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Safety and effectiveness of biphasic insulin aspart 30 in type 2 diabetes: Results from the ASEAN cohort of the A_1chieve study

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ABSTRACT

Aim: To determine the safety and effectiveness of biphasic insulin aspart 30 (BIAsp 30) in the ASEAN cohort of the A_1chieve study.

Methods: Type 2 diabetes patients from Indonesia, Malaysia, Philippines and Singapore prescribed BIAsp 30 therapy were included. The primary outcome was evaluation of serious adverse drug reactions including major hypoglycaemia over 24 weeks. Secondary outcomes were changes in hypoglycaemic events, serious adverse events (SAEs) and effectiveness parameters.

Results: This sub-analysis included 2798 patients (insulin-naive, 1903; insulin-experienced, 895) with mean age ± SD, 55.3±10.8 years, BMI, 24.9±4.6 kg/m^2 and diabetes duration, 7.5±5.9 years. Baseline HbA_{1c} in the entire cohort was poor (9.9%, 85 mmol/mol). A total of 15 SAEs were reported in 7 insulin-experienced patients (1 moderate event was related to BIAsp 30). Overall hypoglycaemia at Week 24 was 0.88 events/patient-year compared to 1.71 events/patient-year reported at baseline (change in proportion of patients affected, $p < 0.0001$). No major hypoglycaemia was reported at Week 24. BIAsp 30 significantly improved glucose control (HbA_{1c}, fasting plasma glucose and postprandial plasma glucose, $p < 0.001$) at Week 24. The proportion of patients achieving HbA_{1c} <7.0% at Week 24 was 35.3% compared to 3.5% at baseline. The lipid profile and systolic blood pressure also improved significantly ($p < 0.001$). Quality of life was positively impacted (mean change in visual analogue scores from EQ-5D = 10.6±13.8 points, $p < 0.001$).

Conclusion: BIAsp 30 was well-tolerated and improved glucose control while decreasing the risk of hypoglycaemia.

1. Introduction

As reported in many regions worldwide, the ASEAN nations are also facing the impact of a confounding increase in the prevalence of diabetes. In 2012, Indonesia, Philippines and Malaysia ranked among the top 10 countries by diabetes cases in the Western Pacific region with reported prevalence of 4.8%, 8.2% and 11.7%, respectively [1]. Currently, the prevalence of diabetes in Singapore is 12.5% [1]. The 2030

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projections of diabetes prevalence in Indonesia (21.3 million people) and Philippines (7.8 million people) also qualify these countries to rank among the top 10 countries for diabetes prevalence worldwide [2]. Socio-economic transition and ageing populations could be the primary factors for the rise of this epidemic.

Type 2 diabetes (T2D) is a progressive debilitating disorder that ultimately mandates the use of insulin in all patients [3]. The United Kingdom Prospective Diabetes Study estimated that >60% of T2D patients would require insulin within 5 years of diagnosis [4]. Timely initiation or active intensification of insulin therapy is highly recommended to maintain adequate glycaemic control [5]. However, despite worsening glycaemic control, compliance to insulin therapy is often challenging due to prominent concerns of hypoglycaemia, weight gain, pain due to injections and the negative impact on quality of life (QoL) [3]. The variability in the pharmacological action of human insulin preparations resulting in unpredictable glucose control has led to the development of insulin analogues such as biphasic insulin aspart 30 (BIAsp 30) [6].

BIAsp 30 is a premix insulin analogue formulation containing both soluble and intermediate acting insulin (30% soluble insulin aspart [IAsp] and 70% IAsp protamine crystals) that can provide prandial insulin peaks to control blood glucose levels following a meal and ensure basal insulin levels between meals [7,8]. The clinical benefits of BIAsp 30 have been well established in randomized controlled trials and multinational observational studies, PRESENT and IMPROVE [9–11].

It has been noted that diabetes treatment strategies in most of the developing ASEAN nations are sub-optimal and non-uniform [12]. Furthermore, the clinical practice guidelines for these countries are based on international evidence-based guidelines due to a scarcity in the number of regional studies. The A_1chieve [13] multinational, prospective, non-interventional study was conducted to determine the real-time efficacy and safety of modern insulin analogues under routine clinical care in less well-resourced countries. A_1chieve study results are available online under www.A1chieve.com. This sub-analysis was carried out with an aim to elucidate the current status of T2D management and to determine the effectiveness and safety of BIAsp 30 in an ASEAN cohort that comprised T2D patients from Indonesia, Malaysia, Philippines and Singapore.

