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# Real-life clinical experience with insulin analogues in the management of type 2 diabetes in Bangladesh and ASEAN countries Indonesia, Malaysia, Philippines, Singapore

*Guest Editor:*

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# Diabetes Research and Clinical Practice

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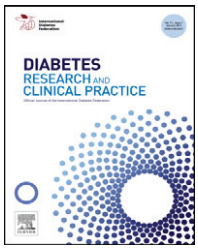

Editorial

# Observational research: an integral part of enhancing diabetes management in south-east Asia

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## 1. The diabetes burden

The prevailing burden of the diabetes epidemic and its associated complications poses a substantial threat to socio-economic development worldwide. This crisis is magnified in developing and recently-developed nations including countries in south-east Asia. Estimates from the International Diabetes Federation suggest an inverse relationship between the economic status of a country and the rise of diabetes; with lower-income countries facing the greatest increase in the prevalence of diabetes [1]. In recent years, the Association of Southeast Asian Nations (ASEAN) has faced an exponential increase in the prevalence of diabetes and associated mortality rate. The current diagnosed and undiagnosed diabetes prevalence in four countries from the ASEAN region and corresponding diabetes-related mortality is presented in Figure 1 [2]. Indonesia with a reported diabetes prevalence of 7.3% in 2011 and a projected prevalence of 11.8% by 2030 ranks among the most affected 10 countries worldwide for adults of 20 to 79 years of age [1]. Although this rise is frequently attributed to population growth, ageing populations, excess calorie intake, and physical inactivity, better disease management contributing to better life expectancy with diabetes will also play a part. Nevertheless there is great scope for further improving this to contain the late adverse outcomes which cause so much of the ill health due to diabetes, and a majority of health-care costs.

A shortcoming of ASEAN clinical practice guidelines is that they are often mapped by necessity to data available from western countries [3]. The establishment and implementation of clinically meaningful strategies customized to each country would logically require direction from more local data in routine clinical care settings. However, availability of such data is limited due to a scarcity in the number of clinical trials conducted in the ASEAN region.

## 2. The need for observational research

Required data should be obtained using a balanced study design assessing the benefits and harms of treatment simultaneously. Under these circumstances, the observational study approach can be more practical than randomized controlled trials (RCTs). Observational research on medical interventions is more valuable post-approval when large datasets of typical real-life patient populations are involved. The frequency of adverse events reported in RCTs is usually limited by the small numbers of participants and by restrictive inclusion criteria of relatively healthy people. People with significant comorbidity are routinely excluded from RCTs but community-based practitioners have to cater to the needs of all patients irrespective of medical history. Furthermore, in clinical practice, therapies will by definition be used according to the local physician and patients needs and customs, while in RCTs use is generally driven by the protocol employed, with discontinuation of therapy or dose limitation discouraged. This is in contrast to routine clinical care where medication adherence is a major determinant of health outcomes for both oral and injection therapies [4]. Evidently observational study results will still be sensitive to the demographical and clinical characteristics of the population studied, but often offer opportunities for co-evaluation of measures such as baseline characteristics, health economic factors, surrogate and actual outcomes, and health-related quality of life.

## 3. The importance of $A_1$chieve in the ASEAN region

The multinational, prospective, non-interventional $A_1$chieve trial [5] is an example of such a study. It was conducted to

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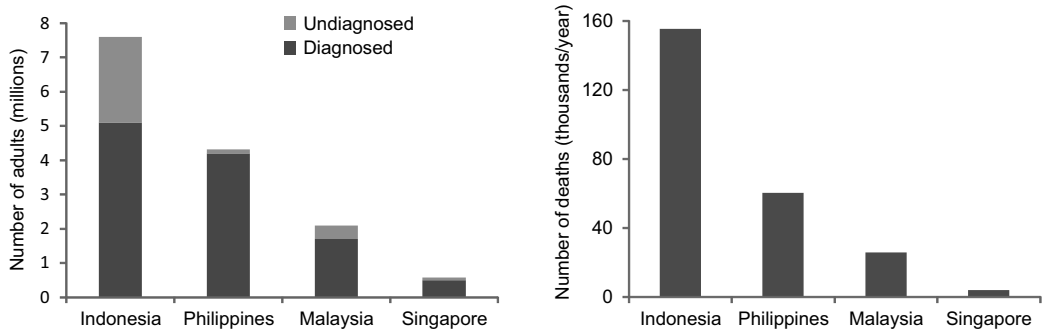


**Fig. 1 – Number of adults with diagnosed and undiagnosed diabetes in selected countries in the ASEAN region in 2012, and annual mortality estimates. Data from IDF Diabetes Atlas [2].**

determine the clinical experience associated with insulin analogue use in local clinical care across 28 non-western nations, including many less well resourced countries, across six continents. Complete study results are now available online under www.A1chieve.com. The advantages of the multinational $A_1$chieve study are revealed by the key statistics it has divulged on the current status of type 2 diabetes management in developing countries at baseline. People with type 2 diabetes from Indonesia, Malaysia, Philippines and Singapore were the representative nations of the ASEAN belt. The general observation at baseline was that people entered the study with grossly inadequate control of blood glucose levels. The average $HbA_{1c}$ level in the entire ASEAN cohort of 5029 participants was 9.7% (82 mmol/mol) while fasting plasma glucose and postprandial plasma glucose levels were 12.0 mmol/L (216 mg/dL) and 15.9 mmol/L (286 mg/dL), respectively.

Despite this poor state of glycaemic control and average diabetes duration of 7.2 years, the majority of participants starting analogue therapy (n = 3635) had not received insulin therapy previously. Clearly, the approach to diabetes care in these areas was sub-optimal. This may relate to factors such as fear of hypoglycaemia, weight gain, injections themselves, and/or perceived negative impact on quality of life, any or all of which may have delayed beginning insulin. However, it is known that nearly all people with type 2 diabetes will eventually require insulin, unless they die early or make major and permanent lifestyle changes.

The development of insulin analogues was intended to improve the benefit:harm risk of insulin therapy. The $A_1$chieve study evaluated the clinical experience with insulin analogues (biphasic insulin aspart 30, insulin detemir and insulin aspart) in a non-interventional local setting so that the results can be easily extrapolated to general patient populations in each country involved, and indeed beyond. The importance of an observational study like $A_1$chieve is thus justified by its contribution to increasing patient and physician awareness of the gains, and any losses, from the deployment of these therapeutic options designed to bolster diabetes management.

## Conflict of interest statement

Philip Home or institutions with which he is associated receive funding from Novo Nordisk and other insulin manufacturers for his research, advisory and educational activities.

## REFERENCES

[1] Whiting DR, Guariguata L, Weil C, Shaw J. IDF diabetes atlas: global estimates of the prevalence of diabetes for 2011 and 2030. Diabetes Res Clin Pract 2011;94:311–21.
[2] International Diabetes Federation. IDF Diabetes Atlas. 5th edn. Brussels, Belgium; 2011, updated 14 November 2012. http://www.idf.org/sites/default/files/WP_5E_Update_Country.pdf
[3] Paz-Pacheco E. Diabetes Clinical Practice Guidelines (CPGs) for the ASEAN region: Country initiatives for collectively enhanced diabetes care in the region. JAFES 2011;26:36–7.
[4] Peyrot M, Barnett AH, Meneghini LF, Schumm-0raeger PM. Insulin adherence behaviours and barriers in the multinational Global Attitudes of Patients and Physicians in Insulin Therapy study. Diabet Med 2012;29:682–9.
[5] Home P, Naggar NE, Khamseh M, Gonzalez-Galvez G, Shen C, Chakkarwar P, Wenying Y. An observational non-interventional study of patients with diabetes beginning or changed to insulin analogue therapy in non-Western countries: The $A_1$chieve study. Diabetes Res Clin Pract 2011;94:352–63.

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# Safety and effectiveness of biphasic insulin aspart 30 in type 2 diabetes: Results from the ASEAN cohort of the $A_1$chieve 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 $A_1$chieve 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 $A_1$chieve [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. $A_1$chieve 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

$A_1$chieve [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 $A_1$chieve 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).

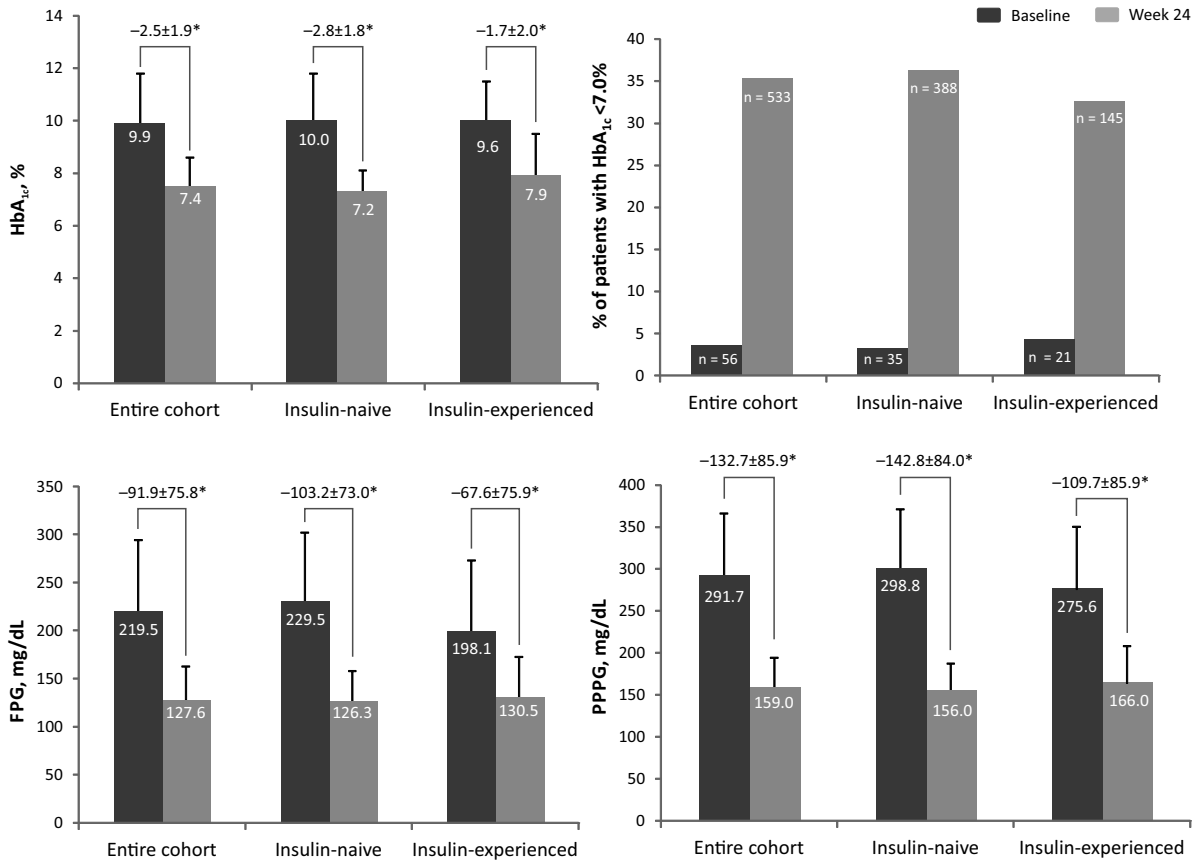


**Fig. 1 – Change in glucose control parameters in patients receiving biphasic insulin aspart 30 from baseline to Week 24. *$p < 0.001$.**

### 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 $A_1$chieve 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 $A_1$chieve 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.

## REFERENCES

[1] International Diabetes Federation. IDF Diabetes Atlas. 5th edn. Brussels, Belgium; 2011, updated 14 November 2012.
[2] Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. Diabetes Care 2004;127(5):1047–3.
[3] Niswender K. Early and aggressive initiation of insulin therapy for type 2 diabetes: What is the evidence? Clin Diab 2009;27:60–8.
[4] Turner RC, Cull CA, Frighi V, Holman RR. Glycemic control with diet, sulfonylurea, metformin, or insulin in patients with type 2 diabetes mellitus: progressive requirement for multiple therapies (UKPDS 49). UK Prospective Diabetes Study (UKPDS) Group. JAMA 1999;281(21):2005–12.
[5] Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, et al. Management of hyperglycaemia in type 2 diabetes: a patient-centered approach. Position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetologia 2012;55(6):1577–96.
[6] Evans M, Schumm-Draeger PM, Vora J, King AB. A review of modern insulin analogue pharmacokinetic and pharmacodynamic profiles in type 2 diabetes: improvements and limitations. Diabetes Obes Metab 2011;13(8):677–84.
[7] Christiansen JS, Vaz JA, Metelko Z, Bogoev M, Dedov I. Twice daily biphasic insulin aspart improves postprandial glycaemic control more effectively than twice daily NPH insulin, with low risk of hypoglycaemia, in patients with type 2 diabetes. Diabetes Obes Metab 2003;5(6):446–54.
[8] Hermansen K, Colombo M, Storgaard H, ØStergaard A, Kølendorf K, Madsbad S. Improved postprandial glycemic control with biphasic insulin aspart relative to biphasic insulin lispro and biphasic human insulin in patients with type 2 diabetes. Diabetes Care 2002;25(5):883–8.
[9] Gough SC, Tibaldi J. Biphasic insulin aspart in type 2 diabetes mellitus: an evidence-based medicine review. Clin Drug Invest 2007;27(5):299–324.
[10] Khutsoane D, Sharma SK, Almustafa M, Jang HC, Azar ST, Danciulescu R, et al.; PRESENT Study Group. Biphasic insulin aspart 30 treatment improves glycaemic control in patients with type 2 diabetes in a clinical practice setting: experience from the PRESENT study. Diabetes Obes Metab 2008;10(3):212–22.
[11] Valensi P, Benroubi M, Borzi V, Gumprecht J, Kawamori R, Shaban J, et al.; on behalf of the IMPROVE™ Study Group Expert Panel. Initiating insulin therapy with, or switching existing insulin therapy to, biphasic insulin aspart 30/70 (NovoMix 30) in routine care: safety and effectiveness in patients with type 2 diabetes in the IMPROVE observational study. Int J Clin Pract 2009;63(3):522–31.
[12] Paz-Pacheco E. Diabetes Clinical Practice Guidelines (CPGs) for the ASEAN region: Country initiatives for collectively enhanced diabetes care in the region. JAFES 2011;26(1):36–7.
[13] Home P, Naggar NE, Khamseh M, Gonzalez-Galvez G, Shen C, Chakkarwar P, et al. An observational non-interventional study of patients with diabetes beginning or changed to insulin analogue therapy in non-Western countries: The $A_1$chieve study. Diabetes Res Clin Pract 2011;94:352–63.
[14] Currie CJ, Peters JR, Tynan A, Evans M, Heine RJ, Bracco OL, et al. Survival as a function of $HbA_{1c}$ in people with type 2 diabetes: a retrospective cohort study. Lancet 2010;375:481–9.
[15] American Diabetes Association. Standards of medical care in diabetes – 2011. Diabetes Care 2011;34(Suppl 1):S11–61.
[16] Rubin RR, Peyrot M. Quality of life and diabetes. Diabetes Metab Res Rev 1999;15(3):205–18.

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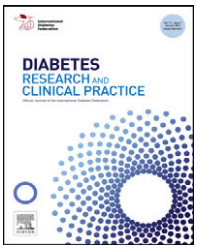

# Safety and effectiveness of insulin detemir in type 2 diabetes: Results from the ASEAN cohort of the A$_1$chieve study

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ABSTRACT

*Aim*: To determine the safety and effectiveness of insulin detemir (IDet) in type 2 diabetes patients from the ASEAN cohort of the A$_1$chieve study.

*Methods*: Patients from Indonesia, Malaysia, Philippines and Singapore prescribed IDet at the discretion of their physicians were included. The primary outcome was the incidence of serious adverse drug reactions including major hypoglycaemia over 24 weeks. Secondary endpoints included changes in the frequency of hypoglycaemia, serious adverse events and effectiveness assessments.

*Results*: This sub-analysis included 1540 patients (insulin-naive, 1239; insulin-experienced, 301) with mean age ± SD 56.4±10.9 years, BMI 25.4±4.6 kg/m$^2$ and diabetes duration 6.9±5.3 years. Insulin-naive patients received a baseline IDet dose of 0.24±0.11 U/kg titrated up to 0.37±0.21 U/kg by Week 24. The pre-study insulin dose in insulin-experienced patients was 0.41±0.25 U/kg and baseline IDet dose was 0.31±0.24 U/kg titrated up to 0.40±0.20 U/kg by Week 24. Overall hypoglycaemia decreased from 1.73 to 0.46 events/patient-year from baseline to Week 24 (change in proportion of patients affected, $p < 0.0001$). At Week 24, 1 major hypoglycaemic event was reported in 1 insulin-experienced patient. IDet significantly improved glucose control ($p < 0.001$) at Week 24. The lipid profile and systolic blood pressure improved ($p < 0.001$) and body weight did not change significantly. Quality of life was positively impacted ($p < 0.001$).

*Conclusion*: IDet was well-tolerated and improved glycaemic control without increasing the risk of hypoglycaemia or weight gain.



## 1. Introduction

The diabetes epidemic worldwide has reached astounding proportions in the recent decade. The International Diabetes Federation estimates that 552 million people would be living with diabetes by the year 2030 [1]. The ASEAN nations have also witnessed this explosive trend in the prevalence of diabetes. In 2012, Indonesia, Malaysia, Philippines and Singapore reported prevalence percentages of 4.8%, 11.7%, 8.2% and 12.5%, respectively, as adjusted to the world population. The 2030 projections for Indonesia

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and Philippines also place them among the top 10 countries for diabetes prevalence worldwide [1]. The spread of this chronic disease is widely attributed to lifestyle modification, urbanization and ageing populations [2]. Revisiting the strategies for diabetes care and management in these countries could be the key to keeping a check on these escalating figures.

Continually declining beta-cell function necessitates insulin use in all people affected with type 2 diabetes (T2D) [3]. Early and active intensification of insulin is known to moderate the progressive nature of T2D and eventually assist in maintaining glucose control [2]. The American Diabetes Association and the European Association for the Study of Diabetes recommend glycated haemoglobin ($HbA_{1c}$) levels <7.0% in order to decrease the risk of chronic complications with T2D [4]. Despite these evidence-based guidelines, several large observational studies have reported sub-optimal glycaemic control at baseline [5–7]. The resistance to human insulin therapy is correlated to its pharmacological profile that leads to unpredictable glucose control [8]. A recent survey reported that non-adherence to insulin therapy is fairly common and is related to practical barriers such as regimen inflexibility, lifestyle burden and injection difficulties [9]. Also, the fear of weight gain and negative impact on the quality of life (QoL) act as retardants to insulin therapy compliance [3]. The basal insulin analogue, insulin detemir (IDet) has a very stable protracted pharmacological profile due to its unique protein binding property that leads to extensive albumin and protein binding in the subcutaneous tissues, plasma and interstitial tissues [10]. Previously, the SOLVE and PREDICTIVE studies have demonstrated that IDet therapy resulted in improved glycaemic control as well as decreased risk of hypoglycaemia. Furthermore, these improvements were not associated with weight gain or other adverse events [5,6].

Clinical practice data from the ASEAN nations indicate that the existing diabetes management strategies lack uniformity and the ability to maintain optimum glycaemic control. Furthermore, the clinical practice guidelines rely upon international rather than local data due to an insufficiency in the regional studies [11]. The $A_1$chieve [7] study was conducted in less well-resourced countries to examine the safety and effectiveness of insulin analogues in regular clinical practice. Complete study results are now available online under www.A1chieve.com. T2D patients from Indonesia, Malaysia, Philippines and Singapore formed the ASEAN cohort of the $A_1$chieve study. This sub-analysis was conducted with an aim to determine the clinical use of IDet in this ASEAN cohort.

## 2. Methods

### 2.1. Study design

$A_1$chieve [7] was a 24-week, international, prospective, multicentre, non-interventional study to evaluate the safety and effectiveness of biphasic insulin aspart 30 (NovoMix®, Novo Nordisk), IDet (Levemir®, Novo Nordisk) and insulin aspart (NovoRapid®, Novo Nordisk), alone or in combination with oral glucose-lowering drugs (OGLDs) in T2D patients from less well-resourced countries. This sub-analysis was conducted in T2D patients on IDet recruited between October 2009 and December 2010 at 65, 23, 255 and 16 centers in Indonesia, Malaysia, Philippines and Singapore (ASEAN cohort), respectively. The decision to start IDet, subsequent changes in dosing and concomitant OGLD use was mutually agreed upon by the patient and their consulting physician. The study drug was available locally and was used in accordance with the local regulatory guidelines. 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/blood glucose meter were collected at baseline and Week 24 and transferred to a standard case report form.

### 2.2. Patients

Any patient starting IDet at the discretion of the physician was included in the sub-analysis. Women who were pregnant, breast-feeding or having the intention of becoming pregnant were excluded. The concurrent use of oral glucose-lowering drugs (OGLDs) was permitted in all patients during the course of the study. All patients signed informed consent to participate in the study and this study was approved by the local ethics committee of all countries involved.

### 2.3. Outcome measures and assessments

The primary objective was to evaluate the clinical safety of IDet therapy based on the incidence of serious adverse drug reactions (SADRs), including major hypoglycaemic events, from baseline to Week 24. 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. Assessments for effectiveness of therapy comprised change from baseline to final visit in $HbA_{1c}$, fasting plasma glucose (FPG), postprandial plasma glucose (PPPG), body weight, lipid profile and systolic blood pressure. All laboratory measurements were National Glycohemoglobin Standardization Program-certified and were evaluated in accordance with local regulations for standardization and quality. Health-related quality of life (QoL) was evaluated using the EQ-5D questionnaire that assesses mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Subsequently, the current QoL was measured using a standard 20 cm visual analogue scale (VAS, 0–100).

### 2.4. Statistical analysis

Statistical analyses were performed by entire cohort and by pre-study therapy type i.e., insulin-naive and insulin-experienced patients. As the patients were not randomized, baseline characteristics including concomitant medical conditions, choice of insulin and time of initiation were not

**Table 1 – Demographic and baseline characteristics**

| Characteristic | All patients (N = 1540) | Insulin-naive (N = 1239) | Insulin-experienced (N = 301) |
|---|---|---|---|
| Gender (male/female), % | 47.1/52.9 | 46.6/53.4 | 49.2/50.8 |
| Age, years | 56.4 (10.9) | 56.0 (10.8) | 57.8 (11.1) |
| Body weight, kg | 65.7 (13.5) | 65.5 (13.5) | 66.4 (13.2) |
| Body mass index, kg/m$^2$ | 25.4 (4.6) | 25.3 (4.6) | 25.8 (4.3) |
| Duration of diabetes, years | 6.9 (5.3) | 6.5 (4.9) | 8.5 (6.5) |
| Time to insulin initiation, years | 6.5 (5.2) | 6.4 (4.9) | 6.8 (6.1) |
| Duration on OGLDs, years | 6.1 (5.1) | 5.9 (4.8) | 7.0 (6.4) |
| Duration on insulin, years | 0.4 (1.4) | 0.0 (0.4) [a] | 1.7 (2.4) |
| $HbA_{1c}$, % | 9.3 (1.8) | 9.4 (1.9) | 9.1 (1.6) |
| $HbA_{1c}$, mmol/mol | 78 (20) | 79 (21) | 76 (18) |
| OGLDs at baseline | | | |
| Metformin | 929 (71.6) | 735 (70.2) | 194 (77.6) |
| Sulfonylureas | 628 (48.4) | 518 (49.5) | 110 (44.0) |
| Thiazolidinediones | 189 (14.6) | 160 (15.3) | 29 (11.6) |
| 1 OGLD | 653 (50.3) | 514 (49.1) | 139 (55.6) |
| 2 OGLDs | 500 (38.6) | 415 (39.6) | 85 (34.0) |
| >2 OGLDS | 144 (11.1) | 118 (11.3) | 26 (10.4) |

$HbA_{1c}$: glycated haemoglobin $A_{1c}$; OGLDs: oral glucose-lowering drugs.
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.

completely elucidated. Hence, comparisons between insulin-naive and insulin-experienced patients were descriptive rather than statistical.

