mmol/mol) at baseline. After switching to BIAsp 30 therapy, glycaemic control improved with reductions in the mean HbA_{1c}, FPG and PPPG values and more patients also achieved the HbA_{1c} target at Week 24. Switching to BIAsp 30 from BHI was associated with statistically significant reductions from baseline to Week 24 in HbA_{1c}, FPG and PPPG in the overall A₁chieve cohort [13].

As reported in other studies [13–15], the event rates of both major and nocturnal hypoglycaemia declined from baseline to Week 24 in this subgroup, subsequent to therapy transfer from BHI to BIAsp 30. Moreover, the event rates of overall and minor hypoglycaemia also declined in this subgroup. Continuing secretagogue treatment together with insulin is associated with a higher risk of hypoglycaemia [18]. However, it is interesting to note that no events of hypoglycaemia were reported at Week 24 in this subgroup in spite of a rise in the proportion of sulfonylurea users from 35.3% to 59.1% between baseline and Week 24. Also, it is possible that the decreased incidence of hypoglycaemia and the more convenient dosing options available with BIAsp 30 therapy may have been contributing factors to the increase in general QoL reported by patients at Week 24.

Overall, the data from this Bangladeshi subgroup must be interpreted with caution due to the small number of patients analysed and the fact that data collection for outcomes such as hypoglycaemia were based upon patient recall. In addition, the study did not have a control group or a strictly controlled population, which could further decrease the certainty with which outcomes may be ascribed to treatment. However, the descriptive analysis of the study data revealed general improvements in glycaemic control and a positive trend in the patients' QoL, without any associated safety concerns. These results support the well-established efficacy and safety profile of BIAsp 30 [19]. Although the sample size was small, it is encouraging to note that the response to the therapy change from BHI to BIAsp 30 is in line with the results from other observational studies that investigated switching from BHI to BIAsp 30 in clinical practice [13–15]. Furthermore, the results from this study could contribute to an evidence base that would ultimately help T2D management in the local healthcare setting in Bangladesh.

In summary, switching to BIAsp 30 was well-tolerated in this subgroup of Bangladeshi T2D patients previously treated with BHI. The demonstrated improvements in glycaemic control were accompanied by a decreased incidence of hypoglycaemic events suggesting that BIAsp 30 could be an effective treatment option for patients with T2D poorly controlled on BHI.

Acknowledgements

The authors would like to thank all participants who provided data, and all investigators involved in the A₁chieve study. The authors would like to thank Chunduo Shen of Novo Nordisk for providing statistical analysis. The authors would also like to thank Anjali Philip of Cognizant

Technology Solutions for writing assistance, funded by Novo Nordisk.

Conflict of interest statement

Prof. Zafar Ahmed Latif has conducted research and received honorarium for conduction of research and for delivering lectures from Novo Nordisk, Sanofi, Eli Lilly, Novartis and Servier. Prof. Md. Faruque Pathan has conducted research and received honorarium for conduction of research and for delivering lectures from Novo Nordisk, Sanofi, Eli Lilly, Novartis and Servier. Prof. Md. Nazrul Islam Siddiqui has conducted research and received honorarium for conduction of research and for delivering lectures from Novo Nordisk, Sanofi, Eli Lilly, Novartis and Servier. Dr. Md. Javed Sobhan was employed by Novo Nordisk Pharma (Pvt.) Ltd. Bangladesh. Dr. Md. Mahfuzur Rahman was employed by Novo Nordisk Pharma (Pvt.) Ltd. Bangladesh. Dr. S.M. Ashrafuzzaman has conducted research and received honorarium for conduction of research and for delivering lectures from Novo Nordisk, Sanofi, Eli Lilly, Novartis and Servier. This study was sponsored by Novo Nordisk A/S, Denmark. The sponsor took part in the development of the protocol, the process of data collection and analysis, funding of medical writing services, and in reviewing the manuscript, but not in participant selection, choice of therapies (study or otherwise), provision of therapies including insulin or continuing clinical management of the participants.

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