2. Methods

2.1. Study design

A_1chieve [13] was an international, prospective, non-interventional study designed to evaluate the safety and efficacy of basal insulin detemir (Levemir®, Novo Nordisk), bolus insulin aspart (NovoRapid®, Novo Nordisk) and biphasic insulin aspart (NovoMix®, Novo Nordisk) alone or in combination in less well-resourced countries. This sub-analysis evaluates the clinical use of BIAsp 30 in T2D patients from the ASEAN region that comprises Indonesia, Malaysia, Philippines and Singapore. Patients were recruited between October 2009 and December 2010 at 65, 23, 255 and 16 centers in Indonesia, Malaysia, Philippines and Singapore, respectively. The study drug was commercially available and used in accordance with the local regulatory guidelines. The administration of BIAsp 30 and subsequent dosing changes were mutually agreed upon by the patients and their consulting physicians. The use of concurrent OGLDs was permitted throughout the study at the discretion of the physician. As the study design was observational, there were no defined study procedures and all assessments were made by the treating physician during routine visits. Data for analysis from the physicians' clinical notes and patients' recall and self-monitoring diary/meter was collected at baseline and final visit (around 24 weeks from baseline).

2.2. Patients

Any patient prescribed BIAsp 30 at the discretion of the physician was included in the sub-analysis. Patients who had received Novo Nordisk insulin analogues (alone or in combination) as the study medication for more than 4 weeks prior to the study were not eligible. Women who were pregnant, breast-feeding or had the intention of becoming pregnant were excluded. All patients signed informed consent to participate in this study and the study was approved by the local ethics committees of all countries in the cohort.

2.3. Outcome measures and assessments

The primary objective was to evaluate the clinical safety of BIAsp 30 based on the number of serious adverse drug reactions (SADRs) including major hypoglycaemia from baseline to Week 24. Secondary safety assessments included changes in occurrence and frequency of hypoglycaemic events, and serious adverse events (SAEs). Effectiveness was assessed using changes in HbA_{1c} levels, fasting plasma glucose (FPG) and post-breakfast postprandial plasma glucose (PPPG), lipid profile and systolic blood pressure from baseline to Week 24. Laboratory parameters were measured in local laboratories and were subject to local standardization and quality control procedures. The health related-quality of life (QoL) was determined using a validated questionnaire, EQ-5D that analyzes changes in mobility, self-care, usual activities, pain/discomfort and anxiety/depression from baseline to Week 24. Subsequently, the current QoL was measured using a standard vertical 20 cm visual analogue scale (VAS, 0–100 [worst imaginable health to best imaginable health]).

2.4. Statistical analysis

Statistical analyses were performed for the entire cohort and by pre-study therapy type i.e., insulin-naive and insulin experienced patients. Baseline characteristics including concomitant medical conditions, choice of insulin and time of initiation that could have influenced the study results were not completely elucidated. Hence, comparisons between insulin-naive and insulin-experienced patients were descriptive.

Table 1 – Demographic and baseline characteristics for all patients receiving biphasic insulin aspart 30 by entire cohort and by pre-study therapy