Continuous and discrete variables were summarized using descriptive statistics and frequency tables (n [%]), respectively. The paired t-test was used to analyze the changes in $HbA_{1c}$, FPG, PPPG, SBP, blood lipids and QoL from baseline to Week 24. The McNemar test was used to analyze changes in hypoglycaemia from baseline in patients reporting at least one hypoglycaemic event. All data were analyzed by Novo Nordisk using SAS.

## 3. Results

### 3.1. Patients

A total of 1540 T2D patients enrolled from the ASEAN cohort started IDet therapy. This cohort constituted 1239 insulin-naive patients and 301 insulin-experienced patients. Demographic and baseline characteristics by entire cohort and by pre-study therapy type are reported in Table 1. The average baseline $HbA_{1c}$ level in insulin-naive patients was 9.4% (79 mmol/mol), while that in insulin-experienced patients was 9.1% (76 mmol/mol). At baseline, $HbA_{1c}$ <7.0% (<53 mmol/mol) was reported in 14 (8.1%) insulin-experienced and 40 (5.0%) insulin-naive patients.

In 95.5% patients, physicians prescribed IDet to improve glucose control. Reducing plasma glucose variability and reducing the risk of hypoglycaemia were the reasons cited for starting IDet in 33.2% and 30.8% patients, respectively.

### 3.2. Insulin dose

The insulin doses and frequency of administration pre-study, at baseline and at Week 24 are reported in Table 2. The pre-study insulin dose in insulin-experienced patients was 0.41±0.25 U/kg. In these patients, the average IDet dose at baseline was 0.31±0.24 U/kg titrated up to 0.40±0.20 U/kg at Week 24. Insulin-naive patients were administered a starting IDet dose of 0.24±0.11 U/kg titrated up to 0.37±0.21 U/kg by Week 24.

In the entire cohort, a total of 1470 patients were administered IDet once-daily (*qd*) while 69 patients received IDet twice-daily (*bid*) and 1 patient received IDet thrice-daily (*tid*) at baseline. At Week 24, 1132 patients received IDet *qd*, 137 patients received IDet *bid* while 89 patients were on ⩾*tid* dosing.

### 3.3. SAEs and SADRs

A total of 3 SAEs were reported in 2 insulin-experienced patients. Of these, 1 event of moderate intensity was possibly related to the study drug. Insulin-naive patients reported 2 SAEs (myocardial infarction and pancreatic carcinoma) in 2 patients that had fatal outcomes. The relation to IDet was unlikely for both these events.

### 3.4. Hypoglycaemia

The incidence of overall hypoglycaemia decreased from 1.73 events/patient-year to 0.46 events/patient-year. Correspondingly, the proportion of patients with at least one event decreased significantly from 6.0% to 1.9% ($p < 0.0001$, Table 3).

**Table 2 – Insulin dose and dosing frequency pre-study, at baseline and at Week 24**

| | | All patients | Insulin-naive | Insulin-experienced |
|---|---|---|---|---|
| Insulin dose, U/day | n | 1540 | 1239 | 301 |
| | Pre-study | 26.1 (16.8) | – | 26.1 (16.8) |
| | Baseline | 16.1 (9.1) | 15.3 (7.0) | 19.7 (14.4) |
| | Week 24 | 23.9 (13.6) | 23.4 (13.3) | 26.1 (14.5) |
| Insulin dose, U/kg | n | 1434 | 1149 | 285 |
| | Pre-study | 0.41 (0.25) | – | 0.41 (0.25) |
| | Baseline | 0.25 (0.15) | 0.24 (0.11) | 0.31 (0.24) |
| | Week 24 | 0.37 (0.21) | 0.37 (0.21) | 0.40 (0.20) |
| Dose frequency | Pre-study (n) | 301 | – | 301 |
| | Once daily | 161 (53.5) | – | 161 (53.5) |
| | Twice daily | 118 (39.2) | – | 118 (39.2) |
| | Thrice daily | 8 (2.7) | – | 8 (2.7) |
| | >Thrice daily | 14 (4.7) | – | 14 (4.7) |
| | Baseline (n) | 1540 | 1239 | 301 |
| | Once daily | 1470 (95.5) | 1188 (95.9) | 282 (93.7) |
| | Twice daily | 69 (4.5) | 50 (4.0) | 19 (6.3) |
| | Thrice daily | 1 (0.1) | 1 (0.1) | – |
| | >Thrice daily | – | – | – |
| | Week 24 (n) | 1358 | 1094 | 264 |
| | Once daily | 1132 (83.4) | 916 (83.7) | 216 (81.8) |
| | Twice daily | 137 (10.1) | 112 (10.2) | 25 (9.5) |
| | Thrice daily | 25 (1.8) | 23 (2.1) | 2 (0.8) |
| | >Thrice daily | 64 (4.7) | 43 (3.9) | 21 (8.0) |

Data are n, n (%) or mean (SD).

**Table 3 – Baseline and 24-week data for hypoglycaemia**

| Hypoglycaemia | | Events per patient-year / percent with at least one event | | |
|---|---|---|---|---|
| | | All patients | Insulin-naive | Insulin-experienced |
| Overall | Baseline | 1.73 / 6.0 | 1.15 / 4.3 | 4.10 / 13.0 |
| | Week 24 | 0.46 / 1.9 | 0.46 / 1.8 | 0.44 / 2.3 |
| | p | <0.0001 | 0.0002 | <0.0001 |
| Minor | Baseline | 1.62 / 5.8 | 1.03 / 4.1 | 4.06 / 12.6 |
| | Week 24 | 0.45 / 1.8 | 0.46 / 1.8 | 0.39 / 1.9 |
| | p | <0.0001 | 0.0005 | <0.0001 |
| Nocturnal | Baseline | 0.66 / 3.3 | 0.42 / 2.3 | 1.64 / 7.3 |
| | Week 24 | 0.12 / 0.6 | 0.14 / 0.6 | 0.05 / 0.4 |
| | p | <0.0001 | 0.0004 | <0.0001 |
| Major | Baseline | 0.11 / 0.6 | 0.13 / 0.6 | 0.04 / 0.3 |
| | Week 24 | 0.010 / 0.07 | 0.0 / 0.0 | 0.05 / 0.4 |
| | p | 0.0196 | 0.0047 | 0.3173 |

p-values are from McNemar test on paired proportions of patients experiencing hypoglycaemia.

Overall hypoglycaemia decreased from 4.10 to 0.44 events/patient-year (change in proportion of patients affected, $p < 0.0001$) in insulin-experienced patients and from 1.15 to 0.46 events/patient-year (change in proportion of patients affected, $p = 0.0002$) in insulin-naive patients. At Week 24, no major hypoglycaemia was reported in insulin-naive patients. In insulin-experienced patients, 0.05 events/patient-year were reported at Week 24 compared to 0.04 events/patient-year at baseline. The proportion of patients experiencing nocturnal and minor hypoglycaemia decreased significantly in the entire cohort from baseline to Week 24 ($p < 0.0001$, Table 3).

### 3.5. *Effectiveness of IDet therapy in lowering glucose*

A significant improvement from baseline in $HbA_{1c}$ (–2.1± 1.7%, –23±16 mmol/mol, $p < 0.001$), FPG (–84.2±73.6 mg/dL, $p < 0.001$) and PPPG (–112.3±81.6 mg/dL, $p < 0.001$) was reported after 24 weeks of IDet therapy (Figure 1). Additionally, from baseline to Week 24, the number of patients achieving $HbA_{1c}$ target levels <7.0% (<53 mmol/mol) increased from

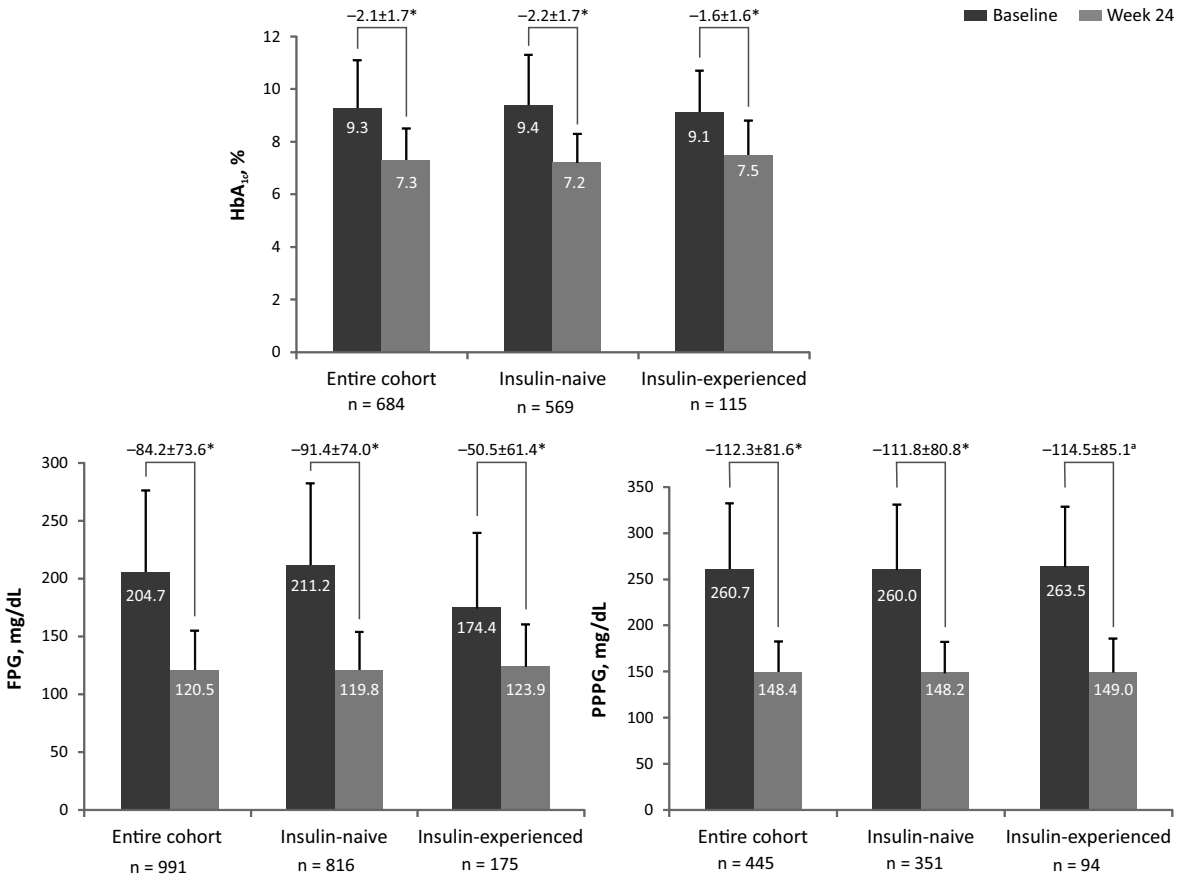


**Fig. 1 – Change in glucose control parameters from baseline to Week 24. *$p < 0.001$.**

5.5% (n = 54) to 40.2% (n = 338) in the entire cohort. The percentage of insulin-naive patients reporting $HbA_{1c}$ <7.0% (<53 mmol/mol) increased from 5.0% to 40.7% by Week 24 while the insulin-experienced patients reported an increase from 8.1% at baseline to 38.2% at Week 24.

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

In the entire cohort, the mean body weight did not change significantly from baseline (65.1±12.6 kg) to Week 24 (65.2±11.9 kg, p = NS, Table 4). Total cholesterol levels decreased significantly in the entire cohort from 5.5±1.3 mmol/L at baseline to 4.6±0.9 mmol/L at Week 24 ($p < 0.001$, Table 4). From baseline to Week 24, significant reductions were observed in low-density lipoprotein cholesterol (3.5±1.2 mmol/L vs. 2.8±0.9 mmol/L, $p < 0.001$) and triglyceride (2.0±1.0 mmol/L vs. 1.5±0.6 mmol/L, $p < 0.001$) levels while high-density lipoprotein cholesterol did not change significantly (1.2±0.5 mmol/L vs. 1.2±0.4 mmol/L, p = 0.712). A significant decrease of 5.9±17.7 mmHg ($p < 0.001$) in SBP was reported from baseline (129.5±17.8 mmHg) to Week 24 (123.5±14.5 mmHg, Table 4).

### 3.7. Quality of life

The EQ-5D VAS scores improved significantly from 70.5±13.9 points at baseline to 82.5±10.7 points at Week 24 ($p < 0.001$). In insulin-naive patients, the QoL improved by 12.3±14.4 points while insulin-experienced patients reported an improvement of 10.6±16.5 points (both, $p < 0.001$).

## 4. Discussion

This sub-analysis demonstrated the clinical safety and effectiveness of IDet in the ASEAN cohort of the $A_1$chieve study. As observed with the overall study data, IDet therapy significantly improved glycaemic control and alleviated the risk of hypoglycaemia in the ASEAN T2D patients.

Poor baseline glycaemic control was evident in this cohort, similar to data reported from previous observational studies [5–7]. Although the mean diabetes duration was 6.9 years, the majority of patients (80.5%) were insulin-naive at baseline. The average $HbA_{1c}$ level at baseline was 9.3% (78 mmol/mol) with 5.5% of the patients reporting target $HbA_{1c}$ levels <7.0%. This data is suggestive of an imperative need to evaluate the existing management strategies for T2D and implement measures to optimize treatment via educating patients and increasing physician awareness.

As observed in the overall $A_1$chieve results, IDet therapy in patients from the ASEAN cohort resulted in marked improvements in glycaemic control irrespective of prior insulin use. Furthermore, these improvements were associated with a significantly lower risk of hypoglycaemia at Week 24 as compared to the baseline incidence. At Week 24, no major

**Table 4 – Baseline and 24-week data for blood lipids, body weight and SBP**

| | | All patients | Insulin-naive | Insulin-experienced |
|---|---|---|---|---|
| Total cholesterol, mmol/L | n | 316 | 256 | 60 |
| | Baseline | 5.5 (1.3) | 5.6 (1.3) | 5.4 (1.3) |
| | Week 24 | 4.6 (0.9) | 4.6 (0.9) | 4.8 (0.8) |
| | Change | −0.9 (1.4) | −1.0 (1.4) | −0.6 (1.3) |
| | p | <0.001 | <0.001 | – [a] |
| Triglycerides, mmol/L | n | 276 | 224 | 52 |
| | Baseline | 2.0 (1.0) | 2.0 (1.0) | 1.8 (1.1) |
| | Week 24 | 1.5 (0.6) | 1.6 (0.6) | 1.5 (0.6) |
| | Change | −0.4 (1.0) | −0.5 (1.0) | −0.3 (1.1) |
| | p | <0.001 | <0.001 | – [a] |
| HDL cholesterol, mmol/L | n | 222 | 176 | 46 |
| | Baseline | 1.2 (0.5) | 1.2 (0.5) | 1.3 (0.4) |
| | Week 24 | 1.2 (0.4) | 1.2 (0.3) | 1.3 (0.5) |
| | Change | 0.0 (0.5) | 0.0 (0.4) | −0.0 (0.6) |
| | p | 0.712 | 0.627 | – [a] |
| LDL cholesterol, mmol/L | n | 229 | 183 | 46 |
| | Baseline | 3.5 (1.2) | 3.5 (1.2) | 3.3 (1.1) |
| | Week 24 | 2.8 (0.9) | 2.8 (0.9) | 2.8 (0.8) |
| | Change | −0.7 (1.3) | −0.8 (1.3) | −0.5 (1.3) |
| | p | <0.001 | <0.001 | – [a] |
| Body weight, kg | n | 1200 | 959 | 241 |
| | Baseline | 65.1 (12.6) | 65.0 (12.9) | 65.6 (11.3) |
| | Week 24 | 65.2 (11.9) | 65.2 (12.1) | 65.3 (11.0) |
| | Change | 0.1 (4.6) | 0.2 (4.6) | −0.3 (4.7) |
| | p | 0.292 | 0.094 | 0.338 |
| SBP, mmHg | n | 1224 | 1000 | 224 |
| | Baseline | 129.5 (17.8) | 129.1 (18.0) | 131.0 (17.2) |
| | Week 24 | 123.5 (14.5) | 122.7 (14.6) | 127.1 (13.3) |
| | Change | −5.9 (17.7) | −6.4 (18.1) | −3.9 (15.1) |
| | p | <0.001 | <0.001 | <0.001 |

HDL, high-density lipoprotein; LDL, low-density lipoprotein; SBP, systolic blood pressure.
Baseline, Week-24 and change data are mean (SD).
[a] p-value not presented since n < 100.

hypoglycaemia was reported in insulin-naive patients and 1 incident of major hypoglycaemia was reported in 1 insulin-experienced patient. The proportion of patients reporting nocturnal hypoglycaemia was significantly lower at Week 24. This data is concordant to reports from clinical studies indicating a reduction in the incidence of hypoglycaemia, particularly nocturnal events, following IDet therapy [12,13]. The lipid profile and SBP in ASEAN patients also improved significantly while body weight did not change significantly following 24 weeks of IDet therapy. Interventions that can positively impact the patients' QoL are highly desired in T2D. In this sub-analysis, IDet exhibited an affirmative effect on health-related QoL outcomes evaluated using the EQ-5D questionnaire.

The effectiveness of IDet therapy was evident without any major increase in dose (0.25±0.15 U/kg at baseline vs. 0.37±0.21 U/kg at Week 24). A total of 83.4% patients continued IDet *qd* up to Week 24. This information could drive physicians towards actively intensifying IDet therapy in order to achieve glycaemic goals without unwarranted adverse effects.

Limitations such as lack of a control arm, retrospective data collection methods, non-standardization of reported data and recall bias for the incidence of hypoglycaemia may have been introduced in this study due to its observational design. Nevertheless, the results are useful in determining the effectiveness of a treatment in a heterogeneous population in local clinical settings. Furthermore, the safety profile for drugs is more comprehensive with observational studies due to the involvement of a wider patient population compared to randomized controlled trials [14]. In conclusion, the use of IDet in T2D patients improved glycaemic control without increasing the risk of hypoglycaemia.

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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. Mafauzy Mohamed received honorarium for conduct of research from Novo Nordisk. Dr. Anand B. Jain was employed by Novo Nordisk Pharma (Malaysia) Sdn Bhd. Chin Meng Khoo received honorarium for conduct of research from Novo Nordisk. Rosa Allyn G. Sy has no 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.

## REFERENCES

[1] International Diabetes Federation. IDF Diabetes Atlas. 5th edn. Brussels, Belgium; 2011, updated 14 November 2012.
[2] Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, et al. Management of hyperglycaemia in type 2 diabetes: a patient-centered approach. Position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetologia 2012;55(6):1577–96.
[3] Niswender K. Early and aggressive initiation of insulin therapy for type 2 diabetes: What is the evidence? Clin Diab 2009;27:60–8.
[4] American Diabetes Association. Standards of medical care in diabetes – 2011. Diabetes Care 2011;34(Suppl 1):S11–61.
[5] Khunti K, Caputo S, Damci T, Dzida GJ, Ji Q, Kaiser M, et al.; on behalf of the SOLVE Study Group. The safety and efficacy of adding once-daily insulin detemir to oral hypoglycaemic agents in patients with type 2 diabetes in a clinical practice setting in 10 countries. Diabetes Obes Metab 2012;14(12):1129–36.
[6] Dornhorst A, Lüddeke HJ, Sreenan S, Kozlovski P, Hansen JB, Looij BJ, et al.; PREDICTIVE Study Group. Insulin detemir improves glycaemic control without weight gain in insulin-naive patients with type 2 diabetes: subgroup analysis from the PREDICTIVE study. Int J Clin Pract. 2008;62(4):659–65.
[7] Home P, Naggar NE, Khamseh M, Gonzalez-Galvez G, Shen C, Chakkarwar P, et al. An observational non-interventional study of patients with diabetes beginning or changed to insulin analogue therapy in non-Western countries: The $A_1$chieve study. Diabetes Res Clin Pract 2011;94:352–63.
[8] Evans M, Schumm-2raeger PM, Vora J, King AB. A review of modern insulin analogue pharmacokinetic and pharmacodynamic profiles in type 2 diabetes: improvements and limitations. Diabetes Obes Metab 2011;13(8):677–84.
[9] Peyrot M, Barnett AH. Factors associated with injection omission/non-adherence in the Global Attitudes of Patients and Physicians in Insulin Therapy study. Diabetes Obes Metab 2012;14(12):1181–7.
[10] Mathieu C. Engineering basal insulin – clinical evidence translating to clinical experience. JAPI 2009;57:16–21.
[11] Paz-Pacheco E. Diabetes clinical practice guideline (CPGs) for the ASEAN region: Country initiatives for collectively enhanced diabetes care in the region. JAFES 2011;26(1): 36–7.
[12] Raslova K, Bogoev M, Raz I, Leth G, Gall MA, Hancu N. Insulin detemir and insulin aspart: a promising basal–bolus regimen for type 2 diabetes. Diabetes Res Clin Pract 2004;66(2):193–201.
[13] Hermansen K, Davies M, Derezinski T, Martinez Ravn G, Clausen P, Home P. A 26-week, randomized, parallel, treat-to-target trial comparing insulin detemir with NPH insulin as add-on therapy to oral glucose-lowering drugs in insulin-naive people with type 2 diabetes. Diabetes Care 2006;29(6):1269–74.
[14] Vandenbroucke JP. What is the best evidence for determining harms of medical treatment? CMAJ 2006;174(5):645–6.

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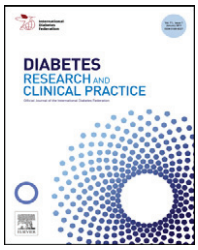

# Safety and effectiveness of insulin aspart in type 2 diabetic patients: Results from the ASEAN cohort of the $A_1$chieve study

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ABSTRACT

*Aim:* To examine the clinical safety and effectiveness of insulin aspart (IAsp) therapy in type 2 diabetes (T2D) patients from the ASEAN cohort of the international, 24-week, non-interventional $A_1$chieve study.

*Methods:* T2D patients from Indonesia, Malaysia, Philippines and Singapore, who started IAsp therapy with or without oral glucose-lowering drugs, were included. The primary endpoint was the incidence of serious adverse drug reactions (SADRs), including major hypoglycaemic events. Secondary endpoints included hypoglycaemia, glycated haemoglobin $A_{1c}$ [$HbA_{1c}$], fasting plasma glucose [FPG], postprandial plasma glucose [PPPG], systolic blood pressure [SBP], body weight and lipids. Quality of life (QoL) was assessed using the EQ-5D questionnaire.

*Results:* Overall, 312 T2D patients (222 insulin-naive and 90 insulin-experienced) with a mean±SD age of 56.6±11.2 years, BMI of 24.2±3.9 kg/m$^2$ and diabetes duration of 7.0±5.7 years were included. The mean daily IAsp dose was 0.51±0.31 U/kg at baseline titrated up to 0.60±0.29 U/kg at Week 24. No SADRs or major hypoglycaemic events were reported in the entire subgroup. The proportion of patients who reported overall hypoglycaemia decreased from baseline to Week 24 (7.1% vs. 0.3%, $p < 0.0001$). The mean $HbA_{1c}$ improved from 9.5±1.6% at baseline to 7.6±1.3% after 24 weeks ($p < 0.001$). The mean FPG, post-breakfast PPPG and SBP also improved ($p < 0.001$). Health-related QoL scores increased in the entire subgroup (mean increase: 9.8±14.6 points, $p < 0.001$).

*Conclusions:* Starting IAsp therapy was well-tolerated and was associated with significantly improved overall glycaemic control in the ASEAN cohort.



## 1. Introduction

Type 2 diabetes (T2D), defined by the progressive loss of beta-cell function, is now a major global health concern. The Western Pacific region, which includes the ASEAN countries, Indonesia, Malaysia, Philippines and Singapore, currently has the highest number of adults with diabetes in the world and this trend is projected to continue over the next 20 years [1]. Indonesia, Malaysia and Philippines are listed among the ten countries with the highest number of diabetes cases in the Western Pacific and Singapore has a

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high diabetes prevalence of 12.45% [2]. These data highlight the pressing need to identify and utilize more effective strategies in the treatment and management of T2D in these countries.

Conventionally, most interventions have primarily targeted glycated haemoglobin $A_{1c}$ ($HbA_{1c}$) and fasting plasma glucose (FPG) levels in managing hyperglycaemia [3]. However, there is increasing evidence that postprandial plasma glucose (PPPG) levels play an equally important role in determining the status of glycaemic control in patients with T2D [4]. In fact, high levels of postprandial hyperglycaemia and hyperlipidaemia have been linked to an increased risk of diabetes-related complications as well as adverse long-term cardiovascular outcomes [4,5].

Prandial therapy with rapid-acting insulin analogues such as insulin aspart (IAsp) has been shown to effectively control PPPG excursions [5]. The faster subcutaneous absorption properties of IAsp compared to regular human insulin (HI) result in significantly lower PPPG and similar or lower $HbA_{1c}$ levels [6–8]. In several randomized controlled clinical trials, IAsp was found to be associated with a lower risk of major or nocturnal hypoglycaemia compared to regular HI [9]. In contrast to HI, which must be injected 30 minutes prior to a meal, IAsp can be injected immediately before the meal, which could benefit patients with erratic schedules [10]. IAsp was also reported to decrease postprandial hyperlipidaemia over two consecutive meals to a greater extent compared to regular HI in a randomized, open-label, crossover trial in 13 patients with T2D [5].

Disparities between evidence-based treatment guidelines and actual clinical practice may result in less than optimal therapeutic effects [11]. In the absence of regional guidelines for T2D management in many developing countries, it is important to evaluate the application of international recommendations in local clinical care [12]. Observational studies that include heterogeneous populations may form the best setting for such research [11].

The large non-interventional $A_1$chieve study has collected safety and effectiveness data on insulin analogue use from over 66,000 T2D patients in 28 countries with the aim of identifying whether the results seen in randomised clinical trials could be obtained in real-life clinical settings [13]. The results from all countries are available under www.A1chieve.com. In our sub-analysis, we identified study data from the ASEAN subgroup consisting of Indonesia, Malaysia, Philippines and Singapore. This analysis aimed to evaluate the safety and effectiveness of IAsp in T2D patients in the ASEAN subgroup of the $A_1$chieve study and to characterize the current status of T2D management in this region.

## 2. Methods

### 2.1. Study design

The $A_1$chieve study's design and treatment groups have been described previously by Home et al. [13]. In brief, this 24-week, prospective, non-interventional study aimed to record information on the use of biphasic insulin aspart (NovoMix®, Novo Nordisk A/S, Denmark), insulin detemir (Levemir®, Novo Nordisk A/S, Denmark) and IAsp (NovoRapid®, Novo Nordisk A/S, Denmark) in T2D management in routine clinical practice in developing nations. This sub-analysis was conducted with the aim of determining the safety and effectiveness of IAsp in T2D patients in the $A_1$chieve ASEAN subgroup (consisting of Indonesia, Malaysia, Philippines and Singapore).

All decisions related to the use of IAsp, including dose and dosing frequency, were left to the discretion of the physicians. The use of concomitant oral glucose-lowering drugs (OGLDs) was permitted throughout the study, again at the physician's discretion. In line with the non-interventional nature of the study, no special investigations were planned apart from the clinical parameters routinely assessed by the physicians. Data were collected from the physicians' notes and the patients' self-monitoring blood glucose meters and diaries and transferred to standard case report forms.

### 2.2. Patients

Patients with T2D were recruited between October 2009 and December 2010 at 359 centers across Indonesia, Malaysia, Philippines and Singapore. Patients who started IAsp therapy at the physician's discretion were included in this sub-analysis. Patients were excluded from the study if they had been treated with any of the study insulin analogues for over 4 weeks prior to baseline. Female patients who were pregnant, breast-feeding or intended to become pregnant were also excluded. Signed informed consent was obtained from all patients and the study was approved by the regulatory authorities of the participating countries.

### 2.3. Assessments and outcome measures

The primary outcome measure was the frequency of serious adverse drug reactions (SADRs), including major hypoglycaemic events, during the study. The secondary outcomes included the change in the number and frequency of hypoglycaemic events, serious adverse events (SAEs) and adverse events between baseline and Week 24.

Additional secondary outcomes included the change from baseline to Week 24 in $HbA_{1c}$, FPG, PPPG, body weight, systolic blood pressure (SBP) and lipid profile (comprising total cholesterol, high-density lipoprotein [HDL] cholesterol, low-density lipoprotein [LDL] cholesterol and triglycerides). Local laboratories performed the laboratory measurements in accordance with local standardisation and quality control procedures.

### 2.4. Statistical analysis

Statistical analyses were performed for all ASEAN patients starting IAsp therapy and by pre-study therapy type i.e., insulin-naive and insulin experienced patients. Descriptive statistics and frequency tables (n, %) were used to summarise continuous and discrete variables, respectively.

**Table 1 – Demographic and baseline characteristics**

| Characteristic | All patients (n = 312) | Insulin-naive (n = 222) | Insulin-experienced (n = 90) |
|---|---|---|---|
| Gender (male/female), % | 49.4/50.6 | 51.4/48.6 | 44.4/55.6 |
| Age, years | 56.6 (11.2) | 56.5 (10.4) | 57.0 (13.0) |
| Body weight, kg | 63.2 (12.0) | 63.1 (12.6) | 63.4 (10.2) |
| Body mass index, $kg/m^2$ | 24.2 (3.9) | 24.2 (4.1) | 24.3 (3.4) |
| Duration of diabetes, years | 7.0 (5.7) | 6.5 (5.8) | 8.0 (5.3) |
| Time to insulin initiation, years | 6.0 (5.2) | 6.0 (5.2) | 5.9 (5.0) |
| Duration on OGLDs, years | 5.5 (4.8) | 5.2 (4.6) | 6.3 (5.2) |
| Duration on insulin, years | 0.6 (1.7) | 0.0 (0.2) [a] | 2.0 (2.6) |
| $HbA_{1c}$, % | 9.5 (1.6) | 9.5 (1.7) | 9.4 (1.6) |
| $HbA_{1c}$, mmol/mol | 80 (17) | 80 (19) | 79 (17) |
| OGLDs, n (%) | | | |
| Metformin | 97 (73.5) | 66 (72.5) | 31 (75.6) |
| Sulfonylureas | 29 (22.0) | 19 (20.9) | 10 (24.4) |
| Thiazolidinediones | 7 (5.3) | 5 (5.5) | 2 (4.9) |
| 1 OGLD | 108 (81.8) | 76 (83.5) | 32 (78.0) |
| 2 OGLDs | 19 (14.4) | 11 (12.1) | 8 (19.5) |
| >2 OGLDs | 5 (3.8) | 4 (4.4) | 1 (2.4) |

$HbA_{1c}$: glycated haemoglobin $A_{1c}$; OGLDs: oral glucose-lowering drugs.
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.

A paired t-test was used to analyze the mean change between baseline and Week 24 in $HbA_{1c}$, FPG, PPPG, blood lipids, body weight, SBP and QoL. The change from baseline to Week 24 in the percentage of patients reporting at least one hypoglycaemic event was analysed using McNemar's paired test. All tests were two-sided with pre-specified 5% significance. P-values are not presented when the number of patients analysed was less than 100.

Data analyses were performed by Novo Nordisk using SAS® Version 9.1.3.

## 3. Results

### 3.1. Patient characteristics

A total of 312 patients (insulin-naive: 222 patients and insulin-experienced: 90 patients) initiated IAsp therapy from the ASEAN region. Baseline and demographic data are presented in Table 1.

The average duration of T2D was 7.0±5.7 years at baseline in the entire subgroup and insulin-experienced patients had been taking insulin for an average of 2.0±2.6 years. The mean baseline $HbA_{1c}$ level was 9.5±1.7% (80±19 mmol/mol) in insulin-naive patients and 9.4±1.6% (79±17 mmol/mol) in insulin-experienced patients. The most commonly reported reasons for changing therapy were to improve glycaemic control (91.0% of patients), try a new insulin (33.8% of patients) and reduce the risk of hypoglycaemia (28.4% of patients).

Pre-study, the majority of patients were receiving metformin (77.6%) and sulfonylureas (66.9%) in the entire subgroup. Among insulin-naive patients, 30.5% of patients were on 1 OGLD, 46.8% were on 2 OGLDs and 22.6% were on more than 2 OGLDs pre-study, while among insulin-experienced patients, 59.4% of patients were on 1 OGLD, 32.8% were on 2 OGLDs and 7.8% were on more than 2 OGLDs.

At baseline in the entire subgroup, the majority of patients (73.5%) continued using metformin and the proportion of sulfonylurea users decreased to 22.0% (Table 1).

### 3.2. SADRs and SAEs

No SADRs were reported during the study. One death (cardiac arrest), considered unlikely to be related to the study drug, was reported among the insulin-experienced patients.

### 3.3. Hypoglycaemia

Baseline and Week 24 data for hypoglycaemia are presented in Table 2.

The percentage of patients who reported overall hypoglycaemia decreased from 7.1% at baseline to 0.3% at Week 24 ($p < 0.0001$) with a decrease in the event rate from 1.50 events per patient-year at baseline to 0.04 events per patient-year at Week 24.

No events of major hypoglycaemia or nocturnal hypoglycaemia were reported at Week 24. A statistically significant reduction from baseline was observed in the percentage of patients who reported minor hypoglycaemia

**Table 2 – Baseline and 24-week data for hypoglycaemia**

| Hypoglycaemia | | Events per patient-year / percent with at least one event | | |
|---|---|---|---|---|
| | | All patients | Insulin-naive | Insulin-experienced |
| Overall | Baseline | 1.50/7.1 | 1.00/4.1 | 2.74/14.4 |
| | Week 24 | 0.04/0.3 | 0.06/0.5 | 0.0/0.0 |
| | p | <0.0001 | 0.0047 | 0.0005 |
| Minor | Baseline | 1.42/6.7 | 1.00/4.1 | 2.46/13.3 |
| | Week 24 | 0.04/0.3 | 0.06/0.5 | 0.0/0.0 |
| | p | <0.0001 | 0.0047 | 0.0009 |
| Nocturnal | Baseline | 0.50/3.5 | 0.35/2.7 | 0.87/5.6 |
| | Week 24 | 0.0/0.0 | 0.0/0.0 | 0.0/0.0 |
| | p | 0.0009 | 0.0143 | 0.0253 |
| Major | Baseline | 0.08/0.3 | 0.0/0.0 | 0.29/1.1 |
| | Week 24 | 0.0/0.0 | 0.0/0.0 | 0.0/0.0 |
| | p | 0.3173 | – | 0.3173 |

p-values are from McNemar's test on paired proportions of patients experiencing hypoglycaemia.

**Table 3 – Insulin dose and dosing frequency pre-study, at baseline and at Week 24**

| | | All patients | Insulin-naive | Insulin-experienced |
|---|---|---|---|---|
| Insulin dose, U/day | n | 312 | 222 | 90 |
| | Pre-study | 37.0 (20.1) | – | 37.0 (20.1) |
| | Baseline | 30.3 (16.3) | 29.2 (15.7) | 32.9 (17.5) |
| | Week 24 | 36.9 (17.0) | 35.3 (15.3) | 41.1 (20.3) |
| Insulin dose, U/kg | n | 297 | 212 | 85 |
| | Pre-study | 0.60 (0.36) | – | 0.60 (0.36) |
| | Baseline | 0.51 (0.31) | 0.49 (0.28) | 0.55 (0.37) |
| | Week 24 | 0.60 (0.29) | 0.59 (0.27) | 0.65 (0.32) |
| Dose frequency, n (%) | Pre-study, n | 90 | – | 90 |
| | Once daily | 15 (16.7) | – | 15 (16.7) |
| | Twice daily | 38 (42.2) | – | 38 (42.2) |
| | Thrice daily | 33 (36.7) | – | 33 (36.7) |
| | >Thrice daily | 4 (4.4) | – | 4 (4.4) |
| | Baseline, n | 312 | 222 | 90 |
| | Once daily | 16 (5.1) | 10 (4.5) | 6 (6.7) |
| | Twice daily | 44 (14.1) | 30 (13.5) | 14 (15.6) |
| | Thrice daily | 246 (78.8) | 178 (80.2) | 68 (75.6) |
| | >Thrice daily | 6 (1.9) | 4 (1.8) | 2 (2.2) |
| | Week 24, n | 299 | 216 | 83 |
| | Once daily | 15 (5.0) | 11 (5.1) | 4 (4.8) |
| | Twice daily | 47 (15.7) | 29 (13.4) | 18 (21.7) |
| | Thrice daily | 189 (63.2) | 149 (69.0) | 40 (48.2) |
| | >Thrice daily | 48 (16.1) | 27 (12.5) | 21 (25.3) |

Pre-study, baseline and Week 24 values are presented as mean (SD) unless specified otherwise.

(6.7% to 0.3%, $p < 0.0001$, Table 2) along with a corresponding decline in the event rate over 24 weeks in the entire subgroup.

### 3.4. Insulin dose and glycaemic control

The mean IAsp doses and dosing frequency details are presented in Table 3. In insulin-naive patients, the mean starting IAsp dose was 0.49±0.28 U/kg, titrated up to 0.59±0.27 U/kg at Week 24. In insulin-experienced patients, the mean pre-study insulin dose was 0.60±0.36 U/kg and the mean starting IAsp dose was 0.55±0.37 U/kg, titrated up to 0.65±0.32 U/kg over 24 weeks. The majority of patients in the entire subgroup injected IAsp thrice-daily at baseline (78.8%) and Week 24 (63.2%).

The baseline and Week 24 values for the glycaemic parameters ($HbA_{1c}$, FPG and post-breakfast PPPG) are presented in Table 4. The mean overall reduction in $HbA_{1c}$

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

| | | All patients | Insulin-naive | Insulin-experienced |
|---|---|---|---|---|
| $HbA_{1c}$, % / mmol/mol | n | 114 | 84 | 30 |
| | Baseline | 9.5 (1.6)/80 (17) | 9.5 (1.7)/80 (19) | 9.4 (1.6)/79 (17) |
| | Week 24 | 7.6 (1.3)/60 (14) | 7.6 (1.1)/60 (12) | 7.8 (1.7)/62 (19) |
| | Change | −1.8 (1.5) / −20 (16) | −1.9 (1.5) / −21 (16) | −1.6 (1.4) / −17 (15) |
| | p | <0.001 | – [a] | – [a] |
| FPG, mg/dL | n | 231 | 171 | 60 |
| | Baseline | 218.3 (70.9) | 222.2 (67.9) | 207.0 (78.2) |
| | Week 24 | 138.1 (38.7) | 137.2 (35.1) | 140.6 (47.8) |
| | Change | −80.2 (62.8) | −85.1 (58.8) | −66.4 (71.8) |
| | p | <0.001 | <0.001 | – [a] |
| PPPG, mg/dL | n | 202 | 150 | 52 |
| | Baseline | 296.5 (83.8) | 298.3 (86.0) | 291.5 (77.5) |
| | Week 24 | 175.3 (48.8) | 168.2 (43.3) | 195.8 (57.9) |
| | Change | −121.3 (81.2) | −130.1 (84.8) | −95.8 (64.1) |
| | p | <0.001 | <0.001 | – [a] |

FPG, fasting plasma glucose; $HbA_{1c}$, glycated haemoglobin $A_{1c}$; PPPG, postprandial plasma glucose. Baseline, Week-24 and change values are presented as mean (SD).
[a] p-value not reported since n < 100.

was −1.8±1.5% (−20±16 mmol/mol) after 24 weeks ($p < 0.001$). Statistically significant reductions in FPG and PPPG, by −80.2±62.8 mg/dL and −121.3±81.2 mg/dL, respectively, were also observed at Week 24 (both $p < 0.001$) in the entire subgroup.

Only 4 insulin-naive patients and none of the insulin-experienced patients had $HbA_{1c}$ levels lower than 7.0% (<53 mmol/mol) at baseline. Following 24 weeks of IAsp therapy, 36 insulin-naive and 19 insulin-experienced patients had $HbA_{1c}$ levels lower than 7.0% (<53 mmol/mol).

### 3.5. Blood lipids, body weight and systolic blood pressure

Baseline and Week 24 data for blood lipids, body weight and SBP are presented in Table 5.

Lower levels of mean total cholesterol, triglyceride and LDL cholesterol were observed at Week 24 compared to baseline in the entire subgroup, while the mean HDL cholesterol level increased by 0.1±0.4 mmol/L.

The mean body weight increased by an average of 1.1±3.5 kg over 24 weeks in the entire subgroup ($p < 0.001$). The mean SBP decreased from 136.3±21.1 mmHg at baseline to 128.9±14.6 mmHg at Week 24 (mean change: −7.4±17.3 mmHg, $p < 0.001$).

### 3.6. Quality of life

An improvement in the mean overall QoL score was observed from baseline (72.1±15.3 points) to Week 24 (81.9±8.9 points) on the 20-cm VAS (mean increase: 9.8±14.6 points, $p < 0.001$) in the entire subgroup. The mean QoL scores also increased at Week 24 in both insulin-naive and insulin-experienced patients.

Improvements at Week 24 were also noted in the five parameters (pain, anxiety, self-care, mobility and usual activity) of the EQ-5D questionnaire in the entire subgroup.

## 4. Discussion

The results from this ASEAN subgroup showed that starting IAsp therapy was well-tolerated and indicated beneficial effects on the status of glycaemic control in a subpopulation of T2D patients from the non-interventional $A_1$chieve study.

Despite the existence of well-established guidelines concerning the appropriate intensification of therapy for T2D patients [14], large numbers of patients continue to exhibit sub-optimal glycaemic control in routine clinical practice [15]. In the overall $A_1$chieve cohort, the average baseline $HbA_{1c}$ value was 9.5% (80 mmol/mol) [13], reflected in this ASEAN subgroup also. This dismal trend of poor glycaemic control was also evidenced by the baseline FPG and PPPG values in this subgroup, which were well beyond the ranges recommended by the American Diabetes Association [14]. The risk of long-term microvascular complications such as retinopathy increases with longer duration of poor blood glucose control [16].

The United Kingdom Prospective Diabetes Study has demonstrated that monotherapy fails to maintain $HbA_{1c}$ <7.0% (<53 mmol/mol) in 50% of patients 3 years from the initial diagnosis of T2D [17]. Pre-study in this subgroup, 30.5% of insulin-naive patients were taking only one OGLD and had been diagnosed approximately 7 years earlier. Insulin-experienced patients took an average of 6 years to initiate insulin therapy.

Significant improvements in the mean $HbA_{1c}$, FPG and post-breakfast PPPG were noted with IAsp therapy in the ASEAN subgroup, consistent with the improvements seen in patients who started IAsp therapy in the overall $A_1$chieve cohort [13]. Also, the improvements in glycaemic parameters in this subgroup were associated with only a small increase in the mean IAsp dose over 24 weeks and with a markedly decreased rate of overall hypoglycaemia. No major hypoglycaemic events were reported after 24 weeks of

**Table 5 – Baseline and 24-week data for blood lipids, body weight and SBP**

| | | All patients | Insulin-naive | Insulin-experienced |
|---|---|---|---|---|
| Total cholesterol, mmol/L | n | 80 | 59 | 21 |
| | Baseline | 5.3 (1.4) | 5.3 (1.4) | 5.2 (1.4) |
| | Week 24 | 4.7 (0.9) | 4.7 (0.9) | 4.7 (1.0) |
| | Change | −0.6 (1.0) | −0.6 (0.9) | −0.6 (1.3) |
| | p | –[a] | –[a] | –[a] |
| Triglycerides, mmol/L | n | 78 | 58 | 20 |
| | Baseline | 2.0 (1.0) | 2.1 (1.0) | 1.8 (0.8) |
| | Week 24 | 1.7 (0.6) | 1.8 (0.7) | 1.6 (0.5) |
| | Change | −0.3 (0.8) | −0.3 (0.8) | −0.2 (0.5) |
| | p | –[a] | –[a] | –[a] |
| HDL cholesterol, mmol/L | n | 71 | 54 | 17 |
| | Baseline | 1.1 (0.4) | 1.1 (0.4) | 1.1 (0.3) |
| | Week 24 | 1.2 (0.3) | 1.2 (0.3) | 1.3 (0.3) |
| | Change | 0.1 (0.4) | 0.1 (0.4) | 0.2 (0.2) |
| | p | –[a] | –[a] | –[a] |
| LDL cholesterol, mmol/L | n | 72 | 55 | 17 |
| | Baseline | 3.3 (1.1) | 3.3 (1.2) | 3.3 (0.9) |
| | Week 24 | 3.0 (0.9) | 3.0 (0.9) | 3.0 (0.7) |
| | Change | −0.3 (0.8) | −0.3 (0.8) | −0.3 (0.8) |
| | p | –[a] | –[a] | –[a] |
| Body weight, kg | n | 279 | 203 | 76 |
| | Baseline | 62.8 (11.4) | 62.4 (11.8) | 63.7 (10.3) |
| | Week 24 | 63.9 (10.5) | 63.8 (10.8) | 64.2 (9.4) |
| | Change | 1.1 (3.5) | 1.3 (3.7) | 0.6 (3.2) |
| | p | <0.001 | <0.001 | –[a] |
| SBP, mmHg | n | 265 | 192 | 73 |
| | Baseline | 136.3 (21.1) | 136.2 (21.1) | 136.7 (21.1) |
| | Week 24 | 128.9 (14.6) | 129.3 (14.3) | 128.0 (15.6) |
| | Change | −7.4 (17.3) | −6.9 (17.8) | −8.7 (16.2) |
| | p | <0.001 | <0.001 | –[a] |

HDL, high-density lipoprotein; LDL, low-density lipoprotein; SBP, systolic blood pressure.
Baseline, Week-24 and change values are presented as mean (SD).
[a] p-value not reported since n < 100.

IAsp therapy. Furthermore, in spite of the clear reduction in pre-breakfast FPG ($p < 0.001$), there were no reported episodes of nocturnal hypoglycaemia at Week 24. These findings correlate with the safety profile of IAsp in published literature [7,9].

Yki-Järvinen [18] has noted that insulin-naive patients in poor glycaemic control but with a good response to insulin therapy are more likely to gain weight. In our subgroup, insulin-naive patients achieved mean $HbA_{1c}$ values of 7.6% (60 mmol/mol) at Week 24 with a mean weight gain of 1.3 kg.

Patient QoL is an important aspect of diabetes care. After 24 weeks of IAsp therapy, patients reported significant improvements in their QoL suggesting that the treatment was well-tolerated and the thrice-daily dosing pattern followed by the majority of patients did not interfere with their daily routines.

Certain limitations of this observational study design must be acknowledged such as the absence of a control group and the possibility that different methods of data collection were used across sites. Also, the recording of hypoglycaemia was based upon patient recollection of the event. However, this analysis provided useful insights into current clinical practice and patient characteristics in the ASEAN region. The 6-month study period was considered sufficient to indicate the treatment trend.

In conclusion, the results from this $A_1$chieve study sub-analysis demonstrated the safety and effectiveness of bolus IAsp therapy in a subgroup of T2D patients from the ASEAN region. Starting IAsp therapy in both insulin-naive and insulin-experienced patients was associated with marked improvements in blood glucose control and a decreased risk of hypoglycaemia. The poor levels of baseline glycaemic control and the lack of appropriate therapy intensification seen in this subgroup indicate the gap between prescribed T2D management strategies and actual practice. Promoting awareness regarding the therapeutic guidelines for T2D management among clinicians and patients remains a high priority. It is important to continue increasing efforts in this direction to ensure that clinical guidelines are uniformly

applied in order to prevent the risk of long-term diabetic morbidity and mortality.

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## Conflict of interest statement

Wan Mohamad Wan Bebakar received honorarium for conduct of research from Novo Nordisk. Dr. Anand B. Jain is employed by Novo Nordisk Pharma Malaysia. 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. 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. 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.

## REFERENCES

[1] Whiting DR, Guariguata L, Weil C, Shaw J. IDF diabetes atlas: global estimates of the prevalence of diabetes for 2011 and 2030. Diabetes Res Clin Pract 2011;94(3):311–21.
[2] International Diabetes Federation. IDF Diabetes Atlas, 5th edn. Brussels, Belgium: International Diabetes Federation, 2011.
[3] Nathan DM, Buse JB, Davidson MB, Heine RJ, Holman RR, Sherwin R, et al. Management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 2006;29:1963–72.
[4] Choi JH, Park CY, Cha BS, Kim IJ, Park TS, Park JY, et al. Perception of clinicians and diabetic patients on the importance of postprandial glucose control and diabetes education status: a cross sectional survey. Diabetes Metab J 2012;36(2):120–7.
[5] Sourij H, Schmoelzer I, de Campo A, Tripolt NJ, Stojakovic T, Scharnagl H, et al. Non-glycemic effects of insulin therapy: a comparison between insulin aspart and regular human insulin during two consecutive meals in patients with type 2 diabetes. Eur J Endocrinol 2011;165(2):269–74.
[6] Lindholm A, Jacobsen LV. Clinical pharmacokinetics and pharmacodynamics of insulin aspart. Clin Pharmacokinet 2001;40(9):641–59.
[7] Chapman TM, Noble S, Goa KL. Insulin aspart: a review of its use in the management of type 1 and 2 diabetes mellitus. Drugs 2002;62(13):1945–81.
[8] Rosenfalck AM, Thorsby P, Kjems L, Birkeland K, Dejgaard A, Hanssen KF, et al. Improved postprandial glycaemic control with insulin aspart in type 2 diabetic patients treated with insulin. Acta Diabetol 2000;37(1):41–6.
[9] Reynolds NA, Wagstaff AJ. Insulin aspart: a review of its use in the management of type 1 or 2 diabetes mellitus. Drugs 2004;64(17):1957–74.
[10] Mayfield JA, White RD. Insulin therapy for type 2 diabetes: rescue, augmentation, and replacement of beta-cell function. Am Fam Physician 2004;70(3):489–500.
[11] Krumholz HM. Outcomes research: generating evidence for best practice and policies. Circulation 2008;118(3):309–18.
[12] Paz-Pacheco E. Diabetes Clinical Practice Guidelines (CPGs) for the ASEAN region: Country initiatives for collectively enhanced diabetes care in the region. JAFES 2011;26(1): 36–7.
[13] Home P, Naggar NE, Khamseh M, Gonzalez-Galvez G, Shen C, Chakkarwar P, et al. An observational non-interventional study of patients with diabetes beginning or changed to insulin analogue therapy in non-Western countries: The $A_1$chieve study. Diabetes Res Clin Pract 2011;94:352–63.
[14] Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, et al. Management of hyperglycaemia in type 2 diabetes: a patient-centered approach. Position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetologia 2012;55(6):1577–96.
[15] Valensi P, Benroubi M, Borzi V, Gumprecht J, Kawamori R, Shaban J, et al.; IMPROVE Study Group Expert Panel. The IMPROVE study – a multinational, observational study in type 2 diabetes: baseline characteristics from eight national cohorts. Int J Clin Pract 2008;62(11):1809–19.
[16] UKPDS Group. Intensive blood glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998;352:837–53.
[17] Turner RC, Cull CA, Frighi V, Holman RR. Glycemic control with diet, sulfonylurea, metformin, or insulin in patients with type 2 diabetes mellitus: progressive requirement for multiple therapies (UKPDS 49). UK Prospective Diabetes Study (UKPDS) Group. JAMA 1999;281(21):2005–12.
[18] Yki-Järvinen H. Combination therapies with insulin in type 2 diabetes. Diabetes Care 2001;24(4):758–67.

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# Switching from biphasic human insulin to biphasic insulin aspart 30 in type 2 diabetes: Results from the ASEAN subgroup of the $A_1$chieve study

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ABSTRACT

*Aim*: To evaluate the safety and effectiveness of biphasic insulin aspart 30 (BIAsp 30) in ASEAN type 2 diabetes (T2D) patients switched from biphasic human insulin (BHI) in the non-interventional 24-week $A_1$chieve study.

*Methods*: Indonesian, Malaysian, Filipino and Singaporean patients switched from BHI to BIAsp 30 at their physicians' discretion were included. The incidence of serious adverse drug reactions (SADRs), including major hypoglycaemia was the primary endpoint. Changes in hypoglycaemia, glycated haemoglobin $A_{1c}$ ($HbA_{1c}$), fasting plasma glucose (FPG), postprandial plasma glucose (PPPG), lipids, body weight and systolic blood pressure were also evaluated. Quality of life (QoL) was measured using the EQ-5D questionnaire.

*Results*: For the 465 patients included (mean±SD age: 56±10.3 years, diabetes duration: 9.7±7.1 years, baseline $HbA_{1c}$: 9.4±1.8%), the mean pre-study BHI dose was 0.62±0.28 IU/kg and 63.4% were dosing BHI twice daily (*bid*). The mean baseline BIAsp 30 dose was 0.65±0.27 U/kg, titrated up to 0.71±0.28 U/kg over 24 weeks, and most patients continued *bid* dosing. No SADRs or major hypoglycaemic episodes were reported. The proportion of patients reporting overall hypoglycaemia decreased significantly from 10.8% at baseline to 3.4% at Week 24 ($p < 0.0001$). Significant improvements in glycaemic control were noted ($HbA_{1c}$: −1.4±1.7%, FPG: −56.7±72.5 mg/dL, post-breakfast PPPG: −84.8±82.8 mg/dL, $p < 0.001$). Mean QoL improved by +6.6±14.6 points ($p < 0.001$).

*Conclusion*: BIAsp 30 was well-tolerated and significantly increased glycaemic control in this ASEAN subgroup poorly controlled on BHI.



## 1. Introduction

The ASEAN countries, including Indonesia, Malaysia, Philippines and Singapore, have seen an alarming rise in the incidence of type 2 diabetes (T2D) over the recent decades [1]. The current prevalence of diabetes is 5.1% in Indonesia, 12.1% in Malaysia, 9.7% in Philippines and 12.45% in Singapore as estimated by the International

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Diabetes Federation. Moreover, Indonesia, Malaysia and Philippines are ranked among the top ten countries by number of diabetes cases in the Western Pacific region. The escalation in the disease burden is directly linked to decreased physical activity, urbanization, dietary transition and increased obesity [2].

With the progressive deterioration of beta-cell function over time, regular testing of blood glucose levels, timely dose titration and appropriate intensification of therapies are essential to maintain near-normal glycaemia in T2D [3]. In the absence of such precautionary measures, T2D patients are at higher risk of developing long-term vascular complications [4]. However, intensification is often delayed in routine clinical practice due to fears of hypoglycaemia and weight gain that may result from high insulin doses [5].

Premixed insulins or biphasic insulins were developed to provide suitable pre-meal and post-meal insulin levels through a combination of fast- and intermediate-acting insulins [6]. However, biphasic human insulin (BHI) is associated with a slow onset of action that necessitates timing injections 30 minutes prior to meals, which may be difficult for patients with varying schedules. In addition, BHI does not adequately control postprandial glucose excursions and patients are at greater risk of hypoglycaemia in case of a delay in the meal timing [7].

Biphasic insulin aspart 30 (BIAsp 30) is a modern premixed analogue that has been found to reach higher serum levels with a shorter time to attain maximum concentration compared to BHI [8]. These enhanced pharmacokinetic properties of BIAsp 30 allow better postprandial glucose (PPPG) control with this formulation compared to BHI. Due to its rapid-acting aspart component, BIAsp 30 can also be injected closer to mealtimes compared to BHI [9]. Transferring patients on BHI therapy to BIAsp 30 is known to be associated with improved PPPG control and decreased nocturnal hypoglycaemia [6].

In a sub-analysis of the international, non-interventional $A_1$chieve study [10], the clinical safety and effectiveness of switching from BHI to BIAsp 30 in patients with T2D was examined [11]. We investigated the safety and effectiveness of BIAsp 30 in T2D patients from Indonesia, Malaysia, Philippines and Singapore, previously treated with BHI. This subgroup analysis also aimed to obtain a perspective on the current standards of T2D care in local outpatient settings in the ASEAN region.

## 2. Materials and Methods

### 2.1. Study design

$A_1$chieve was an open-label, multinational, 24-week, non-interventional study that evaluated the clinical safety and effectiveness of BIAsp 30 (NovoMix® 30, Novo Nordisk A/S, Denmark), insulin detemir (Levemir®, Novo Nordisk A/S, Denmark) and insulin aspart (NovoRapid®, Novo Nordisk A/S, Denmark), in T2D patients in routine clinical practice [10]. Overall study results are available under www.A1chieve.com. Here, we evaluated the clinical safety and effectiveness of BIAsp 30 in patients from Indonesia, Malaysia, Philippines and Singapore, previously treated with BHI.

All decisions related to the dose and administration frequency of BIAsp 30 and concomitant oral glucose-lowering drugs (OGLDs) were left to the attending physicians. Data were collected at each visit from the physicians' notes and the patients' recall and self-monitoring diaries and blood glucose meters. The physicians performed all study assessments.

### 2.2. Study patients

This ASEAN subgroup consisted of T2D patients enrolled between October 2009 and December 2010 at 359 centers across Indonesia, Malaysia, Philippines and Singapore who were switched from BHI to BIAsp 30 therapy by their physicians. Patients who had received treatment with any of the study insulin analogues (alone or in combination) for over 4 weeks prior to baseline were not eligible for study participation. Women who were pregnant, breast-feeding or intended to become pregnant were also excluded. All patients provided signed informed consent. Ethics committee approval was obtained for the countries involved (Indonesia, Malaysia, Philippines and Singapore).

The investigators were trained in the study protocol, CRF completion, informed consent and safety reporting procedures.

### 2.3. Assessments and outcome measures

The primary objective was to evaluate the clinical safety of BIAsp 30 based on the number of serious adverse drug reactions (SADRs), including major hypoglycaemic events, recorded from baseline to Week 24. The secondary safety assessments comprised changes in the number of hypoglycaemic events (overall, major, minor and nocturnal), and serious adverse events (SAEs). The effectiveness assessments comprised change from baseline to Week 24 in $HbA_{1c}$, FPG, PPPG, body weight, blood lipids and systolic blood pressure (SBP). Quality of life (QoL) at baseline and Week 24 was assessed using the EQ-5D questionnaire. Local laboratories performed the laboratory measurements according to local standardization and quality control procedures.

### 2.4. Statistical methods

Statistical analyses were performed for the ASEAN subgroup of patients switching from BHI to BIAsp 30. Discrete and continuous variables were summarised using frequency tables (n, %) and descriptive statistics, respectively.

Paired t-tests were used to analyze the change from baseline to Week 24 in $HbA_{1c}$, FPG, PPPG, body weight, blood lipids, SBP and QoL, while McNemar's paired test was used to analyze the change in the proportion of patients reporting at least one hypoglycaemic event from baseline to Week 24. P-values are not presented when the number of patients analysed was less than 100.

Novo Nordisk performed all data analyses using SAS (Version 9.1.3).

## 3. Results

### 3.1. General characteristics

A total of 465 patients recruited from the ASEAN region switched treatment from BHI to BIAsp 30. The demographic and baseline characteristics of this subgroup are reported in Table 1.

**Table 1 – Demographic and baseline characteristics of patients switching from BHI to BIAsp 30**

| Characteristic | All patients (N = 465) |
|---|---|
| Gender (male/female), % | 50.5/49.5 |
| Age, years | 56.0 (10.3) |
| Body weight, kg | 66.6 (13.6) |
| Body mass index, kg/m$^2$ | 25.6 (4.8) |
| Duration of diabetes, years | 9.7 (7.1) |
| Time to insulin initiation, years | 7.2 (6.1) |
| Duration on OGLDs, years | 8.1 (6.6) |
| Duration on insulin, years | 2.5 (2.7) |
| $HbA_{1c}$, % | 9.4 (1.8) |
| $HbA_{1c}$, mmol/mol | 79 (20) |
| OGLDs at baseline, n (%) | |
| Metformin | 243 (86.8) |
| Sulfonylureas | 45 (16.1) |
| Alpha-glucosidase inhibitors | 29 (10.4) |
| 1 OGLD | 216 (77.1) |
| 2 OGLDs | 54 (19.3) |
| >2 OGLDs | 10 (3.6) |

BHI, biphasic human insulin; BIAsp 30, biphasic insulin aspart 30; OGLD(s), oral glucose-lowering drug(s).
Data are mean (SD) unless specified otherwise.

At baseline, the mean (±SD) age was 56.0±10.3 years and the mean body mass index (BMI) was 25.6±4.8 kg/m$^2$. The mean diabetes duration was 9.7±7.1 years and the mean $HbA_{1c}$ level was 9.4±1.8% (79±20 mmol/mol). The most common physicians' reasons for switching from BHI to BIAsp 30 were to improve glycaemic control (92.7%), try new insulin (52.5%) and reduce plasma glucose variability (42.2%).

Pre-study, the majority of patients (72.3%) used 1 OGLD and the most common OGLD used was metformin (85.3%). At baseline, the majority of patients (77.1%) continued using 1 OGLD with metformin use (86.8%) predominating.

### 3.2. SADRs and SAEs

No SADRs were reported during the study. A total of 2 serious adverse events (SAEs) were reported in 1 patient. Both SAEs were considered unlikely to be related to BIAsp 30.

### 3.3. Hypoglycaemia

After 24 weeks of BIAsp 30 therapy, the event rate of overall hypoglycaemia appeared to decrease from 3.33 to 0.72 events/patient-year (Table 2). Correspondingly, the proportion of patients reporting overall hypoglycaemia decreased from 10.8% at baseline to 3.4% at Week 24 ($p < 0.0001$, Table 2). No major hypoglycaemic events were reported during the study.

**Table 2 – Baseline and 24-week data for hypoglycaemia**

| Hypoglycaemia | Events per patient-year / percent with at least one event | | |
|---|---|---|---|
| | Baseline | Week 24 | p-value |
| Overall | 3.33 / 10.8 | 0.72 / 3.4 | <0.0001 |
| Nocturnal | 1.29 / 5.4 | 0.19 / 1.0 | <0.0001 |
| Major | 0.39 / 1.5 | 0.0 / 0.0 | 0.0143 |
| Minor | 2.94 / 10.3 | 0.72 / 3.4 | <0.0001 |

p-values are from McNemar's test on paired proportions of patients experiencing hypoglycaemia.

The event rates for nocturnal and minor hypoglycaemia also appeared to reduce with a statistically significant decrease in the proportion of patients reporting these events at Week 24 compared to baseline ($p < 0.0001$, Table 2).

### 3.4. Insulin dose and blood glucose lowering

Pre-study, the mean BHI dose was 0.62±0.28 IU/kg (Table 3). The mean BIAsp 30 dose was 0.65±0.27 U/kg at baseline,

**Table 3 – Insulin dose and dosing frequency pre-study, at baseline and at Week 24**

| | | All patients |
|---|---|---|
| Insulin dose, U/day | n | 465 |
| | Pre-study[a] | 41.3 (19.9) |
| | Baseline | 43.2 (19.1) |
| | Week 24 | 47.3 (20.3) |
| Insulin dose, U/kg | n | 453 |
| | Pre-study[b] | 0.62 (0.28) |
| | Baseline | 0.65 (0.27) |
| | Week 24 | 0.71 (0.28) |
| Dose frequency, n (%) | Pre-study (n) | 462 |
| | Once daily | 157 (34.0) |
| | Twice daily | 293 (63.4) |
| | Thrice daily | 12 (2.6) |
| | >Thrice daily | – |
| | Baseline (n) | 465 |
| | Once daily | 7 (1.5) |
| | Twice daily | 290 (62.4) |
| | Thrice daily | 156 (33.5) |
| | >Thrice daily | 12 (2.6) |
| | Week 24, n | 414 |
| | Once daily | 12 (2.9) |
| | Twice daily | 361 (87.2) |
| | Thrice daily | 37 (8.9) |
| | >Thrice daily | 4 (1.0) |

Pre-study, baseline and Week 24 values are presented as mean (SD) unless specified otherwise.
[a] IU/day pre-study.
[b] IU/kg pre-study.

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

| | n | Baseline | Week 24 | Change | p-value |
|---|---|---|---|---|---|
| $HbA_{1c}$, % | 182 | 9.4 (1.8) | 8.0 (1.6) | −1.4 (1.7) | <0.001 |
| $HbA_{1c}$, mmol/mol | 182 | 79 (20) | 64 (17) | −15 (19) | NA |
| FPG, mg/dL | 328 | 190.9 (70.4) | 134.1 (42.6) | −56.7 (72.5) | <0.001 |
| PPPG, mg/dL | 202 | 264.5 (84.2) | 179.7 (49.5) | −84.8 (82.8) | <0.001 |

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

**Table 5 – Baseline and 24-week data for blood lipids, body weight and SBP**

| | n | Baseline | Week 24 | Change | p-value |
|---|---|---|---|---|---|
| Total cholesterol, mmol/L | 121 | 5.2 (1.5) | 4.9 (1.1) | −0.3 (1.5) | 0.074 |
| Triglycerides, mmol/L | 111 | 1.8 (0.9) | 1.7 (0.9) | −0.1 (0.9) | 0.158 |
| HDL cholesterol, mmol/L | 99 | 1.2 (0.4) | 1.3 (0.3) | 0.1 (0.4) | –[a] |
| LDL cholesterol, mmol/L | 98 | 3.1 (1.2) | 2.9 (0.9) | −0.1 (1.1) | –[a] |
| Body weight, kg | 384 | 65.8 (12.7) | 66.5 (12.4) | 0.7 (4.2) | 0.002 |
| SBP, mmHg | 374 | 131.3 (16.6) | 128.8 (15.4) | −2.6 (16.7) | 0.003 |

HDL, high-density lipoprotein; LDL, low-density lipoprotein; SBP, systolic blood pressure.
Baseline, Week-24 and change values are mean (SD).
[a] p-value not reported since n < 100.

titrated up to 0.71±0.28 U/kg at Week 24. In total, 63.4% of patients injected BHI twice daily (*bid*) pre-study, while 62.4% and 87.2% injected BIAsp 30 *bid* at baseline and Week 24, respectively (Table 3).

Statistically significant reductions were noted in the mean $HbA_{1c}$ (−1.4±1.7%/−15±19 mmol/mol), FPG (−56.7±72.5 mg/dL) and post-breakfast PPPG (−84.8±82.8 mg/dL) levels following the therapy switch from BHI to BIAsp 30 ($p < 0.001$, Table 4). The number of patients achieving the $HbA_{1c}$ target of <7.0% (<53 mmol/mol) was 78 (32.6%) at Week 24 compared to 12 (4.6%) at baseline.

### 3.5. Body weight, lipids and blood pressure control

The mean body weight increased by 0.7±4.2 kg from baseline to Week 24 ($p = 0.002$, Table 5) after switching from BHI to BIAsp 30.

There were no statistically significant changes in the mean total cholesterol and triglyceride levels at the end of the study (Table 5). The mean change from baseline to Week 24 in LDL cholesterol levels was −0.1±1.1 mmol/L, while the mean HDL cholesterol levels appeared to increase by 0.1±0.4 mmol/L.

The mean SBP decreased by −2.6±16.7 mmHg from 131.3±16.6 mmHg at baseline to 128.8±15.4 at the end of the study ($p = 0.003$, Table 5).

### 3.6. Quality of life

Health-related QoL improved from 73.4±16.1 at baseline to 80.0±11.2 at Week 24 (mean change: +6.6±14.6 points, $p < 0.001$) on the visual analogue scale of the EQ-5D questionnaire.

## 4. Discussion

This analysis demonstrated the safety and effectiveness of BIAsp 30 therapy in a subgroup of ASEAN patients previously treated with BHI. No SADRs or major hypoglycaemic episodes were reported in this subgroup during the study. Significantly fewer patients reported overall, nocturnal and minor hypoglycaemia at Week 24 compared to baseline showing that the therapy change was well-tolerated and concurring with the results from other non-interventional studies investigating the effects of switching from BHI to BIAsp 30 [11,12].

Poor metabolic and glycaemic control has been observed in the majority of the T2D patients in local clinical practice in the ASEAN region signaling a failure in translating treatment guidelines into real-life practice [1,13–15]. In the DiabCare Asia study conducted in 1998 and 2008, the mean glycated haemoglobin $A_{1c}$ ($HbA_{1c}$) levels were ⩾8.0% (⩾64 mmol/mol) in Malaysia, Singapore and Indonesia [13–15], although the American Diabetes Association (ADA) recommends intensifying treatment when $HbA_{1c}$ is ⩾7.0% (⩾53 mmol/mol) [16]. In this ASEAN subgroup, marked hyperglycaemia was observed at baseline (mean $HbA_{1c}$: 9.4±1.8% [79±20 mmol/mol], FPG: 190.9±70.4 mg/dL and PPPG: 264.5±84.2 mg/dL).

The majority of patients followed BIAsp 30 *bid* dosing at baseline and Week 24. The proportion of patients who reached the ADA target $HbA_{1c}$ level of <7.0% (<53 mmol/mol) was 32.6% at Week 24, comparable to the results from the overall $A_1$chieve switch cohort (33.6%) [11].

At Week 24, mean $HbA_{1c}$ had improved by −1.4±1.7% (−15±19mmol/mol) and the mean FPG and PPPG also decreased in the ASEAN subgroup. These data support

the results from the overall $A_1$chieve switch cohort and the IMPROVE and PRESENT observational studies, where switching from BHI to BIAsp 30 also led to significant improvements in blood glucose levels [11,12,17]. However, although the reductions were statistically significant, the mean values at Week 24 for $HbA_{1c}$ and FPG did not meet the ranges recommended jointly by the ADA and the European Association for the Study of Diabetes [3]. This could be due in part to the high baseline levels. Also, the associated mean dose increase over 24 weeks was small in the ASEAN subgroup (0.65 U/kg at baseline to 0.71 U/kg at Week 24). The 24-week study duration was considered adequate to evaluate the response to therapy change; however, with more aggressive titration, continued monitoring of glycaemic levels over a longer period and possible intensification to BIAsp 30 three times daily (*tid*), it is likely that the target $HbA_{1c}$, FPG and PPPG ranges may be achieved. In fact, in the 1-2-3 study, Garber et al. [18] reported that intensification to BIAsp 30 *tid* after 16 weeks on a *bid* dosing regimen enabled a greater proportion of patients to reach target $HbA_{1c}$ levels.

The mean body weight increased by 0.7 kg in the ASEAN subgroup, similar to the mean increase in the East Asia switch cohort (0.6 kg) of the $A_1$chieve study [9]. Significant improvements in QoL were noted following the switch to BIAsp 30 from BHI, perhaps related to the more convenient dosing options available with this insulin analogue [7].

This study was observational in nature with no control arm and may have been subject to a recall bias in the recording of hypoglycaemic events owing to retrospective data collection methods. It is also possible that data collection may not have occurred consistently across sites. However, the laboratory measurements were performed following local standardization and quality control procedures. Also importantly, the data obtained from this study could form part of an evidence base, together with the data from randomized clinical trials, which would help inform local clinical practice guidelines.

In conclusion, transferring ASEAN T2D patients from BHI to BIAsp 30 therapy was associated with improved glycaemic control and a decreased risk of hypoglycaemia in this sub-analysis of the non-interventional $A_1$chieve study. The baseline data obtained from the patients in this ASEAN subgroup corroborated the urgent need to revisit clinical practice guidelines in this region. Greater adherence to the recommended guidelines needs to be ensured so that the quality of diabetes care in local clinical practice can be optimized.

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## Conflict of interest statement

Zanariah Hussein received honorarium for conduct of research from Novo Nordisk. Dr. Anand B. Jain is employed by Novo Nordisk Pharma Malaysia. Su Yen Goh 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. 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. 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.

## REFERENCES

[1] Paz-Pacheco E. Diabetes Clinical Practice Guidelines (CPGs) for the ASEAN region: Country initiatives for collectively enhanced diabetes care in the region. JAFES 2011;26(1): 36–7.
[2] Whiting DR, Guariguata L, Weil C, Shaw J. IDF diabetes atlas: global estimates of the prevalence of diabetes for 2011 and 2030. Diabetes Res Clin Pract 2011;94(3):311–21.
[3] Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, et al. Management of hyperglycaemia in type 2 diabetes: a patient-centered approach. Position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetologia 2012;55(6):1577–96.
[4] Stratton IM, Adler AI, Neil HA, Matthews DR, Manley SE, Cull CA, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. BMJ 2000;32:405–12.
[5] Campbell RK. Recommendations for improving adherence to type 2 diabetes mellitus therapy – focus on optimizing insulin-based therapy. Am J Manag Care 2012;18(Suppl 3): S55–61.
[6] Liebl A, Prusty V, Valensi P, Kawamori R, Christiansen JS, Palmer AJ. Ten years of experience with biphasic insulin aspart 30: from drug development to the latest clinical findings. Drugs 2012;72(11):1495–520.
[7] Heller S. Reducing hypoglycaemia with insulin analogues Int J Obes Relat Metab Disord 2002;26(Suppl 3):S31–6.
[8] Heise T, Heinemann L, Hövelmann U, Brauns B, Nosek L, Haahr HL. Biphasic insulin aspart 30/70: pharmacokinetics and pharmacodynamics compared with once-daily biphasic human insulin and basal–bolus therapy. Diabetes Care 2009;32(8):1431–3.

[9] Garber AJ, Ligthelm R, Christiansen JS, Liebl A. Premixed insulin treatment for type 2 diabetes: analogue or human? Diabetes Obes Metab 2007;9(5):630–9.
[10] Home P, Naggar NE, Khamseh M, Gonzalez-Galvez G, Shen C, Chakkarwar P, et al. An observational non-interventional study of patients with diabetes beginning or changed to insulin analogue therapy in non-Western countries: The $A_1$chieve study. Diabetes Res Clin Pract 2011;94:352–63.
[11] Naggar NK, Soewondo P, Khamseh ME, Chen JW, Haddad J. Switching from biphasic human insulin 30 to biphasic insulin aspart 30 in type 2 diabetes is associated with improved glycaemic control and a positive safety profile: Results from the $A_1$chieve study. Diabetes Res Clin Pract 2012;98(3):408–13.
[12] Shah S, Benroubi M, Borzi V, Gumprecht J, Kawamori R, Shaban J, et al.; IMPROVE Study Group Expert Panel. Safety and effectiveness of biphasic insulin aspart 30/70 (NovoMix 30) when switching from human premix insulin in patients with type 2 diabetes: subgroup analysis from the 6-month IMPROVE observational study. Int J Clin Pract 2009;63(4):574–82.
[13] Mafauzy M, Hussein Z, Chan SP. The status of diabetes control in Malaysia: results of DiabCare 2008. Med J Malaysia 2011;66(3):175–81.
[14] Lee WR, Lim HS, Thai AC, Chew WL, Emmanuel S, Goh LG, et al.; Diabcare Singapore Local Working Group & Diabetic Society of Singapore. A window on the current status of diabetes mellitus in Singapore – the Diabcare-Singapore 1998 study. Singapore Med J 2001;42(11):501–7.
[15] Soewondo P, Soegondo S, Suastika K, Pranoto A, Soeatmadji DW, Tjokroprawiro A. The DiabCare Asia 2008 study – Outcomes on control and complications of type 2 diabetic patients in Indonesia. Med J Indones 2010;19:235–44.
[16] Nathan DM, Buse JB, Davidson MB, Heine RJ, Holman RR, Sherwin R, et al. Management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 2006;29:1963–72.
[17] Shestakova M, Sharma SK, Almustafa M, Min KW, Ayad N, Azar ST, et al. Transferring type 2 diabetes patients with uncontrolled glycaemia from biphasic human insulin to biphasic insulin aspart 30: experiences from the PRESENT study. Curr Med Res Opin 2007;23(12):3209–14.
[18] Garber AJ, Wahlen J, Wahl T, Bressler P, Braceras R, Allen E, et al. Attainment of glycaemic goals in type 2 diabetes with once-, twice-, or thrice-daily dosing with biphasic insulin aspart 70/30 (The 1-2-3 study). Diabetes Obes Metab 2006;8(1):58–66.

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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 $A_1$chieve study

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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 $A_1$chieve 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 ± SD: 52.3±12.2 years; body mass index: 25.6±3.3 kg/m$^2$) with a mean diabetes duration of 9.5±5.5 years and mean duration on insulin of 2.5±2.4 years were included. The mean BIAsp 30 dose was 0.49±0.20 U/kg at baseline and 0.47±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±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±12.9 points).

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



## 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 $\geqslant$7.0% ($\geqslant$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 $A_1$chieve 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

$A_1$chieve 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 $HbA_{1c}$, the proportion of patients who achieved target $HbA_{1c}$, 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/m$^2$ 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. SADRs, SAEs and hypoglycaemia

No SADRs, 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 SADRs or SAEs 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±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 $A_1$chieve 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.

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## 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.

## REFERENCES

[1] Bhowmik B, Binte Munir S, Ara Hossain I, Siddiquee T, Diep LM, Mahmood S, et al. Prevalence of type 2 diabetes and impaired glucose regulation with associated cardiometabolic risk factors and depression in an urbanizing rural community in Bangladesh: a population-based cross-sectional study. Diabetes Metab J 2012;36(6):422–32.

[2] Bleich SN, Koehlmoos TL, Rashid M, Peters DH, Anderson G. Noncommunicable chronic disease in Bangladesh: overview of existing programs and priorities going forward. Health Policy 2011;100(2–3):282–9.

[3] Whiting DR, Guariguata L, Weil C, Shaw J. IDF diabetes atlas: global estimates of the prevalence of diabetes for 2011 and 2030. Diabetes Res Clin Pract 2011;94(3):311–21.

[4] Saquib N, Saquib J, Ahmed T, Khanam MA, Cullen MR. Cardiovascular diseases and type 2 diabetes in Bangladesh: a systematic review and meta-analysis of studies between 1995 and 2010. BMC Public Health 2012;12:434.

[5] UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998;352(9131):837–53.

[6] Stratton IM, Adler AI, Neil HA, Matthews DR, Manley SE, Cull CA, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. BMJ 2000;32:405–12.

[7] Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, et al. Management of hyperglycaemia in type 2 diabetes: a patient-centered approach. Position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetologia 2012;55(6):1577–96.

[8] Latif ZA, Jain A, Rahman MM. Evaluation of management, control, complications and psychosocial aspects of diabetics in Bangladesh: DiabCare Bangladesh 2008. Bangladesh Med Res Counc Bull 2011;37(1):11–6.

[9] Swinnen SG, Hoekstra JB, DeVries JH. Insulin therapy for type 2 diabetes. Diabetes Care 2009;32(Suppl 2):S253–9.

[10] Evans M, Schumm-5raeger PM, Vora J, King AB. A review of modern insulin analogue pharmacokinetic and pharmacodynamic profiles in type 2 diabetes: improvements and limitations. Diabetes Obes Metab 2011;13(8):677–84.

[11] Halimi S, Raskin P, Liebl A, Kawamori R, Fulcher G, Yan G. Efficacy of biphasic insulin aspart in patients with type 2 diabetes. Clin Ther 2005;27(Suppl B):S57–74.

[12] Davidson J, Vexiau P, Cucinotta D, Vaz J, Kawamori R. Biphasic insulin aspart 30: literature review of adverse events associated with treatment. Clin Ther 2005;27(Suppl B):S75–88.

[13] Home P, Naggar NE, Khamseh M, Gonzalez-Galvez G, Shen C, Chakkarwar P, et al. An observational non-interventional study of patients with diabetes beginning or changed to insulin analogue therapy in non-Western countries: The $A_1$chieve study. Diabetes Res Clin Pract 2011;94:352–63.

[14] Naggar NK, Soewondo P, Khamseh ME, Chen JW, Haddad J. Switching from biphasic human insulin 30 to biphasic insulin aspart 30 in type 2 diabetes is associated with improved glycaemic control and a positive safety profile: Results from the $A_1$chieve study. Diabetes Res Clin Pract 2012;98(3):408–13.

[15] Shah S, Benroubi M, Borzi V, Gumprecht J, Kawamori R, Shaban J, et al.; IMPROVE Study Group Expert Panel. Safety and effectiveness of biphasic insulin aspart 30/70 (NovoMix 30) when switching from human premix insulin in patients with type 2 diabetes: subgroup analysis from the 6-month IMPROVE observational study. Int J Clin Pract 2009;63(4):574–82.

[16] Shestakova M, Sharma SK, Almustafa M, Min KW, Ayad N, Azar ST, et al. Transferring type 2 diabetes patients with uncontrolled glycaemia from biphasic human insulin to biphasic insulin aspart 30: experiences from the PRESENT study. Curr Med Res Opin 2007;23(12):3209–14.

[17] Khanam PA, Mahtab H, Ahmed AU, Sayeed MA, Khan AKA. In Bangladesh diabetes starts earlier now than 10 years back: a BIRDEM study. Ibrahim Med Coll J 2008;2:1–3.

[18] Swinnen SG, Dain MP, Mauricio D, DeVries JH, Hoekstra JB, Holleman F. Continuation versus discontinuation of insulin secretagogues when initiating insulin in type 2 diabetes. Diabetes Obes Metab 2010;12(10):923–5.

[19] Liebl A, Prusty V, Valensi P, Kawamori R, Christiansen JS, Palmer AJ, et al. Ten years of experience with biphasic insulin aspart 30: from drug development to the latest clinical findings. Drugs 2012;72(11):1495–520.

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# Safety and effectiveness of biphasic insulin aspart 30 in type 2 diabetes patients switched from biphasic human insulin 30: Results from the Filipino cohort of the $A_1$chieve study

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ABSTRACT

*Aim*: To evaluate the safety and effectiveness of biphasic insulin aspart 30 (BIAsp 30) in Filipino patients with type 2 diabetes previously treated with biphasic human insulin 30 (BHI 30).

*Methods*: Safety and effectiveness outcomes were measured in all patients switching from BHI 30 to BIAsp 30 in the Filipino cohort of the 24-week, multinational, prospective, non-interventional $A_1$chieve study.

*Results*: A total of 111 Filipino patients (mean age ± SD, 57.4±12.8 years; BMI, 25.8±5.6 kg/m$^2$) with mean diabetes duration of 9.9±7.1 years switched therapy from BHI 30 to BIAsp 30. The mean pre-study BHI 30 dose was 0.65±0.28 IU/kg and the baseline BIAsp 30 dose was 0.65±0.26 U/kg titrated up to 0.70±0.26 U/kg by Week 24. No serious adverse drug reactions were reported. Overall hypoglycaemia was reduced from 5.62 to 1.98 events/patient-year. Minor and nocturnal hypoglycaemia decreased and no major hypoglycaemia was reported at Week 24. Glucose control improved from baseline to Week 24 ($HbA_{1c}$, −2.2±2.1% [24±23 mmol/mol]; FPG, −72.0±71.8 mg/dL; PPPG, −145.5±125.4 mg/dL). A total of 24 patients achieved $HbA_{1c}$ levels <7.0% at Week 24 compared to 6 patients reporting this target at baseline. Quality of life was positively impacted at Week 24 (change in visual analogue scores, 15.3±16.9 points).

*Conclusion*: Switching from BHI 30 to BIAsp 30 improved glycaemic control without increasing the risk of hypoglycaemia.



## 1. Introduction

In 2012, Philippines reported a diabetes prevalence of 8.2% according to a recent report released by the International Diabetes Federation. This figure also places Philippines among the top 10 countries by diabetes cases in the Western Pacific region [1]. By the year 2030, more than 7.4 million Filipinos are expected to be living with diabetes [2]. A 9-year cohort study in the Philippines provided evidence for an alarming increase in the pre-diabetes indicators, impaired fasting glucose levels and impaired glucose tolerance, thus implying a critical need for early aggressive interventions for diabetes prevention and control [3]. In the Philippines, incomplete or incorrect self-medication and selective

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compliance to medical advice is highly prevalent, acting as a potential barrier to adequate T2D management [4].

The American Diabetes Association recommends an $HbA_{1c}$ target level <7.0% (53 mmol/mol) that is achieved by maintaining fasting plasma glucose (FPG) at 130 mg/dL and postprandial plasma glucose at 180 mg/dL (PPPG) [5]. However, it has been observed in several large observational studies that baseline glycaemic control is poor among people with type 2 diabetes (T2D) [6–8]. Early intensification of insulin is strongly recommended for this chronic debilitating condition but negative perceptions of hypoglycaemia, weight gain and impaired quality of life (QoL) often govern non-compliance to insulin therapy [9]. Furthermore, the variability in the pharmacological profile of human insulin preparations, such as biphasic human insulin 30 (BHI 30) results in unpredictable effects on glycaemic control [10]. Biphasic insulin aspart 30 (BIAsp 30) is a new generation insulin analogue that was designed to provide a more stable glycaemic control pattern. BIAsp 30 is a dual release formulation containing 30% soluble and 70% protamine-crystallized insulin aspart that offers the convenience of both prandial and basal coverage in a single injection [11,12]. Previously, a number of trials have established the superiority of glycaemic control with BIAsp 30 when compared to BHI 30 [13–16]. The glycaemic objectives were met with BIAsp 30 therapy resulting in similar or improved incidence of hypoglycaemia or weight gain [13–16]. Observational studies, PRESENT and IMPROVE, have also provided similar data in heterogeneous cohorts worldwide that switched therapy from BHI 30 to BIAsp 30 [7,8].

A recent evaluation of diabetes management in Philippines indicated that diabetes care is restricted to specialized centers with loopholes in the referral systems and diagnostic tools. Patient adherence to treatment was also affected due to lack of drug availability as well as patient education [17]. Also, public health insurance schemes and decentralized health systems did not encourage access to diabetes care [4]. Furthermore, due to a scarcity in regional study data, the clinical practice guidelines are based on North American standards that do not reflect the local standards [18]. The multinational $A_1$chieve study [6] was conducted primarily to throw light on local diabetes management and address the clinical benefits of insulin analogues in routine clinical practice. The overall study results are available online under www.A1chieve.com. In this sub-analysis, the clinical safety and effectiveness of BIAsp 30 was evaluated in a Filipino cohort of the $A_1$chieve study that switched treatment from BHI 30.

## 2. Methods

### 2.1. Study design

$A_1$chieve [6] was a 24-week, international, prospective, multicentre, non-interventional study to evaluate the safety and effectiveness of BIAsp 30 (NovoMix 30®, Novo Nordisk), insulin detemir (Levemir®, Novo Nordisk) and insulin aspart (NovoRapid®, Novo Nordisk), alone or in combination with oral glucose-lowering drugs (OGLDs) in T2D patients from developing countries. This sub-analysis was conducted to evaluate the clinical benefits of BIAsp 30 in T2D patients from Philippines who were previously on BHI 30 therapy. Patients were recruited between January 2010 and December 2010 at 255 sites across the Philippines. The switch from BHI 30 to BIAsp 30 and subsequent changes in dose or frequency of administration was mutually agreed upon by the patients and their respective consulting physicians. Due to the observational study design, there were no defined study procedures. All assessments were made by the physicians as a part of routine clinical care. The study drug was commercially available and administered in accordance with local regulations.

### 2.2. Patients

All T2D patients recruited from Philippines that switched therapy from BHI 30 to BIAsp 30 were included in the sub-analysis. The concurrent use of OGLDs was permitted in all patients during the course of the study at the discretion of the physician. Patients who were administered any of the study insulin analogues up to 4 weeks prior to enrollment were excluded. Pregnant women and women who were breast-feeding or had the intention of becoming pregnant were not eligible for study participation. All patients signed informed consent to participate in the study and this study was approved by the local ethics committee of Philippines.

### 2.3. Outcome measures and assessments

The primary safety outcome 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 and serious adverse events (SAEs). The effectiveness outcomes included the change from baseline to final visit in $HbA_{1c}$, FPG, PPPG, body weight, lipid profile and systolic blood pressure (SBP). Health-related quality of life (QoL) was evaluated using the EQ-5D questionnaire that assesses mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Subsequently, the current QoL was measured using a standard 20 cm visual analogue scale (VAS, 0–100). All laboratory parameters were subject to local standardization and were National Glycohemoglobin Standardization Program-certified.

### 2.4. Statistical analyses

Continuous and discrete variables were summarized using descriptive statistics and frequency tables (n [%]), respectively. Due to the small sample size, all comparisons are presented descriptively. All data were analyzed by Novo Nordisk using SAS Version 9.1.3.

## 3. Results

### 3.1. Patient characteristics

A total of 111 T2D patients in Philippines switched from BHI 30 to BIAsp 30 therapy. The demographic and baseline characteristics of this cohort are reported in Table 1. The average T2D duration in this cohort was 9.9±7.1 years and the duration on prior insulin therapy was 2.7±3.5 years. In 93.7% patients, the physicians decided to switch to BIAsp 30 in order to improve glycaemic control. Other common reasons for initiating BIAsp 30 were to reduce the risk of hypoglycaemia in 42.3% patients and to reduce plasma glucose variability in 39.6% patients.

**Table 1 – Baseline demographics and characteristics**

| Parameters | Entire cohort (n = 111) |
|---|---|
| Gender (male/female), % | 43.2/56.8 |
| Age, years | 57.4 (12.8) |
| Body weight, kg | 65.4 (13.9) |
| BMI, kg/m$^2$ | 25.8 (5.6) |
| Diabetes duration, years | 9.9 (7.1) |
| Duration on prior insulin therapy, years | 2.7 (3.5) |
| $HbA_{1c}$, % | 9.4 (2.4) |
| $HbA_{1c}$, mmol/mol | 79 (26) |
| Prior OGLDs, n (%) | |
| Metformin | 72 (91.1) |
| Sulfonylureas | 23 (29.1) |
| Thiazolidinediones | 13 (16.5) |
| 1 OGLD | 47 (59.5) |
| 2 OGLDs | 26 (32.9) |
| >2 OGLDs | 6 (7.6) |

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

### 3.2. Insulin dose

The insulin dose and frequency of administration are reported in Table 2. The pre-study BHI 30 dose was 0.65±0.28 IU/kg and the baseline BIAsp 30 dose was 0.65±0.26 U/kg titrated up to 0.70±0.26 U/kg at Week 24. The majority of patients received insulin twice-daily (*bid*) pre-study (92.8% patients), at baseline (88.3% patients) and at Week 24 (88.0% patients).

### 3.3. SADRs and SAEs

No SADRs or SAEs were reported throughout the study duration in patients that switched to BIAsp 30 therapy.

### 3.4. Hypoglycaemia

Overall hypoglycaemia decreased from 5.62 to 1.98 events/patient-year with a corresponding decrease from 14.4% to 8.7% in the proportion of patients affected. No major hypoglycaemia was reported at Week 24. From baseline to Week 24, minor hypoglycaemia decreased from 4.33 to 1.98 events/patient-year and nocturnal hypoglycaemia decreased from 2.23 to 0.85 events/patient-year (Table 3).

**Table 2 – Insulin dose and frequency**

| Parameter | | Entire cohort |
|---|---|---|
| Insulin dose per day | n = 111 | |
| | Pre-study, IU/day[a] | 41.4 (17.2) |
| | Baseline, U/day | 41.8 (17.1) |
| | Week 24, U/day | 43.7 (18.1) |
| Insulin dose by body weight | n = 106 | |
| | Pre-study, IU/kg[a] | 0.65 (0.28) |
| | Baseline, U/kg | 0.65 (0.26) |
| | Week 24, U/kg | 0.70 (0.26) |
| Dose frequency, n (%) | Pre-study | n = 111 |
| | Once daily | 6 (5.4) |
| | Twice daily | 103 (92.8) |
| | Thrice daily | 2 (1.8) |
| | Baseline | n = 111 |
| | Once daily | 6 (5.4) |
| | Twice daily | 98 (88.3) |
| | Thrice daily | 7 (6.3) |
| | Week 24 | n = 92 |
| | Once daily | 5 (5.4) |
| | Twice daily | 81 (88.0) |
| | Thrice daily | 5 (5.4) |
| | >Thrice daily | 1 (1.1) |

Data are presented as mean (SD) unless specified otherwise.
[a] The unit of measurement for biphasic human insulin 30 pre-study was IU/day or IU/kg.

**Table 3 – Baseline and 24-week data for hypoglycaemia**

| Hypoglycaemia | Events per patient-year / Percent with at least one event | |
|---|---|---|
| Overall | Baseline | 5.62 / 14.4 |
| | Week 24 | 1.98 / 8.7 |
| Minor | Baseline | 4.33 / 14.4 |
| | Week 24 | 1.98 / 8.7 |
| Nocturnal | Baseline | 2.23 / 9.0 |
| | Week 24 | 0.85 / 4.3 |
| Major | Baseline | 1.29 / 3.6 |
| | Week 24 | 0.0 / 0.0 |

### 3.5. Glucose lowering, body weight and SBP

BIAsp 30 therapy improved $HbA_{1c}$ (–2.2±2.1%, 24±23 mmol/mol), FPG (–72.0±71.8 mg/dL) and PPPG (–145.5±125.4 mg/dL) over 24 weeks (Table 4). Also, the number of patients with $HbA_{1c}$ <7.0% (<53 mmol/mol) increased from 6 (7.0%) at baseline to 24 (43.6%) at Week 24.

Total cholesterol and triglycerides decreased while HDL levels increased and LDL levels remained unchanged (Table 5). The mean body weight increased from 63.4±12.8 kg at baseline to 63.8±13.5 kg at Week 24. The average SBP decreased by 1.7±20.3 mmHg from baseline (126.7±21.1 mmHg) to Week 24 (124.9±18.4 mmHg) (Table 5).

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

| Parameter | | All patients |
|---|---|---|
| $HbA_{1c}$, % | n | 52 |
| | Baseline | 9.4 (2.4) |
| | Week 24 | 7.1 (1.0) |
| | Change | −2.2 (2.1) |
| $HbA_{1c}$, mmol/mol | n | 52 |
| | Baseline | 79 (26) |
| | Week 24 | 54 (11) |
| | Change | −24 (23) |
| FPG, mg/dL | n | 68 |
| | Baseline | 188.5 (68.8) |
| | Week 24 | 116.5 (26.8) |
| | Change | −72.0 (71.8) |
| PPPG, mg/dL | n | 11 |
| | Baseline | 283.8 (119.9) |
| | Week 24 | 138.3 (24.4) |
| | Change | −145.5 (125.4) |

FPG, fasting plasma glucose; $HbA_{1c}$, glycated haemoglobin; PPPG, postprandial plasma glucose.

**Table 5 – Lipid profile, systolic blood pressure and body weight**

| Parameter | | Mean (SD) |
|---|---|---|
| Total cholesterol, mmol/L | n | 20 |
| | Baseline | 5.3 (2.5) |
| | Week 24 | 4.7 (0.9) |
| | Change | −0.7 (2.3) |
| HDL cholesterol, mmol/L | n | 9 |
| | Baseline | 1.1 (0.4) |
| | Week 24 | 1.4 (0.3) |
| | Change | 0.3 (0.4) |
| LDL cholesterol, mmol/L | n | 10 |
| | Baseline | 2.9 (1.8) |
| | Week 24 | 2.9 (0.8) |
| | Change | 0.0 (1.4) |
| Triglycerides, mmol/L | n | 16 |
| | Baseline | 1.7 (0.9) |
| | Week 24 | 1.4 (0.5) |
| | Change | −0.3 (0.9) |
| SBP, mmHg | n | 79 |
| | Baseline | 126.7 (21.1) |
| | Week 24 | 124.9 (18.4) |
| | Change | −1.7 (20.3) |
| Body weight, kg | n | 79 |
| | Baseline | 63.4 (12.8) |
| | Week 24 | 63.8 (13.5) |
| | Change | 0.4 (5.7) |

HDL, high-density lipoprotein; LDL, low-density lipoprotein; SBP, systolic blood pressure.

### 3.6. Quality of life

The EQ-5D VAS scores improved from 68.1±18.3 points at baseline to 83.4±11.0 points at Week 24 (mean change = 15.3±16.9 points) for the entire cohort.

## 4. Discussion

This sub-analysis demonstrated the clinical safety and effectiveness of BIAsp 30 in Filipino patients that switched from BHI 30 therapy. As observed in the $A_1$chieve data [6] from other less well-resourced countries worldwide, Filipinos with T2D also presented with poor glycaemic control at baseline. The average baseline $HbA_{1c}$ level was 9.4% (79 mmol/mol) and only 6 patients had $HbA_{1c}$ <7.0% (<53 mmol/mol). Despite the evident need for therapy intensification, there was a significant delay in insulin initiation. The average diabetes duration in the cohort was 9.9 years but patients had received insulin for a mean duration of 2.7 years. This data suggests an urgent need to revisit clinical practice guidelines and seek measures for active implementation.

BIAsp 30 therapy could be a useful tool to achieve adequate glycaemic control as shown in this Filipino cohort that switched from BHI 30. The improvements in the glucose control parameters, $HbA_{1c}$, FPG and PPPG, were associated with a low incidence of hypoglycaemia and modest weight gain. Overall hypoglycaemia decreased from 5.62 to 1.98 events/patient-year from baseline to Week 24, while nocturnal hypoglycaemia decreased from 2.23 to 0.85 events/patient-year. At Week 24, no major hypoglycaemia was reported as opposed to the incidence of 1.29 events/patient-year at baseline. These notable improvements with BIAsp 30 in patients who previously received BHI 30 were also evidenced in the overall $A_1$chieve data as well as the PRESENT and IMPROVE studies [7,8,19]. Also, a meta-analysis of clinical trials comparing BIAsp 30 to BHI 30 validated that the former therapy is associated with a decreased risk of nocturnal hypoglycaemia [20]. A cross-over study employing continuous glucose monitoring to examine the frequency of low interstitial glucose levels demonstrated an increased incidence of low nocturnal glucose resulting in higher rates of hypoglycaemia with BHI 30 as compared to BIAsp 30 [21]. No SAEs or SADRs were reported during the study, thus reinforcing the safety of switching therapy to BIAsp 30. Additionally, the effectiveness of BIAsp 30 was visible with a small dose increase from 0.65 U/kg at baseline to 0.70 U/kg at Week 24. It has been noted that improved T2D control often acts as a stimulus to lifestyle changes and can benefit longevity. BIAsp 30 therapy positively impacted the QoL which could augment compliance and amend self-care behaviors amongst people affected with T2D.

The $A_1$chieve study results could be subject to limitations arising from the observational study design. These include the lack of a control arm, retrospective data collection and non-standardization of reported data. Additionally, parameters such as hypoglycaemia depended solely on the patients' ability to recall the event. This potential for recall bias may have led to an underestimation of the real incidence of hypoglycaemia. Nevertheless, the study provides an opportunity to access treatment in a heterogeneous real-life local setting. Also, observational studies are proven tools to identify safety concerns in a larger population that are often masked in a controlled trial due to the limited scope and selected population [22]. In

conclusion, the results of this sub-analysis were reflective of T2D management in routine clinical care in the Philippines. Switching from BHI 30 to BIAsp 30 resulted in improved glycaemic control with a reduction in the occurrence of hypoglycaemia and improved QoL. The clinical benefits of BIAsp 30 in this population indicate its therapeutic potential in T2D management without associated concerns of safety and tolerability.

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## Conflict of interest statement

Dr. Anand B. Jain is employed by Novo Nordisk Pharma Malaysia. 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. 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.

## REFERENCES

[1] International Diabetes Federation. IDF Diabetes Atlas. 5th edn. Brussels, Belgium; 2011, updated 14 November 2012.
[2] Whiting DR, Guariguata L, Weil C, Shaw J. IDF diabetes atlas: global estimates of the prevalence of diabetes for 2011 and 2030. Diabetes Res Clin Pract 2011;94(3):311–21.
[3] Soria ML, Sy RG, Vega BS, Ty-Willing T, Abenir-Gallardo A, Velandria F, et al. The incidence of type 2 diabetes mellitus in the Philippines: a 9-year cohort study. Diabetes Res Clin Pract 2009;86(2):130–3.
[4] Higuchi M. Access to diabetes care and medicines in the Philippines. Asia Pac J Public Health 2010;22(3 Suppl):96S–102S.
[5] Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, et al. Management of hyperglycaemia in type 2 diabetes: a patient-centered approach. Position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetologia 2012;55(6):1577–96.
[6] Home P, Naggar NE, Khamseh M, Gonzalez-Galvez G, Shen C, Chakkarwar P, et al. An observational non-interventional study of patients with diabetes beginning or changed to insulin analogue therapy in non-Western countries: The $A_1$chieve study. Diabetes Res Clin Pract 2011;94:352–63.
[7] Shah S, Benroubi M, Borzi V, Gumprecht J, Kawamori R, Shaban J, et al.; on behalf of the IMPROVE Study Group Expert Panel. Safety and effectiveness of biphasic insulin aspart 30/70 (NovoMix 30) when switching from human premix insulin in patients with type 2 diabetes: subgroup analysis from the 6-month IMPROVE observational study. Int J Clin Pract 2009;63:574–82.
[8] Shestakova M, Sharma SK, Almustafa M, Min KW, Ayad N, Azar ST, et al. Transferring type 2 diabetes patients with uncontrolled glycaemia from biphasic human insulin to biphasic insulin aspart 30: experiences from the PRESENT study. Curr Med Res Opin 2007;23(12):3209–14.
[9] Niswender K. Early and aggressive initiation of insulin therapy for type 2 diabetes: What is the evidence? Clin Diab 2009;27:60–8.
[10] Evans M, Schumm-6raeger PM, Vora J, King AB. A review of modern insulin analogue pharmacokinetic and pharmacodynamic profiles in type 2 diabetes: improvements and limitations. Diabetes Obes Metab 2011;13(8):677–84.
[11] Christiansen JS, Vaz JA, Metelko Z, Bogoev M, Dedov I. Twice daily biphasic insulin aspart improves postprandial glycaemic control more effectively than twice daily NPH insulin, with low risk of hypoglycaemia, in patients with type 2 diabetes. Diabetes Obes Metab 2003;5(6):446–54.
[12] Hermansen K, Colombo M, Storgaard H, ØStergaard A, Kølendorf K, Madsbad S. Improved postprandial glycemic control with biphasic insulin aspart relative to biphasic insulin lispro and biphasic human insulin in patients with type 2 diabetes. Diabetes Care 2002;25(5):883–8.
[13] Velojic-Golubovic M, Mikic D, Pesic M, Dimic D, Radenkovic S, Antic S. Biphasic insulin aspart 30: better glycemic control than with premixed human insulin 30 in obese patients with type 2 diabetes. J Endocrinol Invest 2009;32:23–7.
[14] Schmoelzer I, de Campo A, Pressl H, Stelzl H, Dittrich P, Oettl K, et al. Biphasic insulin aspart compared to biphasic human insulin reduces postprandial hyperlipidemia in patients with type 2 diabetes. Exp Clin Endocrinol Diabetes 2005;113:176–81.
[15] Abrahamian H, Ludvik B, Schernthaner G, Prager R, Zellenka U, Knudsen L, et al. Improvement of glucose tolerance in type 2 diabetic patients: traditional vs. modern insulin regimens (results from the Austrian Biaspart Study). Horm Metab Res 2005;37:684–9.
[16] Boehm BO, Vaz JA, Brøndsted L, Home PD. Long-term efficacy and safety of biphasic insulin aspart in patients with type 2 diabetes. Eur J Intern Med 2004;15:496–502.
[17] Beran D, Higuchi M. Delivering diabetes care in the Philippines and Vietnam: policy and practice issues. Asia Pac J Public Health 2013;25(1):92–101.
[18] Paz-Pacheco E. Diabetes Clinical Practice Guidelines (CPGs) for the ASEAN region: Country initiatives for collectively enhanced diabetes care in the region. JAFES 2011;26(1): 36–7.
[19] El Naggar NK, Soewondo P, Khamseh ME, Chen J, Haddad J. Switching from biphasic human insulin 30 to biphasic insulin aspart 30 in type 2 diabetes is associated with improved glycaemic control and a positive safety profile:

Results from the $A_1$chieve study. Diabetes Res Clin Pract 2012;98(3):408–13.
[20] Davidson JA, Liebl A, Christiansen JS, Fulcher G, Ligthelm RJ, Brown P, et al. Risk for nocturnal hypoglycemia with biphasic insulin aspart 30 compared with biphasic human insulin 30 in adults with type 2 diabetes mellitus: a meta-analysis. Clin Ther 2009;31(8):1641–51.
[21] McNally PG, Dean JD, Morris AD, Wilkinson PD, Compion G, Heller SR. Using continuous glucose monitoring to measure the frequency of low glucose values when using biphasic insulin aspart 30 compared with biphasic human insulin 30: a double-blind crossover study in individuals with type 2 diabetes. Diabetes Care 2007;30:1044–8.
[22] Vandenbroucke JP. What is the best evidence for determining harms of medical treatment? CMAJ 2006;174(5):645–6.

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# Clinical safety and effectiveness of biphasic insulin aspart 30 in type 2 diabetes patients switched from biphasic human insulin 30: Results from the Indonesian cohort of the $A_1$chieve study

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ABSTRACT

*Aim:* To evaluate the safety and effectiveness of biphasic insulin aspart 30 (BIAsp 30) in Indonesian type 2 diabetes patients switched from biphasic human insulin 30 (BHI 30) as a sub-analysis of the $A_1$chieve study.

*Methods:* Clinical safety and effectiveness over 24 weeks was evaluated in Indonesian patients who switched from BHI 30 to BIAsp 30 at the discretion of their physician.

*Results:* A total of 244 patients with mean age ± SD 55.6±9.5 years, BMI 24.6±3.8 kg/m$^2$, and mean diabetes duration 7.8±5.7 years were included. The mean pre-study BHI 30 dose was 0.56±0.25 IU/kg and the baseline BIAsp 30 dose was 0.60±0.26 U/kg titrated up to 0.65±0.25 U/kg by Week 24. No serious adverse drug reactions were reported throughout the study. Overall hypoglycaemia decreased from 2.18 to 0.06 events/patient-year with a significant decrease in the proportion of patients affected ($p < 0.0001$). No nocturnal or major hypoglycaemia was reported at Week 24. $HbA_{1c}$ improved from 8.8±1.2% at baseline to 7.3±0.8% at Week 24. A total of 45 patients achieved $HbA_{1c}$ <7.0% as compared to 5 patients with $HbA_{1c}$ <7.0% at baseline. FPG and PPPG improved significantly after 24 weeks ($p < 0.001$). Quality of life was positively impacted (change in visual analogue scores, 3.0±11.6 points, $p < 0.001$).

*Conclusion:* Switching from BHI 30 to BIAsp 30 in this Indonesian cohort was well-tolerated and improved glycaemic control with a decreased risk of hypoglycaemia.



## 1. Introduction

The prevalence of diabetes in Indonesia is projected to increase from 7.3 million in 2011 to 11.8 million in 2030 among people in the age group of 20–79 years [1]. Indonesia also ranks among the top 10 countries for diabetes prevalence worldwide and has the second highest number of diabetes cases in the Western Pacific region [1,2]. A cross-sectional study in Indonesia indicated that age, smoking, obesity and hypertension were the primary determinants

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of impaired glucose tolerance leading to a high risk of diabetes [3]. There is an immense need to contain this growing epidemic with the help of early intensification of adequate therapy.

According to the United Kingdom Prospective Diabetes Study, insulin therapy is ultimately required in all patients with type 2 diabetes (T2D) due to its chronic progressive nature that causes a continual decline in β-cell function [4]. However, it is observed that compliance to insulin therapy is very poor owing to barriers such as fear of hypoglycaemia, weight gain and the negative impact on quality of life (QoL) [5]. Furthermore, glycaemic control, especially postprandial glucose, with human insulin preparations such as biphasic human insulin 30 (BHI 30) is often sub-optimal and efficacy is largely dependent on the time of injection. The slow onset of action with BHI 30 therapy necessitates injecting the drug at least 30 minutes prior to meals. Hence, in case of erratic meal timings, BHI 30 is rendered ineffective to control postprandial glucose levels [6,7].

The insulin analogue, biphasic insulin aspart 30 (BIAsp 30), has a more physiological pharmacokinetic and pharmacodynamic profile as compared to BHI 30 that enables more convenient dosing [8]. Furthermore, short- and long-term studies have proven that the frequency of major hypoglycaemia in patients using BIAsp 30 twice-daily (*bid*) is lower than those on the same BHI 30 regimen [9–11]. Boehm et al. demonstrated that although the $HbA_{1c}$ lowering effect of BIAsp 30 was comparable to BHI 30, the former resulted in more favorable postprandial glucose control [10]. In addition to data from RCTs, observational studies – IMPROVE and PRESENT – have also concluded that switching from BHI 30 to BIAsp 30 improves glycaemic control without increasing the risk of hypoglycaemia [12–16].

$A_1$chieve [14] was a multinational, prospective, non-interventional study to determine the safety and efficacy of insulin analogues, including BIAsp 30 in routine clinical care in 28 countries across Asia, Africa, Latin America and Europe. The overall results from all countries are available online under www.A1chieve.com. The current clinical practice guidelines in Indonesia are a simplified set of recommendations on screening and diagnosis of pre-diabetes and diabetes that are derived from diabetes organizations in the US [17]. This is largely due to the absence of local study data that is specific and applicable only to Indonesia. In this sub-analysis of the $A_1$chieve study, we aim to shed light on the existing status of T2D management in Indonesia and evaluate the clinical effects of BIAsp 30 in patients that received prior BHI 30 therapy.

## 2. Methods

### 2.1. Study design

The $A_1$chieve study [14] was a 24-week, 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). This sub-analysis focuses on T2D patients from Indonesia that switched therapy from BHI 30 to BIAsp 30. These patients were recruited between October 2009 and August 2010 at 65 centers in Indonesia. The study was approved by the local ethics committee of Indonesia. Based on a mutual agreement between the patients and their consulting physicians, T2D therapy was switched from BHI 30 to BIAsp 30. The dosing, frequency of administration, and subsequent changes were at the discretion of the physician. The study drug was commercially available and used in accordance with local regulations. The study procedures were not pre-defined and all assessments were made by physicians during routine clinical visits. Data for analysis from the physicians' clinical notes and patients' 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).

### 2.2. Patients

All patients recruited from Indonesia who switched therapy from BHI 30 to BIAsp 30 were included in this sub-analysis. Patients who had received any of the study insulin analogues 4 weeks prior to the study were excluded. Pregnant women or those intending to become pregnant or were breast-feeding were also excluded. Signed informed consent was obtained from all patients and they could withdraw from the study at any time. After withdrawal, the data collected were used for analysis until the time that consent was withdrawn.

### 2.3. Outcome measures and assessments

The primary objective of this study was to evaluate the clinical safety of BIAsp 30 as determined by the incidence of serious adverse drug reactions (SADRs), including major hypoglycaemic events 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.

Glycaemic control was evaluated using changes in $HbA_{1c}$ levels, fasting plasma glucose (FPG) and post-breakfast postprandial glucose (PPPG) from baseline to Week 24. The change in lipid profile, systolic blood pressure (SBP), and body weight was also reported. All laboratory parameters were measured in local laboratories and were subject to local standardization and quality control procedures. Health-related QoL was assessed using the EQ-5D questionnaire that rates patient pain/discomfort, anxiety/depression, mobility, usual activity and self-care. 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 methods

Continuous and discrete variables were summarized using descriptive statistics and frequency tables (n [%]), respectively. The paired t-test was used to analyse the changes

in $HbA_{1c}$, FPG and PPPG, SBP, blood lipids, body weight and QoL from baseline to Week 24. P-values were not reported when the number of patients evaluated was less than 100. The McNemar test was used to analyse the change in the proportion of patients reporting at least one hypoglycaemic event from baseline to Week 24. All data were analysed by Novo Nordisk using SAS (Version 9.1.3).

## 3. Results

### 3.1. Patient characteristics

A total of 244 patients from the Indonesian cohort of the $A_1$chieve study switched from BHI 30 to BIAsp 30. Demographic and baseline characteristics for the entire cohort are reported in Table 1. The average duration of diabetes was 7.8±5.7 years and the mean duration on prior insulin therapy was 1.9±1.5 years. At baseline, patients reported a mean $HbA_{1c}$ level of 8.8±1.2% and 5 patients, 6.9% of the cohort, had $HbA_{1c}$ values <7.0% (<53 mmol/mol). Physicians decided to switch therapy in 93.4% patients in order to improve glucose control. Other prominent reasons for switching therapy were to try new insulin (75.0% patients) and to reduce plasma glucose variability (58.2% patients).

**Table 1 – Baseline demographics and characteristics**

| Parameter | Entire cohort (n = 244) |
|---|---|
| Gender (male/female), % | 50.4/49.6 |
| Age, years | 55.6 (9.5) |
| Body weight, kg | 64.0 (11.8) |
| BMI, kg/m$^2$ | 24.6 (3.8) |
| Diabetes duration, years | 7.8 (5.7) |
| Duration on prior insulin therapy, years | 1.9 (1.5) |
| $HbA_{1c}$, % | 8.8 (1.2) |
| $HbA_{1c}$, mmol/mol | 73 (13) |
| Prior OGLDs, n (%) | |
| Metformin | 152 (82.2) |
| Sulfonylureas | 59 (31.9) |
| Thiazolidinediones | 8 (4.3) |
| 1 OGLD | 139 (75.1) |
| 2 OGLDs | 27 (14.6) |
| >2 OGLDs | 19 (10.3) |

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

### 3.2. Insulin dose

The mean pre-study BHI 30 dose was 0.56±0.25 IU/kg in the entire cohort (Table 2). At baseline, patients initiated an average BIAsp 30 dose of 0.60±0.26 U/kg that was titrated up to 0.65±0.25 U/kg by Week 24. The majority of patients received BIAsp 30 twice-daily (*bid*) at baseline (95.9% patients) and Week 24 (90.8% patients).

**Table 2 – Insulin dose and frequency**

| Parameter | | Entire cohort |
|---|---|---|
| Insulin dose by day | n | 244 |
| | Pre-study, IU/day[a] | 35.1 (15.9) |
| | Baseline, U/day | 38.1 (16.6) |
| | Week 24, U/day | 41.3 (15.3) |
| Insulin dose by body weight | n | 242 |
| | Pre-study, IU/kg[a] | 0.56 (0.25) |
| | Baseline, U/kg | 0.60 (0.26) |
| | Week 24, U/kg | 0.65 (0.25) |
| Dose frequency, n (%) | Pre-study (n) | 244 |
| | Once daily | 2 (0.8) |
| | Twice daily | 232 (95.1) |
| | Thrice daily | 10 (4.1) |
| | Baseline (n) | 244 |
| | Once daily | 2 (0.8) |
| | Twice daily | 234 (95.9) |
| | Thrice daily | 8 (3.3) |
| | Week 24 (n) | 228 |
| | Once daily | 5 (2.2) |
| | Twice daily | 207 (90.8) |
| | Thrice daily | 13 (5.7)/3 (1.3) |

Data are represented as mean (SD) unless specified otherwise.
[a] The unit of measurement for BHI 30 pre-study was IU/day or IU/kg.

### 3.3. SADRs and SAEs

From baseline to Week 24, no SADRs or SAEs were reported in patients that switched therapy to BIAsp 30.

### 3.4. Hypoglycaemia

The proportion of patients reporting overall hypoglycaemia decreased significantly from baseline (8.2%) to Week 24 (0.4%, $p < 0.0001$, Table 3). The corresponding decrease in the incidence of overall hypoglycaemia was from 2.18 events/patient-year at baseline to 0.06 events/patient-year at Week 24. No nocturnal or major hypoglycaemic events were reported at Week 24 (Table 3).

**Table 3 – Baseline and 24-week data for hypoglycaemia**

| Hypoglycaemia | Events per patient-year / Percent with at least one event | |
|---|---|---|
| Overall | Baseline | 2.18/8.2 |
| | Week 24 | 0.06/0.4 |
| | P | <0.0001 |
| Minor | Baseline | 2.18/8.2 |
| | Week 24 | 0.06/0.4 |
| | P | <0.0001 |
| Nocturnal | Baseline | 0.64/4.5 |
| | Week 24 | 0.0/0.0 |
| | P | 0.0009 |
| Major | Baseline | 0.0/0.0 |
| | Week 24 | 0.0/0.0 |
| | P | – |

p-values are from McNemar test on paired proportions of patients experiencing hypoglycaemia.

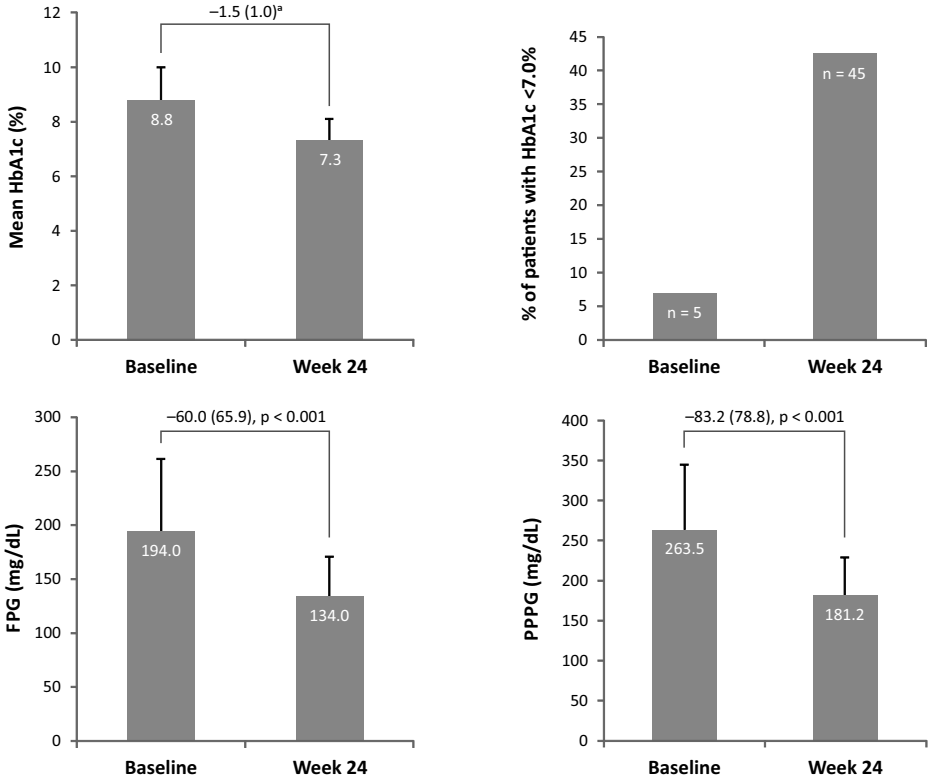


**Fig. 1 – Changes in $HbA_{1c}$, FPG and PPPG from baseline to Week 24. All data presented are mean (SD). [a] p-value for $HbA_{1c}$ not reported since n < 100.**

### 3.5. Glucose control

The mean $HbA_{1c}$ level in the entire cohort decreased from 8.8±1.2% (73±13 mmol/mol) at baseline to 7.3±0.8% (56±9 mmol/mol) at Week 24. The proportion of patients achieving $HbA_{1c}$ target levels <7.0% (<53 mmol/mol) increased from 6.9% (n = 5) at baseline to 42.5% (n = 45) at Week 24. Significant decreases in FPG and PPPG were also observed after 24 weeks of BIAsp 30 therapy (p < 0.001, Figure 1).

### 3.6. Body weight, lipids and SBP

The mean body weight increased by 0.8±3.9 kg from baseline to Week 24 (p = 0.003). At Week 24, total cholesterol decreased by 0.3±1.6 mmol/L, low-density lipoprotein cholesterol decreased by 0.3±1.2 mmol/L and triglycerides decreased by 0.1±0.7 mmol/L while high-density lipoprotein cholesterol increased by 0.2±0.5 mmol/L. A significant decrease in SBP of 3.4±15.0 mmHg was observed in the entire cohort following 24 weeks of BIAsp 30 treatment (p = 0.001) (Table 4).

### 3.7. Quality of life

The QoL improved significantly from 78.9±13.0 points at baseline to 82.0±8.7 points at Week 24 (mean change, 3.0±11.6 points, p < 0.001).

**Table 4 – Lipid profile, SBP, body weight and hypoglycaemia in the entire cohort**

| Parameter | | Mean (SD) |
|---|---|---|
| Total cholesterol, mmol/L (n = 44) | Baseline | 5.4 (1.3) |
| | Week 24 | 5.1 (1.1) |
| | Change | −0.3 (1.6) |
| | p | –[a] |
| HDL cholesterol, mmol/L (n = 33) | Baseline | 1.3 (0.5) |
| | Week 24 | 1.5 (0.3) |
| | Change | 0.2 (0.5) |
| | p | –[a] |
| LDL cholesterol, mmol/L (n = 37) | Baseline | 3.5 (1.1) |
| | Week 24 | 3.2 (0.8) |
| | Change | −0.3 (1.2) |
| | p | –[a] |
| Triglycerides, mmol/L (n = 40) | Baseline | 1.7 (0.7) |
| | Week 24 | 1.6 (0.7) |
| | Change | −0.1 (0.7) |
| | p | –[a] |
| SBP, mmHg (n = 212) | Baseline | 131.4 (14.3) |
| | Week 24 | 128.0 (12.4) |
| | Change | −3.4 (15.0) |
| | p | 0.001 |
| Body weight, kg (n = 219) | Baseline | 63.7 (11.4) |
| | Week 24 | 64.5 (10.3) |
| | Change | 0.8 (3.9) |
| | p | 0.003 |

[a] p-value not reported since n < 100.

## 4. Discussion

This sub-analysis demonstrated the safety and effectiveness of BIAsp 30 therapy in Indonesian T2D patients previously treated with BHI 30. At baseline, this cohort presented with poor glycaemic control. This observation is reflected in the $A_1$chieve data [14] from other countries as well. Additionally, the delay in insulin intiation was evident in this cohort as the average diabetes duration was 7.8±5.7 years but patients had been on insulin therapy for 1.9±1.5 years only.

Evidence-based guidelines from the American Diabetes Association recommend a glycaemic target of $HbA_{1c}$ levels <7.0% (<53 mmol/mol) that can be achieved by maintaining FPG at 130 mg/dL and PPPG at 180 mg/dL [18]. At baseline, patients failed to achieve any of these targets with BHI 30 (HbA1c, 8.8±1.2%, 73±13 mmol/mol; FPG, 194.0±67.4 mg/dL; PPPG, 263.5±81.3 mg/dL). However, after 24 weeks of BIAsp 30 therapy, significant improvements were observed in $HbA_{1c}$ (7.3±0.8%, 56±9 mmol/mol), FPG (134.0±36.9 mg/dL) and PPPG (181.2±47.6 mg/dL). Furthermore, the proportion of patients reporting $HbA_{1c}$ target levels <7.0% (<53 mmol/mol) increased from 6.9% (n = 5) at baseline to 42.5% (n = 45) at Week 24. The increase in body weight was modest and SBP improved significantly. Notably, these improvements were observed with a very small increase in dose from 0.60±0.26 U/kg at baseline to 0.65±0.25 U/kg at Week 24.

While achieving and maintaining glycaemic control is the primary aim of T2D management, it is also important to reduce the risk of hypoglycaemia associated with intensive therapy. BIAsp 30 therapy could effectively decrease the occurrence of hypoglycaemia in this Indonesian cohort. There was no major hypoglycaemia reported in the entire cohort at baseline or final visit. A significant decrease in the proportion of patients reporting overall, minor and nocturnal hypoglycaemia was observed. Previously, a crossover study also demonstrated that individuals on BHI 30 reported higher rates of nocturnal hypoglycaemia when compared to those on BIAsp 30 therapy [19]. The efficiency of glycaemic control and reduction in the risk of hypoglycaemia in patients treated with BIAsp 30 was also observed in the overall $A_1$chieve cohort receiving pre-study BHI 30 [20]. Previously, similar data had also been reported in the PRESENT and IMPROVE studies from other regions worldwide [15,16].

Anti-diabetic therapy often has a major impact on the health and well-being of patients, primarily owing to the risk of hypoglycaemia. In this Indonesian cohort it was observed that the QoL as measured using the EQ-5D questionnaire significantly improved in patients after 24 weeks of BIAsp 30 treatment. These results could be a contributing factor to improving patient compliance to therapy.

Due to the observational study design, the results are subject to obvious limitations such as lack of a control arm, retrospective data collection methods and non-standardization of reported data. Also, recall bias may have been introduced in the reporting of hypoglycaemia. Nevertheless, this study provides an opportunity to witness the safety and effectiveness on BIAsp 30 therapy in heterogeneous local clinical settings. Observational studies such as these are also more reliable in terms of reporting safety in a wider population which may otherwise be masked in the restricted cohorts of randomized controlled trials [21]. In conclusion, the switch from BHI 30 to BIAsp 30 in Indonesian T2D patients was well-tolerated and improved glycaemic control while decreasing the risk of hypoglycaemia.

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## Conflict of interest statement

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## REFERENCES

[1] Whiting DR, Guariguata L, Weil C, Shaw J. IDF diabetes atlas: global estimates of the prevalence of diabetes for 2011 and 2030. Diabetes Res Clin Pract 2011;94(3):311–21.
[2] International Diabetes Federation. IDF Diabetes Atlas. 5th edn. Brussels, Belgium; 2011, updated 14 November 2012.
[3] Mihardja L, Delima, Manz HS, Ghani L, Soegondo S. Prevalence and determinants of diabetes mellitus and impaired glucose tolerance in Indonesia (a part of basic health research/Riskesdas). Acta Med Indones 2009;41(4):169–74.
[4] Wright A, Burden ACF, Paisey RB, Cill CA, Holman RR, and the UK Prospective Diabetes Study Group. Sulphonylurea inadequacy: efficacy of addition of insulin over 6 years in patients with type 2 diabetes in the UK. Prospective Diabetes Study (UKPDS 57). Diabetes Care 2002;25:330–6.

[5] Niswender K. Early and aggressive initiation of insulin therapy for type 2 diabetes: What is the evidence? Clin Diab 2009;27:60–8.
[6] Heller S. Reducing hypoglycaemia with insulin analogues. Int J Obes Relat Metab Disord 2002;26(Suppl 3):S31–6.
[7] Evans M, Schumm-7raeger PM, Vora J, King AB. A review of modern insulin analogue pharmacokinetic and pharmacodynamic profiles in type 2 diabetes: improvements and limitations. Diabetes Obes Metab 2011;13(8):677–84.
[8] Jacobsen LV, Sogaard B, Riis A. Pharmacokinetics and pharmacodynamics of a premixed formulation of soluble and protamine-retarded insulin aspart. Eur J Clin Pharmacol 2000;56:399–403.
[9] Boehm BO, Vaz JA, Brøndsted L, Home PD. Long-term efficacy and safety of biphasic insulin aspart in patients with type 2 diabetes. Eur J Intern Med 2004;15:496–502.
[10] Boehm BO, Home PD, Behrend C, Kamp NM, Lindholm A. Premixed insulin aspart 30 vs. premixed human insulin 30/70 twice daily: a randomized trial in type 1 and type 2 diabetic patients. Diabet Med 2002;19:393–9.
[11] Davidson JA, Liebl A, Christiansen JS, Fulcher G, Ligthelm RJ, Brown P, et al. Risk for nocturnal hypoglycemia with biphasic insulin aspart 30 compared with biphasic human insulin 30 in adults with type 2 diabetes mellitus: a meta-analysis. Clin Ther 2009;31:1641–51.
[12] Velojic-Golubovic M, Mikic D, Pesic M, Dimic D, Radenkovic S, Antic S. Biphasic insulin aspart 30: better glycemic control than with premixed human insulin 30 in obese patients with type 2 diabetes. J Endocrinol Invest 2009;32:23–7.
[13] Schmoelzer I, de Campo A, Pressl H, Stelzl H, Dittrich P, Oettl K, et al. Biphasic insulin aspart compared to biphasic human insulin reduces postprandial hyperlipidemia in patients with type 2 diabetes. Exp Clin Endocrinol Diabetes 2005;113:176–81.
[14] Home P, Naggar NE, Khamseh M, Gonzalez-Galvez G, Shen C, Chakkarwar P, et al. An observational non-interventional study of patients with diabetes beginning or changed to insulin analogue therapy in non-Western countries: The $A_1$chieve study. Diabetes Res Clin Pract 2011;94:352–63.
[15] Shah S, Benroubi M, Borzi V, Gumprecht J, Kawamori R, Shaban J, et al.; on behalf of the IMPROVE Study Group Expert Panel. Safety and effectiveness of biphasic insulin aspart 30/70 (NovoMix 30) when switching from human premix insulin in patients with type 2 diabetes: subgroup analysis from the 6-month IMPROVE observational study. Int J Clin Pract 2009;63:574–82.
[16] Shestakova M, Sharma SK, Almustafa M, Min KW, Ayad N, Azar ST, et al. Transferring type 2 diabetes patients with uncontrolled glycaemia from biphasic human insulin to biphasic insulin aspart 30: experiences from the PRESENT study. Curr Med Res Opin 2007;23(12):3209–14.
[17] Paz-Pacheco E. Diabetes Clinical Practice Guidelines (CPGs) for the ASEAN region: Country initiatives for collectively enhanced diabetes care in the region. JAFES 2011;26(1): 36–7.
[18] Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, et al. Management of hyperglycaemia in type 2 diabetes: a patient-centered approach. Position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetologia 2012;55(6):1577–96.
[19] McNally PG, Dean JD, Morris AD, Wilkinson PD, Compion G, Heller SR. Using continuous glucose monitoring to measure the frequency of low glucose values when using biphasic insulin aspart 30 compared with biphasic human insulin 30: a double-blind crossover study in individuals with type 2 diabetes. Diabetes Care 2007;30:1044–8.
[20] El Naggar NK, Soewondo P, Khamseh ME, Chen J, Haddad J. Switching from biphasic human insulin 30 to biphasic insulin aspart 30 in type 2 diabetes is associated with improved glycaemic control and a positive safety profile: Results from the $A_1$chieve study. Diabetes Res Clin Pract 2012;98(3):408–13.
[21] Vandenbroucke JP. What is the best evidence for determining harms of medical treatment? CMAJ 2006;174(5):645–6.

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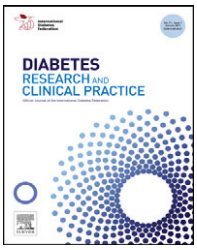

# Clinical experience with insulin detemir: Results from the Indonesian cohort of the international $A_1$chieve study

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ABSTRACT

*Aim:* To determine the safety and efficacy of insulin detemir in Indonesian patients with type 2 diabetes (T2D) as a sub-analysis of the 24-week, prospective, multinational, non-interventional $A_1$chieve study.

*Methods:* This study included 477 Indonesian T2D patients starting insulin detemir at the discretion of their physicians. Safety and efficacy was measured in routine clinical practice at baseline, interim (around 12 weeks from baseline) and final (around 24 weeks from baseline) visit.

*Results:* At baseline the mean age, duration of diabetes and mean BMI were 55.3±8.5 years, 5.9±4.0 years and 24±3.6 kg/m$^2$, respectively. Of these patients, 78% were insulin-naive and 22% were prior insulin users. Glycaemic control was poor at baseline. After 24 weeks, significant reductions were observed in mean $HbA_{1c}$ (2.2%, $p < 0.001$), fasting plasma glucose (90.0 mg/dL, $p < 0.001$) and postprandial plasma glucose (115.4 mg/dL, $p < 0.001$) levels, in the entire cohort. Similar significant reductions were also seen in insulin-naive patients and prior insulin users. In the entire cohort, 32.5% patients achieved $HbA_{1c}$ levels <7.0% while 32.0% insulin-naive patients and 33.9% prior insulin users achieved this target after 24 weeks. No hypoglycaemic events were reported in the entire cohort. Modest increase in body weight was noted in the insulin-naive group, while mean body weight decreased in prior insulin users after 24 weeks of insulin detemir therapy.

*Conclusion:* This sub-analysis suggests that insulin detemir can be a safe and effective option for initiating insulin therapy in people with T2D in Indonesia.



## 1. Introduction

The prevalence of type 2 diabetes (T2D) is increasing worldwide, but the increase is particularly rapid in Asian countries. This current trend also proposes that 60% of the world's diabetic population will be in Asia. The epidemic increase in T2D is primarily attributed to lifestyle changes as a result of rapid socioeconomic growth especially in countries including Indonesia that report a high rate of urbanization [1]. The International Diabetes Federation places Indonesia among the top 10 countries worldwide with a diabetes prevalence of 7.6 million in 2012 [2].

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The stepwise approach in the management of T2D includes lifestyle modifications, use of oral glucose lowering drugs (OGLDs) and insulin. Due to the progressive nature of the disease, the majority T2D patients are unable to maintain $HbA_{1c}$ targets on a regimen of lifestyle changes and OGLDs, alone [3]. Results from an epidemiological study demonstrated that $HbA_{1c}$ values were as high as 9.0% (75 mmol/mol) and 10.0% (86 mmol/mol) before treatment intensification to combination OGLDs or the initiation of insulin, respectively [4]. In patients with severe β-cell dysfunction, exogenous insulin treatment is essential for controlling glycaemia and reducing risks of diabetes-related complications and mortality [5]. The American Diabetes Association 2012 guidelines recommend insulin therapy, with or without additional agents, in newly diagnosed patients having markedly symptomatic and/or elevated blood glucose levels or $HbA_{1c}$, from the outset [6].

Insulin replacement therapies are limited in their capacity to match physiologic conditions due to the complexity of normal insulin secretion patterns and various pharmacokinetic factors. For example, intermediate-acting preparations, or neutral protamine Hagedorn (NPH) insulin, are associated with unpredictable peaks. Furthermore, patients and healthcare providers are often reluctant to initiate insulin due to concerns over injections, fear of hypoglycaemia and additional weight gain, and also because insulin treatment is perceived as complex [7]. The reluctance of physicians and patients to initiate insulin therapy can contribute to periods of poor glycaemic control in individuals with T2D, ultimately increasing the risk of micro- and macrovascular complications.

The newly introduced insulin analogues help patients and physicians overcome these barriers [5]. It has been shown that a very simple approach of adding a basal insulin analogue to a current OGLD regimen can improve glycaemic control with a reduced frequency of hypoglycaemia in insulin-naive T2D patients [8].

Insulin detemir, a biosynthetic long-acting insulin analogue, has been developed to provide a predictable, protracted and flat pharmacodynamic profile, limiting the risk of hypoglycaemia. It is structurally modified to self-associate and bind reversibly to albumin and is soluble at a neutral pH. These characteristics mediate insulin detemir's slow absorption from the subcutaneous administration site and result in a protracted duration of action compared with conventional human insulin formulations. Also, insulin detemir has duration of action of up to 24 hours [9]. Data from randomized controlled trials (RCTs) and observational studies have shown that use of insulin detemir significantly reduces $HbA_{1c}$ and blood glucose levels, is associated with a very low risk of hypoglycaemia and have a weight neutral effect [3,8,10–12].

The beneficial effects reported in RCTs require validation during routine clinical practice in large patient populations, with varying stages of the disease, having other co-morbidities and on multiple medications [13]. To evaluate the clinical safety of various insulin analogues in people with T2D in routine clinical practice, the multinational $A_1$chieve trial was conducted [3]. Complete study results are now available online under www.A1chieve.com. The study was carried out in 28 countries across four continents. Here we present a subgroup analysis of the $A_1$chieve study which examined the safety and efficacy of insulin detemir in the Indonesian T2D population. It also evaluated the effect of insulin detemir on quality of life in individuals with T2D.

## 2. Methods

### 2.1. Study design

$A_1$chieve [3] was a 24-week, international, prospective, non-interventional study of Indonesian T2D patients who had begun using biphasic insulin aspart 30 (premix), insulin aspart, or insulin detemir with or without OGLDs. This sub-analysis was conducted to determine the safety and efficacy of insulin detemir in T2D patients recruited between October 2009 and August 2010 at 65 centers in Indonesia. The local ethics committee approval was obtained and all patients signed informed consent. The prescription for insulin detemir and use of concurrent OGLDs as well as all subsequent treatment decisions was at the discretion of the physician in accordance with local 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 measurements made at usual clinic visits. Data points were captured at baseline, interim (around 12 weeks from baseline) and final (around 24 weeks from baseline) visit. The time period of 4 weeks prior to the baseline visit, was defined as a pre-study period. Information was gathered from the physician's usual clinical notes, the participants' recall and self-monitoring glucose diary at each visit and transferred to a standard case report form (CRF).

### 2.2. Inclusion and exclusion criteria

All patients with T2D, who had not used any of the study insulins previously or who had been started on any of the insulins in the 4 weeks prior to the study, were included in the study. 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 the women who were pregnant, breast-feeding, or who intended to become pregnant within 6 months of the study.

### 2.3. Primary and secondary endpoints

The primary endpoint was the number of serious adverse drug reactions (SADRs) including major hypoglycaemic events recorded from baseline to 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

**Table 1 – Demography of the Indonesian cohort**

| Parameter | Entire cohort (n = 477) | Insulin-naive (n = 372) | Prior insulin users (n = 105) |
|---|---|---|---|
| Gender (male/female), % | 49.3/50.7 | 48.7/51.3 | 51.4/48.6 |
| Age, years | 55.3 (8.5) | 55.1 (8.8) | 55.8 (7.6) |
| Duration of diabetes, years | 5.9 (4.0) | 5.9 (4.4) | 5.7 (2.7) |
| Body weight, kg | 62.8 (10.6) | 61.6 (11.0) | 65.8 (8.2) |
| BMI, kg/m$^2$ | 24.0 (3.6) | 23.5 (3.7) | 25.5 (2.9) |
| $HbA_{1c}$, % | 9.5 (1.7) | 9.5 (1.7) | 9.3 (1.4) |
| $HbA_{1c}$, mmol/mol | 80 (19) | 80 (19) | 78 (15) |

BMI, Body Mass Index.
Data are presented as mean (SD) unless specified otherwise.

last 4 weeks before the baseline visit. Secondary efficacy endpoints included change in: (1) $HbA_{1c}$, fasting plasma glucose (FPG), and postprandial plasma glucose (PPPG) at interim visit and final visit compared with baseline; (2) Body weight, blood pressure, and serum lipids at final visit compared with baseline; (3) Health-related quality of life (QoL).

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 < 3.1 mmol/L or 56 mg/dL or (2) reversal of symptoms after either food intake or glucagon or intravenous glucose administration. All other hypoglycaemic events were classified as minor. Hypoglycaemic events occurring between bedtime and before getting up in the morning were classified as nocturnal.

QoL was measured using the EQ-5D questionnaire and EQ visual analogue scale (EQ VAS) at baseline and after 24 weeks of therapy with insulin analogues. EQ-5D consisted 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.

### 2.4. Statistical methods

The sample size calculation for the entire $A_1$chieve cohort was based on the number of patients (60,000) exposed for 6 months required to confirm a frequency of $\geqslant$15 events/100,000 patient-years of any one SADR, including major hypoglycaemic events, at the 95% confidence level. Statistical analyses were performed for the entire cohort and for the entire cohort classified as insulin-naive or prior insulin users. Descriptive statistics were used to summarize continuous variables and frequency tables (number and percentage) were used for discrete variables. All statistical analyses 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 analyzed using McNemar's test. The change from baseline in $HbA_{1c}$, FPG, PPPG, SBP, body weight, blood lipids and QoL was analyzed using a paired t-test using 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 477 patients were recruited and analyzed in the insulin detemir subgroup of the Indonesian cohort, out of which 372 were insulin-naive (including 22 treatment-naive) and 105 patients were prior insulin users. The treatment-naive group included those patients who had not received any anti-diabetic therapy (insulin or OGLD) prior to enrolment. The male/female ratio was equal in all groups. The average duration of diabetes was 5.9 years for entire cohort. The mean body weight was 62.8 kg. Detailed demographic characteristics are reported in Table 1.

Metformin was the most commonly prescribed OGLD pre-study (74.9%), at baseline (72.6%) and at the end of study (85.8%). Sulfonylureas were the second most commonly prescribed OGLDs (69.4%, 38.6% and 40.9% pre-study, at baseline and at Week 24, respectively). Thiazolidinediones were prescribed in 11.4% of patients pre-study, 3.2% at baseline and 0.5% at Week 24. Combinations of $\geqslant$2 OGLDs were prescribed in 39.6% patients at baseline and 26% patients at the end of study.

### 3.2. SADRs and hypoglycaemia

No SADRs were reported during the study. At baseline, overall hypoglycaemic episodes were experienced by 5.9%, patients in the entire cohort, 5.1% insulin-naive patients and 8.6% prior insulin users. In the entire cohort, 0.2% and 5.7% patients reported major and nocturnal hypoglycaemic episodes respectively at baseline. After 24 weeks of insulin detemir therapy no hypoglycaemic events were reported in this cohort (Table 2).

### 3.3. Glycaemic control and insulin detemir dosage

The entire cohort had poor glycaemic control at baseline with a mean±SD $HbA_{1c}$ 9.5±1.7% (80±11 mmol/mol). Insulin-naive patients had mean $HbA_{1c}$ levels of 9.5±1.7% (80±11 mmol/mol) while the prior insulin users had $HbA_{1c}$ levels of 9.3±1.4% (78±15 mmol/mol). Baseline FPG for the

**Table 2 – Proportion of patients experiencing hypoglycaemia**

| Hypoglycaemia | Percent with at least one event | | | |
|---|---|---|---|---|
| | | Entire cohort (n = 477) | Insulin naive (n = 372) | Prior insulin users (n = 105) |
| Overall | Baseline | 5.9 | 5.1 | 8.6 |
| | 24 weeks | 0 | 0 | 0 |
| | p | <0.0001 | <0.0001 | 0.0027 |
| Minor | Baseline | 5.9 | 5.1 | 8.6 |
| | Week 24 | 0 | 0 | 0 |
| | p | <0.0001 | <0.0001 | 0.0027 |
| Major | Baseline | 0.2 | 0.3 | 0 |
| | Week 24 | 0 | 0 | 0 |
| | p | 0.3173 | 0.3173 | –[a] |
| Nocturnal | Baseline | 5.7 | 4.8 | 8.6 |
| | Week 24 | 0 | 0 | 0 |
| | p | <0.0001 | <0.0001 | 0.0027 |

p-values are from McNemar's test on paired proportions of patients experiencing hypoglycaemia.
[a] No value available.

**Table 3 – Glucose control, insulin dose and body weight**

| Parameter | | Entire cohort (n = 477) | Insulin naive (n = 372) | Prior insulin users (n = 105) |
|---|---|---|---|---|
| $HbA_{1c}$, % | n | 175 | 147 | 28 |
| | Baseline | 9.5 (1.7) | 9.5 (1.7) | 9.3 (1.4) |
| | Week 24 | 7.3 (1.0) | 7.3 (1.0) | 7.1 (0.7) |
| | p | <0.001 | <0.001 | –[a] |
| $HbA_{1c}$, mmol/mol | n | 175 | 147 | 28 |
| | Baseline | 80 (19) | 80 (19) | 78 (15) |
| | Week 24 | 57 (11) | 57 (11) | 54 (8) |
| | p | <0.001 | <0.001 | –[a] |
| Proportion with $HbA_{1c}$ <7%, % | Baseline | 2.7 | 2.6 | 3.2 |
| | Week 24 | 32.5 | 32 | 33.9 |
| Fasting plasma glucose, mg/dL | n | 383 | 317 | 66 |
| | Baseline | 209.0 (66.0) | 219.1 (63.3) | 160.5 (56.7) |
| | Week 24 | 119.0 (20.6) | 118.5 (20.9) | 121.2 (18.9) |
| | p | <0.001 | <0.001 | –[a] |
| Post-prandial plasma glucose, mg/dL | n | 377 | 295 | 82 |
| | Baseline | 263.7 (81.6) | 263.0 (78.1) | 266.0 (93.5) |
| | Week 24 | 148.3 (39.6) | 147.8 (41.0) | 149.8 (34.3) |
| | p | <0.001 | <0.001 | –[a] |
| Insulin dose, U/kg | Pre-study | 0.37 (0.20) | – | 0.37 (0.20) |
| | Baseline | 0.22 (0.16) | 0.21 (0.08) | 0.26 (0.30) |
| | Week 24 | 0.34 (0.17) | 0.34 (0.17) | 0.36 (0.18) |
| Body weight, kg | n | 431 | 337 | 94 |
| | Baseline | 62.5 (10.6) | 61.6 (11.0) | 65.8 (8.2) |
| | Week 24 | 63.2 (9.3) | 62.6 (9.5) | 65.4 (7.9) |
| | p | 0.003 | <0.001 | 0.351 |

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

entire cohort was 209.0±66.0 mg/dL. Insulin-naive patients and prior insulin users had mean FPG levels of 219.1±63.3 and 160.5±56.7 mg/dL, respectively. PPPG levels were also high at baseline, 263.7±81.6 mg/dL for the entire cohort and 263.0±78.1 and 266.0±93.5 mg/dL for insulin-naive and prior insulin users groups, respectively (Table 3).

After 24 weeks of treatment with insulin detemir, there was significant improvement in all parameters of glycaemic control. Mean $HbA_{1c}$ level for the entire cohort was reduced to 7.3±1.0% (57±11 mmol/mol) with a change of 2.2% (24 mmol/mol) from baseline ($p < 0.001$). Insulin-naive patients showed a significant improvement of 2.2% (24 mmol/mol) from baseline ($p < 0.001$). Prior insulin users also showed a similar $HbA_{1c}$ improvement of 2.2% (24 mmol/mol) from baseline to Week 24. On further analysis into insulin-naive group, a reduction of

1.7±2.0%, 19±22 mmol/mol (from 8.2±1.8 [66±20 mmol/mol] to 6.6±1.2% [49±13 mmol/mol]) was seen in treatment naive patients. Mean FPG and PPPG levels decreased significantly in the entire cohort and in the insulin-naive group ($p < 0.001$). Prior insulin users also experienced a reduction of 39.3±51.6 mg/dL in FPG and 116.2±84.9 mg/dL in PPPG after 24 weeks of therapy. More than 32% patients were able to achieve target $HbA_{1c}$ of <7.0% (53 mmol/mol) at the end of study (Table 3).

Among insulin-naive patients, the mean starting dose of insulin detemir at baseline was 0.21±0.08 U/kg which was titrated to 0.34±0.17 U/kg during the course of 24 weeks. The baseline insulin detemir dose in prior insulin users was titrated to 0.36±0.18 U/day at Week 24 from a baseline dose of 0.26±0.30 U/kg (Table 3).

### 3.4. Body weight, blood lipids and blood pressure measurements

Prior insulin users had a mean weight loss of 0.4 kg after 24 weeks while the entire cohort and the insulin-naive group showed a mean weight gain of 0.7 kg and 0.9 kg, respectively (Table 3). These small changes in weight were clinically insignificant. Total cholesterol levels decreased from 5.4 to 4.7 mmol/L after 24 weeks (–0.7 mmol/L) and LDL cholesterol levels decreased from 3.3±1.1 to 2.8±0.7 mmol/L (–0.5 mmol/L) in the entire cohort. Reduction in systolic blood pressure, from 129.2±15.9 to 123.5±13.9 mmHg, was significant for the entire cohort (–5.7 mmHg, $p < 0.001$).

### 3.5. QoL

EQ VAS scores increased significantly by 11.6 points ($p < 0.001$) i.e. from 70.3 points at baseline to 81.9 points after 24 weeks. The highest improvement (12.4 points, $p < 0.001$) was seen in insulin-naive group. A significantly greater proportion of subjects reported that they were not as anxious or depressed at 24 weeks as compared to baseline (86.3% vs 74.6%, $p < 0.0001$). The majority of patients (96.4%) stated that they have no problems with self-care after 24 weeks, as compared to 87.7% at the baseline ($p < 0.0001$). A total of 74.6% patients reported no problems with performing their usual activities at the baseline, while the number rose to 90.8% at the end of study ($p < 0.0001$). No pain or discomfort was reported in 86.1% patients at Week 24 as compared to 69.1% patients at baseline ($p < 0.0001$).

## 4. Discussion

Basal insulin with or without OGLDs is an effective option for insulin initiation. Long-acting insulins, such as insulin detemir, could be regarded as one of the foundation insulins for building glycaemic control, especially as a once-daily regimen. However, data on the safety and effectiveness of insulin detemir was not available in the Indonesian population. This is the first study to evaluate safety and efficacy of insulin detemir and its effect on quality of life in Indonesian T2D patients.

Overall, this Indonesian T2D cohort demonstrated poor glycaemic control with $HbA_{1c}$ in the range of 9.5% (80 mmol/mol) at baseline. This observation was also made in the DiabCare study suggesting an immediate need to intensify pharmacotherapy while adopting multi-disciplinary T2D management approaches in Indonesia [14]. In order to effectively reduce the micro/macrovascular complications of diabetes, the American Diabetes Association suggests a target $HbA_{1c}$ <7.0% (53 mmol/mol) [6]. At baseline, only 2.7% patients had $HbA_{1c}$ levels <7.0% (53 mmol/mol) while after 24 weeks of insulin detemir therapy 32.5% patients achieved the target.

Insulin detemir has been shown to reduce $HbA_{1c}$ levels effectively. The 26-week, randomized, controlled PREDICTIVE study reported a decrease in mean $HbA_{1c}$ value from 8.9% (74 mmol/mol) to 7.8% (62 mmol/mol) with once-daily insulin detemir [15]. In another randomized, open-label, multi-center trial of patients with poorly controlled T2D, morning (pre breakfast) and evening insulin detemir doses were associated with 1.58% (17 mmol/mol) and 1.48% (16 mmol/mol), reductions in $HbA_{1c}$ respectively [16]. TITRATE, a 20-week, randomized, controlled, open-label, multi-center, treat-to-target study of insulin-naive T2D patients, showed a 1.2% (13 mmol/mol) reduction in $HbA_{1c}$ levels [17]. The current sub-group analysis from the $A_1$chieve study shows a 2.2% (24 mmol/mol) decrease in $HbA_{1c}$ levels in Indonesian patients. This decrease will have multifold effects on risk reduction for diabetic complications as each 1% reduction in mean $HbA_{1c}$ has been shown to reduce the risk of deaths by 21%, the risk of myocardial infarction by 14% and reduce microvascular complications by 37% [18]. Additionally, this Indonesian cohort of the $A_1$chieve study showed a clinically significant decrease of 90.0 mg/dL (5.0 mmol/L) in FPG levels with a numerically higher decrease of 100.6 mg/dL (5.6 mmol/L) in the insulin-naive group. A subgroup analysis of the PREDICTIVE study had shown a reduction of 3.7 mmol/L in FPG after 14 weeks of insulin detemir treatment [19]. Similarly, FPG improved from 10.8 to 7.1 mmol/L in a 52 weeks multinational, randomized, open-labeled treat-to-target trial comparing insulin detemir with insulin glargine when administered as add-on to OGLDs in insulin-naive patients [20].

Hypoglycaemia remains a major side effect of attempts to improve glycaemic control in diabetes. The deleterious effects of hypoglycaemia in diabetes include vasoconstriction, tachycardia, and platelet aggregation due to the sympatho-adrenal epinephrine response. All of these effects are thought to increase risk for acute coronary events and sudden cardiac death in high-risk cardiovascular patients with diabetes suffering frequent or severe hypoglycaemia [21–23]. Minimizing hypoglycaemia, is thus of utmost importance when treating diabetes and considering appropriate glycaemic goals patients. Across the trials that reported incidences of hypoglycaemic event in patients with type 1 diabetes or T2D, episodes of major hypoglycaemia were documented in fewer than 10% of patients receiving insulin detemir [24]. In the $A_1$chieve study, 5.9% of the 66,726 patients enrolled experienced at least

one episode of hypoglycaemia during the study [3]. In this Indonesian cohort none of the patients experienced hypoglycaemia. However, due to the observational study design, recall bias may have led to an under-reporting of hypoglycaemic events.

Weight gain is also an important concern as a potential side effect of treatment for patients with T2D receiving certain oral therapies or insulin. The increase in body weight associated with anti-diabetic therapy may blunt the clinical benefit of improved glycaemic control associated with such therapy. A report of data pooled from two randomized, parallel group trials of 22 and 24 weeks' duration reported that patients treated with insulin detemir had minimal weight gain (mean <1 kg) regardless of their BMI at entry; whereas, in patients treated with NPH insulin, weight gain increased with BMI after treatment (mean weight gain approx. 2.4 kg) [25]. In this Indonesian cohort receiving insulin detemir, the mean weight gain was 0.7 kg. Interestingly, prior insulin users actually lost 0.4 kg of weight. The decreased risk of hypoglycaemia with insulin detemir and a more consistent and reliable delivery of the desired dose, can be a possible mechanism that contributes to decreased defensive snacking and in turn helps to limit weight gain. Improved lipid profile and blood pressure control at the end of the study further reduce cardiovascular risk in T2D patients.

Duration and type of diabetes are not consistently associated with quality of life. It is difficult to ascertain which part of disease or management affects the quality of life. However, having better glycaemic control is associated with better quality of life [26]. Statistically significant improvement was observed in most measures of quality of life with insulin detemir in the Indonesian cohort. Better glycaemic control with decreased episodes of hypoglycaemia may be the contributors in improved quality of life.

Although this subgroup analysis has provided novel insight about T2D population status, safety and efficacy of insulin detemir in Indonesia, being an observational study, there are some inherent limitations. Concomitant medications were not controlled. The study was non-randomized and no standardized treatment protocol was enforced. The study lacked a control arm and most safety parameters were based on participant recall or diaries.

In conclusion, this study has shown that insulin detemir was effective in poorly controlled T2D patients from Indonesia. The safety and efficacy of insulin detemir has been established in both insulin-naive patients as well as prior insulin users. Furthermore, it may also help in improving other metabolic parameters and improve patients' QoL. The observations of this study may help overcome the fear of hypoglycaemia and clinical inertia in early initiation of insulin in T2D patients.

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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 Ida Ayu Kshanti has received honorarium for lectures from Novo Nordisk, Eli Lilly, Aventis, Takeda, MSD, Dexa Medica, Boehringer Ingelheim, Bayer, Merck and BD. R. Bowo Pramano has no conflict of interest to report. 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. Tjokorda Gde Dalem-Pemayun has served as a consultant (Advisory board) for MSD, AstraZeneca and sanofi aventis and has received honorarium for lectures from Novo Nordisk, sanofi aventis, Merck, MSD, AstraZeneca, Eli Lilly and Kalbe Farma. 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.

## REFERENCES

[1] Ramachandran A, Snehalatha C, Shetty AS, Nanditha A. Trends in prevalence of diabetes in Asian countries. World J Diabetes 2012;3(6):110–7.
[2] International Diabetes Federation. IDF Diabetes Atlas. 5th edn. Brussels, Belgium; 2011, updated 14 November 2012.
[3] Home P, Naggar NE, Khamseh M, Gonzalez-Galvez G, Shen C, Chakkarwar P, et al. An observational non-interventional study of people with diabetes beginning or changed to insulin analogue therapy in non-Western countries: the $A_1$chieve study. Diabetes Res Clin Pract 2011;94(3):352–63.
[4] Currie CJ, Peters JR, Tynan A, Evans M, Heine RJ, Bracco OL, et al. Survival as a function of $HbA_{1c}$ in people with type 2 diabetes: a retrospective cohort study. Lancet 2010;375:481–9.
[5] Qayyum R, Greene L. AHRQ's comparative effectiveness research on premixed insulin analogues for adults with type 2 diabetes: understanding and applying the systematic review findings. J Manag Care Pharm 2011;17(3):S3–19.
[6] American Diabetes Association. Standards of medical care in diabetes – 2012. Diabetes Care 2012;35(1):S11–63.

[7] Vaag A, Lund SS. Insulin initiation in patients with type 2 diabetes mellitus: treatment guidelines, clinical evidence and patterns of use of basal vs premixed insulin analogues. Eur J Endocrinol 2012;166(2):159–70.
[8] Dornhorst A, Lüddeke HJ, Sreenan S, Kozlovski P, Hansen JB, Looij BJ, et al.; PREDICTIVE Study Group. Insulin detemir improves glycaemic control without weight gain in insulin-naïve patients with type 2 diabetes: subgroup analysis from the PREDICTIVE study. Int J Clin Pract 2008;62(4):659–65.
[9] Nelson SE. Detemir as once-daily basal insulin in type 2 diabetes. Clin Pharmacol 2011;3:27–37.
[10] John M. Basal insulin analogues – a review of recent data on efficacy and safety. J Assoc Physicians India 2011;59: 25–8.
[11] Philis-Tsimikas A. An update on the use of insulin detemir, with a focus on type 2 diabetes (drug evaluation update). Expert Opin Pharmacother 2008;9:2181–95.
[12] Soewondo P, Jain A. Effect of insulin detemir (Levemir®) on risk of hypoglycaemia and glycaemic parameters: Experience from real life practice in Indonesian patients with diabetes mellitus. JAFES 2012;26(1):51–5.
[13] Yang W, Zilov A, Soewondo P, Bech OM, Sekkal F, Home PD. Observational studies: going beyond the boundaries of randomized controlled trials. Diabetes Res Clin Pract 2010;88(1):S3–9.
[14] Soewondo P, Soegondo S, Suastika K, Pranoto A, Soeatmadji DW, Tjokroprawiro A. The DiabCare Asia 2008 study – Outcomes on control and complications of type 2 diabetic patients in Indonesia. Med J Indones 2010;19(4):235–44.
[15] Fajardo Montañana C, Hernández Herrero C, Rivas Fernández M. Less weight gain and hypoglycaemia with once-daily insulin detemir than NPH insulin in intensification of insulin therapy in overweight type 2 diabetes patients: the PREDICTIVE BMI clinical trial. Diabet Med 2008;25(8):916–23.
[16] Philis-Tsimikas A, Charpentier G, Clauson P, Ravn GM, Roberts VL, Thorsteinsson B. Comparison of once-daily insulin detemir with NPH insulin added to a regimen of oral antidiabetic drugs in poorly controlled type 2 diabetes. Clin Ther 2006;28(10):1569–81.
[17] Blonde L, Merilainen M, Karwe V, Raskin P; TITRATE Study Group. Patient-directed titration for achieving glycaemic goals using a once-daily basal insulin analogue: an assessment of two different fasting plasma glucose targets – the TITRATE study. Diabetes Obes Metab 2009;11(6):623–31.
[18] Stratton IM, Adler AI, Neil HA, Matthews DR, Manley SE, Cull CA, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. BMJ 2000;321(7258):405–12.
[19] Dornhorst A, Lüddeke HJ, Honka M, Ackermann RW, Meriläinen M, Gallwitz B, et al. Safety and efficacy of insulin detemir basal–bolus therapy in type 1 diabetes patients: 14-week data from the European cohort of the PREDICTIVE study. Curr Med Res Opin 2008;24(2):369–76.
[20] Rosenstock J, Davies M, Home PD, