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Clinical experience with BIAsp 30: Results from the Indonesian cohort of the international A_1chieve study

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ABSTRACT

Aim: To evaluate the safety and effectiveness of biphasic insulin aspart 30 (BIAsp 30) in Indonesian patients with type 2 diabetes (T2D) as part of the 24-week, international, prospective, non-interventional A_1chieve study.

Methods: Indonesian patients who started BIAsp 30 were included. Safety and efficacy was measured as part of routine clinical practice at baseline, Week 12 and Week 24.

Results: Overall, 1324 patients having a mean±SD age, duration of diabetes and body mass index of 55.2±9.9 yrs, 6.8±5.2 yrs and 24.1±3.6 kg/m^2, respectively, were enrolled. 67% of patients were insulin-naive and 33% were prior insulin users. Glycaemic control was poor at baseline. After 24 weeks, significant reductions from baseline were observed in the mean glycated haemoglobin A_{1c} (HbA_{1c}) (–2.6%), fasting plasma glucose (–93.8 mg/dL) and postprandial plasma glucose (–134.8 mg/dL) levels in the entire cohort ($p < 0.001$). Significant reductions were also seen in insulin-naive patients and prior insulin users. At Week 24, 29.9% of patients in the entire cohort achieved target HbA_{1c} level of <7.0%, while 26.7% and 39.2% achieved this target among insulin-naive patients and prior insulin users, respectively. The proportion of patients reporting overall hypoglycaemia significantly decreased in the entire cohort after 24 weeks of BIAsp 30 therapy. A small significant increase in body weight was noted in the entire cohort, insulin-naive patients and prior insulin users.

Conclusion: The current study suggests that BIAsp 30 can be considered as a safe and effective option for initiating as well as intensifying insulin therapy in Indonesian patients with T2D.

1. Introduction

Indonesia is expected to have about 21.3 million people with diabetes mellitus (DM) in 2030 compared to 8.4 million in 2000. The World Health Organization further categorized Indonesia as fourth highest in the number of diabetes cases globally [1]. By the time most patients are diagnosed with type 2 diabetes (T2D), 50% of normal β-cell function is already lost and the further decline of β-cell function cannot be avoided [2]. This suggests that chronically high levels of blood glucose often precede the clinical diagnosis of T2D by more than ten years. Most patients with T2D have complications at diagnosis [3]. Nearly 75% of patients will

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require multiple therapies after 9 years of T2D, including the addition of insulin to obtain a glycated haemoglobin A_{1c} (HbA_{1c}) level of <7.0% (<53 mmol/mol) [4]. Timely augmentation with additional therapy, including the early initiation of insulin, is recommended by the American Diabetes Association and the European Association for the Study of Diabetes for the management of hyperglycaemia in T2D [5].

Additionally, the decreased risk of complications observed in the United Kingdom Prospective Diabetes Study with intensive therapy was found to be maintained over 10 years post study [6]. Since most patients with T2D will eventually require supplemental insulin, physicians should consider the early prescription of insulin and more vigorous treatment intensification to maintain glycaemic control without compromising safety. Biphasic insulin analogues were designed to fulfill prandial and basal insulin needs. Biphasic insulin aspart 30 (BIAsp 30) is constituted of 30% soluble rapid-acting insulin aspart, providing prandial coverage, and 70% protaminated insulin aspart, providing basal coverage [7]. BIAsp 30 could be a convenient option for initiating insulin treatment for patients unable to sustain good glycaemic control on oral glucose-lowering drugs (OGLDs) alone. Also, BIAsp 30 can be injected once daily (*qd*), twice daily (*bid*) or even thrice daily (*tid*) if required [8,9].

Although many randomised controlled trials (RCTs) have established the efficacy and safety of BIAsp 30, the clinical data from observational studies is still needed to portray the effects of treatment in actual patient populations. A_1chieve is one of the largest multinational non-interventional studies on insulin analogues [10]. Complete study results are available online under www.A1chieve.com. The safety and effectiveness of BIAsp 30 in the Indonesian population is not well established due to a scarcity of published data. Therefore, this subgroup analysis was conducted with an aim to evaluate the safety and effectiveness of BIAsp 30 therapy, as well as health-related quality of life (QoL) parameters, in the Indonesian cohort.

2. Methods

2.1. Study design

A_1chieve was a 24-week, international, prospective, non-interventional study of patients with T2D who had begun using BIAsp 30 (premix), insulin detemir or insulin aspart, alone or in combination, with or without OGLDs, in 28 countries across four continents (Asia, Africa, Latin America and Europe) [10]. This subgroup analysis evaluates the safety and effectiveness of BIAsp 30 therapy in Indonesian patients with T2D. The patients were recruited between October 2009 and August 2010 at 65 centers across Indonesia. Ethics committee approval was obtained for Indonesia, and signed informed consent from all patients.

2.2. Inclusion and exclusion criteria

All Indonesian patients with T2D, who had not used any of the study insulins previously and who had been started on BIAsp 30 therapy in the 4 weeks prior to the study start, were included. Patients who had once participated in the study were not enrolled again during the study period. Also, patients with hypersensitivity to the study insulins or excipients were excluded, as were women who were pregnant, breast-feeding, or who intended to become pregnant within 6 months of the study.

The choice of BIAsp 30, use of concurrent OGLDs and all subsequent treatment decisions were at the discretion of the physician, according to his or her usual practice. Patients were free to withdraw from the study at any time. There were no defined study-related procedures. Safety and effectiveness of therapy were determined from the measurements made at the usual clinic visits. Data points were captured at baseline, interim (around 12 weeks from baseline) and final (around 24 weeks from baseline) visits. The time period of 4 weeks prior to the baseline visit was defined as the pre-study period. Information was gathered from the physician's clinical notes and the patient's recall and self-monitoring glucose diary at each visit and transferred to a standard case report form.

2.3. Primary and secondary endpoints

The primary safety endpoint was the number of serious adverse drug reactions (SADRs), including major hypoglycaemic events, recorded from baseline to the final visit. Secondary safety endpoints included the change in the number of minor, major, and nocturnal hypoglycaemic events between baseline and the final visit. If the study insulin was started 4 weeks before the baseline visit date, the number of hypoglycaemic events in the last 4 weeks before the final visit was compared to the number of events in the last 4 weeks before the baseline visit. Efficacy endpoints included the change in: (1) HbA_{1c}, FPG and PPPG at the interim visit and final visit compared to baseline; (2) Body weight, blood pressure and serum lipids at the final visit compared to baseline; (3) QoL at the final visit compared to baseline.

Major hypoglycaemia was defined as an event with severe central nervous system symptoms consistent with hypoglycaemia in which the affected individual was unable to treat himself/herself and had one of the following characteristics: (1) plasma glucose <56 mg/dL or (2) reversal of symptoms after either food intake or glucagon or intravenous glucose administration. All other hypoglycaemic events defined as above in which the affected individual was able to treat himself/herself were classified as minor. Hypoglycaemic events occurring after bedtime and before getting up in the morning were classified as nocturnal.

QoL was measured using the EQ-5D questionnaire and the EQ visual analogue scale (EQ-VAS) at baseline and after 24 weeks of therapy with insulin analogues. EQ-5D consists of five dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) having three severity levels each. EQ-VAS is a standard vertical 20-cm scale on which the best health state is marked as 100 and the worst state as 0.

Table 1 – Baseline characteristics of the Indonesian cohort

	Entire cohort (n = 1324)	Insulin naive (n = 888)	Prior insulin users (n = 436)
Gender (male/female), n (%)	650 (49.1)/674 (50.9)	449 (50.6)/439 (49.4)	201 (46.1)/235 (53.9)
Age, years	55.2 (9.9)	54.2 (10.0)	57.1 (9.5)
Duration of diabetes, years	6.8 (5.2)	5.9 (4.6)	8.5 (5.9)
Body weight, kg,	61.7 (11.2)	61.3 (11.0)	62.6 (11.4)
BMI, kg/m^2	24.1 (3.6)	23.9 (3.6)	24.4 (3.8)
HbA_{1c}, % / mmol/mol	9.9 (1.4 / 85 (15)	10.0 (1.3 / 86 (14)	9.4 (1.7 / 79 (19)

BMI, body mass index; HbA_{1c}, glycated haemoglobin A_{1c}.
Data are presented as mean (SD) unless specified otherwise.

Table 2 – Effectiveness of BIAsp 30 in controlling hyperglycaemia

		Full cohort (n = 1324)	Insulin naive (n = 888)	Prior insulin users (n = 436)
HbA_{1c}, % / mmol/mol	n	477	385	92
	Baseline	9.9 (1.4) / 85 (15)	10.0 (1.3) / 86 (14)	9.4 (1.7) / 79 (19)
	Week 24	7.3 (0.7) / 56 (8)	7.3 (0.7) / 56 (8)	7.3 (0.8) / 56 (9)
	Change	−2.6 (1.4) / −28 (15)	−2.8 (1.4) / −31 (15)	−2.1 (1.6) / −23 (17)
	p	<0.001	<0.001	–[a]
Proportion with HbA_{1c} <7%, %	Baseline	1.3	0.5	4.5
	Week 24	29.9	26.7	39.2
Fasting plasma glucose, mg/dL	n	1152	769	383
	Baseline	222.3 (74.2)	231.7 (71.7)	203.6 (75.6)
	Week 24	128.5 (31.1)	127.0 (26.3)	131.6 (38.8)
	Change	−93.8 (74.8)	−104.6 (72.9)	−72.0 (73.9)
	p	<0.001	<0.001	<0.001
Postprandial plasma glucose, mg/dL	n	1080	752	328
	Baseline	295.4 (80.0)	303.1 (77.9)	277.7 (82.2)
	Week 24	160.6 (38.9)	157.6 (35.3)	167.5 (45.5)
	Change	−134.8 (84.7)	−145.4 (82.6)	−110.3 (84.3)
	p	<0.001	<0.001	<0.001

Data are presented as mean (SD) unless specified otherwise.
[a] p-value not reported since n < 100.

2.4. Statistical methods

Statistical analyses were performed for the entire cohort and for the entire cohort classified as insulin-naive patients or prior insulin users. Descriptive statistics were used to summarise continuous variables and frequency tables (number and percentage) were used for discrete variables. All statistical tests were two-sided, with 5% significance level, unless otherwise stated. For the change in hypoglycaemia from baseline, the percentage of patients reporting at least one event was analysed using McNemar's test. The change from baseline in HbA_{1c}, FPG, PPPG, systolic blood pressure, body weight, blood lipids and QoL was analysed using a paired t-test with baseline and end-of-study values. Data analyses were performed by Novo Nordisk using SAS (Version 9.1.3).

3. Results

3.1. Demography of the Indonesian cohort

A total of 1324 patients from Indonesia with T2D, who were treated with BIAsp 30, were studied in this subgroup. Of these, 888 patients (67%) were insulin naive. The mean age in the entire cohort was 55.2±9.9 yrs with 49.1% males and 50.9% of female patients. Patients were enrolled in the study following a mean period of 6.8±5.2 yrs from diagnosis. The mean body mass index (BMI) was 24.1±3.6 kg/m^2. The entire cohort had a mean HbA_{1c} of 9.9±1.4% at baseline, depicting poor glycaemic control (Table 1).

Metformin was the most commonly prescribed OGLD pre-study (78.7% of patients) and at baseline (72.5% of patients). Sulfonylureas were the second most commonly prescribed OGLD, reported for 67.4% and 37.8% of patients, respectively, pre-study and at baseline. By the end of the study, 89.9% of patients were taking metformin, while 15.6% were taking sulfonylureas. Thiazolidinediones were prescribed to 5.9% of the patients pre-study, and to 0.3% at the end of the study.

3.2. Glycaemic control and BIAsp dosage

Glycaemic control (HbA_{1c}, FPG and PPPG) was poor at baseline. The mean HbA_{1c} was observed to be 9.9% (85 mmol/mol) in the entire cohort, 10.0% (86 mmol/mol) in the insulin-naive group, and 9.4% (79 mmol/mol) among prior insulin users (Table 1). The mean baseline FPG level was 222.3 mg/dL for the entire cohort, 231.7 mg/dL for insulin-naive patients and 203.6 mg/dL for prior insulin users (Table 2). At baseline, the average PPPG level was 295.4 mg/dL

Table 3 – Hypoglycaemia and effect on body weight

Hypoglycaemia		Full cohort (n = 1324)	Insulin naive (n = 888)	Prior insulin users (n = 436)
Hypoglycaemia, %				
Overall	Baseline	4.1	2.8	6.7
	Week 24	0.3	0.3	0.2
	p[a]	<0.0001	<0.0001	<0.0001
Minor	Baseline	3.9	2.6	6.7
	Week 24	0.3	0.3	0.2
	p[a]	<0.0001	<0.0001	<0.0001
Major	Baseline	0.3	0.5	0
	Week 24	0	0	0
	p[a]	0.0455	0.0455	–[b]
Nocturnal	Baseline	2.3	1.6	3.7
	Week 24	0.08	0.1	0
	p[a]	<0.0001	0.0008	<0.0001
Body weight, kg	n	1247	848	399
	Baseline	61.6 (10.9)	61.2 (10.9)	62.4 (11.0)
	Week 24	62.9 (9.7)	62.8 (9.5)	63.1 (10.0)
	Change	1.3 (3.8)	1.6 (3.8)	0.7 (3.8)
	p	<0.001	<0.001	<0.001

Data for body weight are presented as mean (SD).
[a] p-values are from McNemar's test on paired proportions of patients experiencing hypoglycaemia.
[b] No value available.

for the entire cohort and 303.1 mg/dL and 277.7 mg/dL for insulin-naive patients and prior insulin users, respectively.

After 24 weeks of treatment with BIAsp 30, there was a significant improvement in glycaemic control. In the entire cohort, the mean HbA_{1c} level was reduced significantly from baseline by 2.6% (–28 mmol/mol) to 7.3±0.7% (56±8 mmol/mol) at Week 24 ($p < 0.001$). Insulin-naive patients and prior insulin users also had improvements of –2.8% (–31 mmol/mol) and –2.1% (–23 mmol/mol), respectively. FPG decreased by 93.8±74.8 mg/dL ($p < 0.001$) for the entire cohort. PPPG also showed significant improvement with a change of –134.8±84.7 mg/dL after 24 weeks (160.6±38.9 mg/dL at Week 24, $p < 0.001$). Significant reductions in PPPG were also observed in the insulin-naive and prior insulin user groups (by –145.4±82.6 mg/dL and –110.3±84.3 mg/dL, respectively, $p < 0.001$, Table 2). Approximately 30% of patients in the entire cohort were able to achieve the target HbA_{1c} of <7.0% (<53 mmol/mol) at the end of the study.

The mean starting dose of BIAsp 30 was 0.38±0.16 U/kg in insulin-naive patients, which was titrated to 0.53±0.20 U/kg over 24 weeks. In prior insulin users, the baseline dose was 0.53±0.26 U/kg, which increased to 0.59±0.24 U/kg after 24 weeks.

3.3. SADRs and hypoglycaemia

No SADRs were reported during the study.

At baseline, the overall hypoglycaemic event rate was 1.02 events per patient-year for the entire cohort. Out of 104 hypoglycaemic events at baseline, 94 were minor events and 10 were major events. At baseline, 2.8% of insulin-naive patients and 6.7% of the prior insulin users experienced at least one hypoglycaemic event. A total of 33 nocturnal hypoglycaemic events were reported in the entire cohort at baseline (2.3% of patients).

After 24 weeks of BIAsp 30 treatment, overall hypoglycaemia was reduced to 0.05 events per patient-year (0.3% of patients at Week 24 vs. 4.1% of patients at baseline, $p < 0.0001$). No episodes of major hypoglycaemia occurred during 24 weeks of treatment. Only 2 episodes (0.08%) of nocturnal hypoglycaemia were reported, both of which occurred in insulin-naive patients. The reduction in overall, major, minor and nocturnal hypoglycaemia was significant in the entire cohort ($p < 0.05$) (Table 3).

3.4. Body weight, blood lipids and blood pressure control

From baseline to Week 24, the mean weight gain in the entire cohort was 1.3 kg (from 61.6±10.9 to 62.9±9.7 kg, $p < 0.001$). Between groups, lower weight gain was noted in the prior insulin user group (0.7 kg) compared to the insulin-naive group (1.6 kg).

Total cholesterol levels decreased from 5.8±1.4 at baseline to 4.9±0.9 mmol/L after 24 weeks ($p < 0.001$). LDL cholesterol levels decreased significantly in both the prior insulin users (–0.6 mmol/L, $p < 0.001$) and the insulin-naive group (–0.5 mmol/L, $p < 0.001$).

Systolic blood pressure in the entire cohort decreased from 133.3±16.1 to 124.7±13.6 (–8.6 mmHg, $p < 0.001$).

3.5. Health-related quality of life (QoL)

EQ-VAS scores increased significantly by 8.8 points i.e., from 71.1 points at baseline to 79.9 points after 24 weeks ($p < 0.001$) in this Indonesian subgroup.

4. Discussion

This subgroup analysis was performed to evaluate the safety and efficacy of BIAsp 30 in Indonesian patients with T2D.

The improved glycaemic control seen in this subgroup was achieved with a reduced risk of both major and minor hypoglycaemic events in the local clinical setting.

Glycaemic control was poor in this Indonesian subgroup at baseline as was also reported in the 2008 DiabCare study in Indonesia [11]. At the end of the study, the mean HbA_{1c} was reduced by 2.6% (28 mmol/mol) from baseline, consistent with previous published reports of BIAsp 30 efficacy. The EuroMix trial reported a reduction in HbA_{1c} of 1.6% (–17 mmol/mol) after 26 weeks in insulin-naive patients starting BIAsp 30 therapy in combination with metformin [12]. In the observational study, IMPROVE, conducted in over 52,000 patients globally, the mean HbA_{1c} was reduced by –2.3% (–25 mmol/mol) after 26 weeks of BIAsp 30 therapy [13]. The 1-2-3 study reported HbA_{1c} reductions of 1.4% (–15 mmol/mol), 1.9% (–21 mmol/mol) and 1.8% (–20 mmol/mol) with BIAsp 30 dosed *qd*, *bid* and *tid*, respectively [9].

At baseline, only 1.3% of Indonesian patients had an HbA_{1c} level <7.0% (<53 mmol/mol), which increased to 30% after 24 weeks of BIAsp 30 therapy. In a 26-week trial by Bebakar et al., 46% of patients attained HbA_{1c} levels of <7.0% (<53 mmol/mol) on BIAsp 30 (0.2 U/kg/day) *qd* before dinner in combination with OGLDs [14]. In the IMPROVE study, approximately 40% of patients switching to BIAsp 30 from pre-study basal insulin reached HbA_{1c} levels <7.0% (<53 mmol/mol). In the 1-2-3 study, 41%, 70% and 77% of patients attained HbA_{1c} <7.0% (<53 mmol/mol) on *qd*, *bid* and *tid* regimens of BIAsp 30, respectively [9]. The difference in baseline HbA_{1c} levels at the time of initiation of BIAsp 30 (9.9% [85 mmol/mol] in this Indonesian sub-analysis vs. 8.6% [70 mmol/mol] in the 1-2-3 study) may be the reason for this variation between the current study and the 1-2-3 study.

In the Chinese cohort of the IMPROVE study (representing a large proportion of Asian patients), patients switched to BIAsp 30 from human premix insulin experienced improved glycaemic control [15]. Significant reductions in both FPG (–93.8 mg/dL) and PPPG (–134.8 mg/dL) were also observed in the Indonesian cohort after 24 weeks of BIAsp 30 therapy ($p < 0.001$) [15]. These reductions were even greater than the reductions observed for the complete BIAsp 30 cohort of the A_1chieve study [10], perhaps due to the higher baseline values of both FPG and PPPG in the Indonesian cohort.

The improvements in glycaemic control should not be linked to a risk of increased hypoglycaemia. BIAsp 30 therapy is associated with a low incidence of major hypoglycaemia in observational studies, in line with the results from RCTs [13,16]. In the PRESENT study, patients switching to BIAsp 30 therapy (with or without OGLDs) experienced significantly lower rates of minor hypoglycaemia by the end of the study (from approximately 9.0 to 2.3 events per patient-year) [16]. Low rates of hypoglycaemia with BIAsp 30 therapy were also reported in the IMPROVE study [13], and also in patients from the Western Pacific [14] and Japan [17]. The proportion of patients that reported minor hypoglycaemia and nocturnal hypoglycaemia decreased significantly at the end of the study compared to the baseline proportions in this Indonesian cohort. The total number of hypoglycaemic episodes decreased from 104 to 5 and the number of major episodes from 10 to 0 in 24 weeks of treatment. These results from this non-interventional study could be clinically more meaningful than those observed in RCTs, as they depict the real-world scenario, although limited by bias and various confounders.

One of the major barriers to beginning insulin in T2D patients is the ensuing weight gain. In the IMPROVE [13] and PRESENT [16] studies, there were small reductions in mean body weight after 26 weeks of therapy with BIAsp 30 (by –0.1 kg and –0.32 kg, respectively, both $p < 0.001$). It is possible that dietary advice from the physicians may have influenced the patients' nutritional intake and thereby compensated any potential weight gain. However, this Indonesian cohort observed a small weight gain (1.3 kg), which may be attributed to the effect of insulin.

Blood pressure and lipid profile are also important cardiovascular risk factors in patients with T2D. The results from this analysis are encouraging as they show significant improvements in both systolic blood pressure and lipid levels.

In the 28-week, treat-to-target INITIATE study, the mean BIAsp 30 dose was titrated up to 0.82±0.40 U/kg by the end of the study, associated with a reduction in mean HbA_{1c} of 2.8% [18]. In this Indonesian cohort of the A_1chieve study, the initiation dose of BIAsp 30 was 0.43 U/kg, titrated to 0.55 U/kg over 24 weeks. However, in the 1-2-3 study, the mean insulin dose was higher in patients on *qd*, *bid* and *tid* BIAsp 30 dosing strategies than in this Indonesian sub-analysis. This may be attributable to the difference in insulin sensitivity of the patients included, as the average BMI was higher in the 1-2-3 study (34 kg/m^2) than in the current study (24.1 kg/m^2).

The significant increase noted in the EQ-VAS score after 24 weeks reflected the heightened patient satisfaction with BIAsp 30 therapy. Our observations also echo the findings of the IMPROVE study that reported improved DiabMedSat scores in T2D patients following the use of BIAsp 30 [19].

Although this subgroup analysis has provided novel insights about the T2D population status and the safety and efficacy of BIAsp 30 therapy in Indonesia, there are some limitations of this study. Being an observational study, no standardized treatment protocol was used and concomitant medications were not controlled. The study was not randomized and lacked a control arm. Furthermore, most safety parameters were based on patient recall or diaries.

The current analysis showed poor glycaemic control at baseline in this Indonesian subgroup. The results from this sub-analysis showed that BIAsp 30 therapy facilitated good glycaemic control without any concomitant risk of hypoglycaemia in insulin-naive patients as well as prior insulin users. Furthermore, BIAsp 30 may also help in improving other metabolic parameters and thereby provide patients with better quality of life. Therefore, BIAsp 30 could be considered a safe and effective option for initiating as well as intensifying insulin therapy for patients with T2D.

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Conflict of interest statement

Dr. Pradana Soewondo has authored an article sponsored by Novo Nordisk and sanofi aventis, and has served as a consultant (Advisory Board) for Novo Nordisk, sanofi aventis, and Novartis. Dr. Pradana Soewondo has also received research grants from World Diabetes Foundation and grants for lectures from Novo Nordisk, sanofi aventis, Novartis and MSD. Dr Yuanita Asri Langi received research grants from Novo Nordisk and received honorarium for lectures from Novo Nordisk, Merck, Sanofi, Pfizer, Astra Zeneca, and Boehringer Ingelheim. Dr Ida Ayu Kshanti has received honorarium for lectures from Novo Nordisk, Eli Lilly, Aventis, Takeda, MSD, Dexa Medica, Boehringer Ingelheim, Bayer, Merck and BD. No other author has any conflict of interest to report. 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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