Parameter	Entire cohort (n = 2798, 100%)	Insulin-naive (n = 1903, 68%)	Prior insulin users (n = 895, 32%)
Gender (male/female), %	47.5/52.5	48.4/51.6	45.5/54.5
Age, years	55.3 (10.8)	54.5 (10.6)	56.8 (10.9)
Body weight, kg	64.1 (13.5)	63.5 (13.5)	65.2 (13.4)
BMI, kg/m^2	24.9 (4.6)	24.7 (4.6)	25.4 (4.6)
Diabetes duration, years	7.5 (5.9)	6.3 (5.0)	9.8 (7.0)
Duration on insulin, years	0.8 (1.9)	0.0 (0.3)[a]	2.3 (2.6)
HbA_{1c}, mmol/mol	85 (21)	86 (20)	81 (21)
HbA_{1c}, %	9.9 (1.9)	10.0 (1.8)	9.6 (1.9)
Duration on OGLDs, years	6.5 (5.6)	5.5 (4.7)	8.4 (6.7)
Prior OGLDs, n (%)			
Metformin	1957 (80.8)	1408 (81.2)	549 (79.6)
Sulfonylureas	1509 (62.3)	1246 (71.9)	263 (38.1)
Thiazolidinediones	286 (11.8)	241 (13.9)	45 (6.5)
1 OGLD	871 (35.9)	443 (25.6)	428 (62.0)
2 OGLDs	1030 (42.5)	828 (47.8)	202 (29.3)
>2 OGLDs	522 (21.5)	462 (26.7)	60 (8.7)

Data are presented as mean (SD) unless specified otherwise.
[a] Some patients were on insulin for a short period in the past, but were not on insulin when they were enrolled into the study.

Continuous and discrete variables were summarized using descriptive statistics and frequency tables (n [%]), respectively. Unless otherwise stated, all statistical analyses were conducted using two-sided tests at a pre-specified 5% significance level. The paired t-test was used to analyze the changes in HbA_{1c}, FPG, PPPG, SBP, blood lipids, body weight, and QoL from baseline to Week 24. The McNemar's test was used to analyze changes from baseline to end of study in the proportion of patients reporting at least one hypoglycaemic event. Detailed statistical analyses of the A_1chieve study are discussed elsewhere [Home 2011]. All data were analyzed by Novo Nordisk using SAS (Version 9.1.3).

3. Results

3.1. Patients

A total of 2798 T2D patients enrolled from the ASEAN region started BIAsp 30 therapy. This cohort constituted 1903 insulin-naive patients (OGLD alone, 1733; no therapy, 170) and 895 insulin-experienced patients. Demographic and baseline characteristics of patients by entire cohort and pre-study therapy type are reported in Table 1.

At baseline, HbA_{1c} <7.0% (<53 mmol/mol) was reported in 21 (4.3%) insulin-experienced and 35 (3.1%) insulin-naive patients. The average baseline HbA_{1c} level in insulin-naive patients was 10.0±1.8% (86±20 mmol/mol), while that in insulin-experienced patients was 9.6±1.9% (81±21 mmol/mol). The majority of patients (95.0%) were prescribed BIAsp 30 by their physicians to improve glycaemic control. The other predominant physicians' reasons to prescribe BIAsp 30 were to reduce plasma glucose variability (41.3% patients) and to try new insulin (31.6% patients).

3.2. Insulin dose and dosing frequency

The insulin doses and frequency of administration throughout the study are reported in Table 2. The mean pre-study insulin dose in insulin-experienced patients was 0.56±0.33 U/kg and the mean BIAsp 30 dose at baseline was 0.60±0.28 U/kg titrated up to 0.68±0.29 U/kg at Week 24. Insulin-naive patients initiated an average BIAsp 30 dose of 0.45±0.21 U/kg that was titrated up to 0.58±0.23 U/kg by Week 24.

3.3. SAEs and SADRs

A total of 15 SAEs were reported in 7 insulin-experienced patients. The relation to the study drug was considered unlikely for 14 events and 1 moderate SADR probably related to the study drug was reported in 1 insulin-experienced patient. There were 4 deaths related to 11 SAEs. No SAEs or SADRs were reported in the insulin-naive group.

3.4. Hypoglycaemia

The incidence of overall hypoglycaemia at Week 24 was 0.88 events/patient-year compared to the reported incidence of 1.71 events/patient-year at baseline in the entire cohort. Correspondingly, the proportion of patients with at least one event decreased significantly from 5.4% to 2.5% ($p < 0.0001$). As expected, there appeared to be a slight increase in the incidence of overall hypoglycaemia from 0.66 to 0.72 events/patient year (change in proportion of patients affected, $p = 0.0103$) in insulin-naive patients from baseline to Week 24. Overall hypoglycaemia in insulin-experienced patients appeared to be lower at Week 24 compared to baseline (1.24 events/patient-year at Week 24 vs. 3.95 events/patient-year at baseline). The corresponding decrease in the

Table 2 – Insulin dose and frequency by pre-study regimen – ASEAN patients receiving biphasic human insulin aspart

		Entire cohort	Insulin-naive	Insulin-experienced
Insulin dose, U/day	n	2798	1903	895
	Pre-study[a]	36.4 (22.0)	–	36.4 (22.0)
	Baseline	31.6 (16.0)	28.1 (12.8)	39.0 (19.3)
	Week 24	39.0 (16.8)	36.6 (14.2)	44.2 (20.4)
Insulin dose, U/kg	n	2683	1811	872
	Pre-study[a]	0.56 (0.33)	–	0.56 (0.33)
	Baseline	0.50 (0.24)	0.45 (0.21)	0.60 (0.28)
	Week 24	0.61 (0.26)	0.58 (0.23)	0.68 (0.29)
Dose frequency, n (%)	Pre-study (n)	895	–	895
	Once daily	220 (24.6)		220 (24.6)
	Twice daily	588 (65.7)		588 (65.7)
	Thrice daily	45 (5.0)		45 (5.0)
	>Thrice daily	42 (4.7)		42 (4.7)
	Baseline (n)	2798	1903	895
	Once daily	269 (9.6)	202 (10.6)	67 (7.5)
	Twice daily	2384 (85.2)	1617 (85.0)	767 (85.7)
	Thrice daily	145 (5.2)	84 (4.4)	61 (6.8)
	>Thrice daily	0 (0)	0 (0)	0 (0)
	Week 24 (n)	2519	1722	797
	Once daily	207 (8.2)	152 (8.8)	55 (6.9)
	Twice daily	2110 (83.8)	1447 (84.0)	663 (83.2)
	Thrice daily	192 (7.6)	119 (6.9)	73 (9.2)
	>Thrice daily	10 (0.4)	4 (0.2)	6 (0.8)

Data are presented as mean (SD) unless specified otherwise.
[a] IU/day or IU/kg pre-study.

Table 3 – Baseline and 24-week hypoglycaemia data for patients receiving biphasic insulin aspart 30 by entire cohort and by pre-study therapy

Hypoglycaemia		Entire cohort		Insulin-naive		Insulin-experienced	
		Incidence	%[a]	Incidence	%[a]	Incidence	%[a]
Overall	Baseline	1.71	5.4	0.66	2.6	3.95	11.3
	Week 24	0.88	2.5	0.72	1.5	1.24	4.8
	p	NA	<0.0001	NA	0.0103	NA	<0.0001
Minor	Baseline	1.57	5.1	0.57	2.4	3.67	10.9
	Week 24	0.88	2.5	0.72	1.5	1.24	4.8
	p	NA	<0.0001	NA	0.0244	NA	<0.0001
Nocturnal	Baseline	0.57	2.5	0.20	1.1	1.34	5.4
	Week 24	0.22	1.0	0.20	0.7	0.28	1.5
	p	NA	<0.0001	NA	0.1172	NA	<0.0001
Major	Baseline	0.14	0.5	0.08	0.3	0.28	1.0
	Week 24	0.0	0.0	0.0	0.0	0.0	0.0
	p	NA	0.0003	NA	0.0143	NA	0.0082

p-values are from McNemar test on paired proportions of patients experiencing hypoglycaemia.
[a] % of patients experiencing at least one hypoglycaemic event.

proportion of patients affected was significant ($p < 0.0001$). At Week 24, no major hypoglycaemia was reported in the entire cohort (Table 3). In the insulin-naive group, the rate of nocturnal hypoglycaemia did not appear to differ from baseline to Week 24, while the rate in insulin-experienced patients was 0.28 events/patient-year at Week 24 compared to the 1.34 events/patient-year reported at baseline (change in the proportion of patients affected, $p < 0.0001$). The proportion of insulin-experienced patients experiencing minor hypoglycaemia decreased from 10.9 to 4.8% ($p < 0.0001$) while the proportion of insulin-naive patients reporting minor hypoglycaemia decreased from 2.4 to 1.5% ($p = 0.0244$). (Table 3).

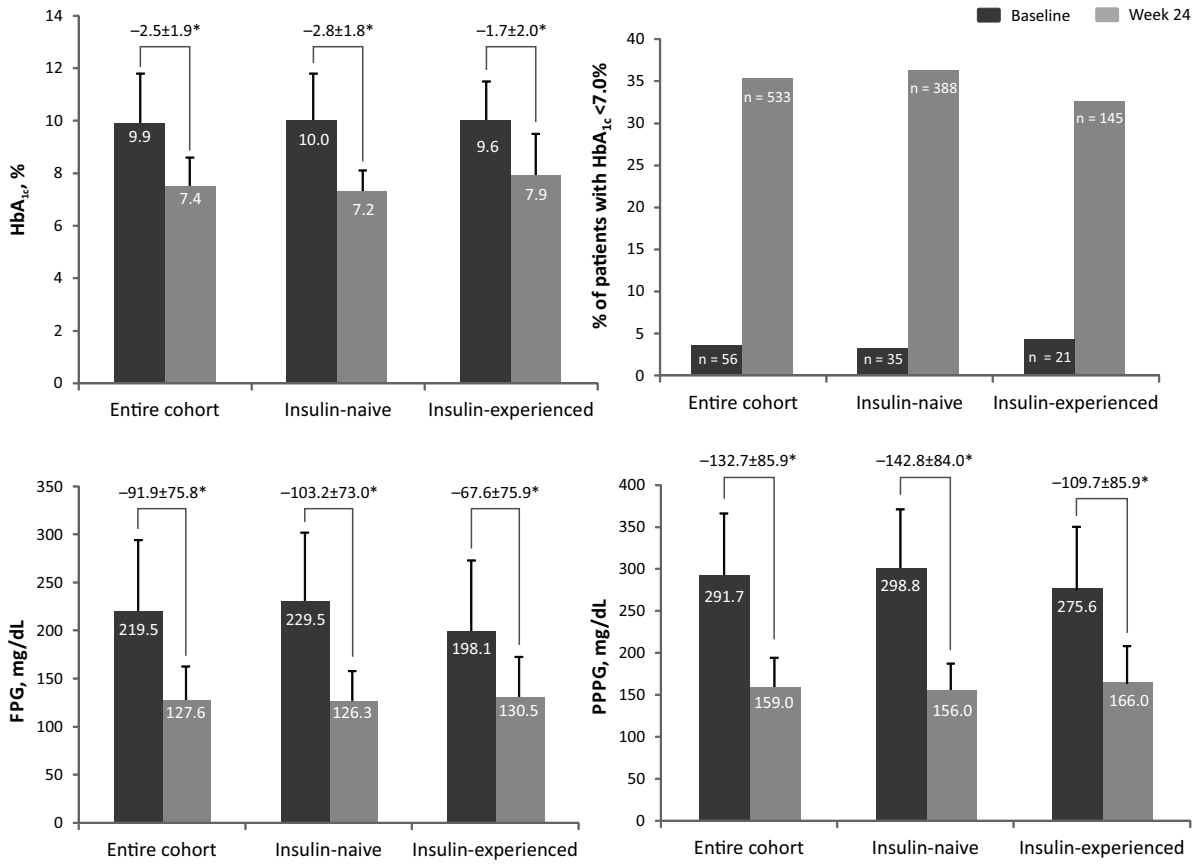

Fig. 1 – Change in glucose control parameters in patients receiving biphasic insulin aspart 30 from baseline to Week 24. *$p < 0.001$.

3.5. *Effectiveness*

Following 24 weeks of BIAsp 30 therapy, significant improvements in HbA_{1c} (–2.5±1.9%, –27±21 mmol/mol, $p < 0.001$), FPG (–91.9±75.8 mg/dL, $p < 0.001$) and PPPG (–132.7±85.9 mg/dL, $p < 0.001$) were observed in the entire cohort (Figure 1). The changes in HbA_{1c}, FPG and PPPG in insulin-experienced patients appeared to be lower than those reported in insulin-naive patients at Week 24 (Figure 1). The proportion of patients achieving HbA_{1c} target levels <7.0% (<53 mmol/mol) was 3.5% (n = 56) at baseline compared to 35.3% (n = 533) at Week 24 in the entire cohort. The insulin-naive group reported an increase from 3.1% to 36.3% and the insulin-experienced group showed an increase from 4.3% to 32.7% in the proportion of patients achieving HbA_{1c} <7.0% (<53 mmol/mol) from baseline to Week 24 (Figure 1).

3.6. *Body weight, blood lipids and systolic blood pressure*

In the entire cohort, the mean change in body weight from baseline to Week 24 was +0.9 kg ($p < 0.001$, Table 4). Total cholesterol levels decreased significantly in the entire cohort from 5.6±1.5 mmol/L at baseline to 4.8±1.0 mmol/L at Week 24 ($p < 0.001$). From baseline to Week 24, significant reductions in low-density lipoprotein cholesterol (3.6±1.2 mmol/L vs. 3.0±0.9 mmol/L, $p < 0.001$) and triglyceride (2.0±1.0 mmol/L vs. 1.6±0.7 mmol/L, $p < 0.001$) levels were observed while high-density lipoprotein cholesterol increased from 1.3±0.4 mmol/L to 1.3±0.3 mmol/L ($p < 0.001$). A significant decrease of 7.1±18.4 mmHg in SBP was reported from baseline (131.8±17.7 mmHg) to Week 24 (124.6±13.9 mmHg). These changes were observed irrespective of the pre-study therapy type i.e., insulin-naive and insulin-experienced patients.

3.7. *Quality of life*

The EQ-5D VAS scores improved significantly from 69.9±14.3 points at baseline to 80.5±10.6 points at Week 24 ($p < 0.001$). In insulin naive patients, the QoL improved by 12.1±13.4 points while insulin-experienced patients reported an improvement of 7.3±14.2 points (both, $p < 0.001$).

4. Discussion

This sub-analysis demonstrated the efficacy and safety of BIAsp 30 in an ASEAN cohort presenting with T2D. As demonstrated in the international A_1chieve data, BIAsp 30 was well-tolerated and resulted in significant improvements in glucose control irrespective of the pre-study therapy type. The proportion of patients reporting overall hypoglycaemia decreased significantly and no major hypoglycaemia was reported at the end of 24 weeks.

Table 4 – Baseline and 24-week data for body weight, blood lipids and systolic blood pressure

		Entire cohort	Insulin-naive	Insulin-experienced
Body weight, kg	n	2326	1588	738
	Baseline	63.4 (12.6)	63.0 (12.6)	64.4 (12.6)
	Week 24	64.3 (11.9)	64.0 (11.6)	65.0 (12.3)
	Change	0.9 (4.1)	1.0 (4.1)	0.7 (4.0)
	p	<0.001	<0.001	<0.001
Total cholesterol, mmol/L	n	825	547	278
	Baseline	5.6 (1.5)	5.8 (1.3)	5.4 (1.7)
	Week 24	4.8 (1.0)	4.8 (1.0)	4.9 (1.1)
	Change	−0.8 (1.5)	−1.0 (1.4)	−0.5 (1.5)
	p	<0.001	<0.001	<0.001
HDL cholesterol, mmol/L	n	599	408	191
	Baseline	1.3 (0.4)	1.3 (0.5)	1.2 (0.4)
	Week 24	1.3 (0.3)	1.3 (0.3)	1.3 (0.3)
	Change	0.1 (0.4)	0.1 (0.4)	0.1 (0.4)
	p	<0.001	<0.001	<0.001
LDL cholesterol, mmol/L	n	611	422	189
	Baseline	3.6 (1.2)	3.7 (1.1)	3.2 (1.3)
	Week 24	3.0 (0.9)	3.1 (0.8)	2.9 (0.9)
	Change	−0.5 (1.2)	−0.6 (1.2)	−0.3 (1.3)
	p	<0.001	<0.001	0.006
Triglycerides, mmol/L	n	688	464	224
	Baseline	2.0 (1.0)	2.1 (1.0)	1.9 (1.1)
	Week 24	1.6 (0.7)	1.6 (0.6)	1.7 (0.9)
	Change	−0.4 (0.9)	−0.5 (0.9)	−0.2 (1.0)
	p	<0.001	<0.001	0.011
SBP, mmHg	n	2258	1531	727
	Baseline	131.8 (17.7)	131.4 (18.0)	132.6 (17.0)
	Week 24	124.6 (13.9)	123.7 (13.0)	126.5 (15.4)
	Change	−7.1 (18.4)	−7.6 (18.2)	−6.1 (18.7)
	p	<0.001	<0.001	<0.001

HDLC, high density lipoprotein cholesterol; LDLC, low-density lipoprotein cholesterol; SBP, systolic blood pressure. Data are presented as mean (SD).

Poor baseline glucose control was evident in this cohort akin to reports from several large observational studies [10,11,13]. The average HbA_{1c} level in insulin-naive patients was 10% (86 mmol/mol) while insulin-experienced patients reported an average HbA_{1c} level of 9.6% (81 mmol/mol). Despite the average diabetes duration of 7.5 years, 68% of the patients in this cohort were insulin-naive at baseline. Furthermore, the insulin-experienced patients had received insulin for an average of only 2.3 years although the mean diabetes duration was 9.8 years. Previously, an epidemiological study also reported that although population median HbA_{1c} was 7.8–8.1% (62–65 mmol/mol), patients reported HbA_{1c} levels of 9% (75 mmol/mol) before treatment intensification to combination oral glucose-lowering drugs (OGLDs) and 10% (86 mmol/mol) prior to initiation of insulin [14]. Evidence-based guidelines from the American Diabetes Association recommend a treatment goal of HbA_{1c} <7.0% in order to prevent the onset and retard the progression of long-term complications in T2D. Also, a 25% increase in the risk of diabetes-related mortality is estimated for each 1% increase in HbA_{1c} [15]. However, only 3.5% patients reported HbA_{1c} <7.0% pre-study. This baseline data reflects the status of T2D management in the ASEAN region and is indicative of an urgent need to revisit the routine clinical practice approach to therapeutic strategies for T2D.

Following 24 weeks of BIAsp 30 therapy, patients included in this sub-analysis exhibited significant improvements in HbA_{1c}, FPG and post-breakfast PPPG irrespective of prior insulin use. The proportion of patients achieving HbA_{1c} target levels <7.0% increased from 3.5% to 35.3%. Furthermore, these improvements were associated with a significant decrease in the proportion of patients experiencing overall hypoglycaemia. No major hypoglycaemia was reported at Week 24 in the entire cohort. The increase in body weight, although statistically significant was not deemed clinically relevant. The lipid profile and SBP improved significantly in all patients. These results are similar to the international A_1chieve data [13] as well as reports from the IMPROVE and PRESENT studies on BIAsp 30 [10,11].

A negative correlation between T2D progression and health-related QoL has been long-established. Psychosocial aspects are primary determinants that govern self-care behaviours, ultimately impacting glycaemic control [16]. In this ASEAN cohort, a significant improvement in all 5 dimensions of the EQ-5D was reported at the end of 24 weeks indicating a positive impact of BIAsp 30 therapy on QoL.

The lack of a control arm, retrospective data collection methods and recall bias for hypoglycaemic episodes are obvious limitations of this observational study design compared with randomized trials. However, all measurements

were in accordance with local regulations and by methods that are NGSP-certified. Early and rapid responses are often desired among T2D patients; hence, the 24-week duration, although short, could be reasonable to assess efficacy and safety of drugs that are already FDA or EMA approved. In conclusion, this sub-analysis provides beneficial insights to a heterogeneous group of T2D patients from Indonesia, Malaysia, Philippines and Singapore in their respective local clinical settings. The 24-week data demonstrates that initiating the premixed insulin analogue, BIAsp 30, increases the probability of achieving and maintaining glycaemic targets while reducing the risk of complications generally associated with insulin use.

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Conflict of interest statement

Mary Anne Lim-Abrahan received honorarium for conduct of research from Novo Nordisk, and has served as a consultant (Advisory Board) for sanofi aventis, Merck, and Novo Nordisk. Dr. Anand B. Jain is employed by Novo Nordisk Pharma Malaysia. Wan Mohamad Wan Bebakar received honorarium for conduct of research from Novo Nordisk. Darren Seah received honorarium for conduct of research from Novo Nordisk. 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. 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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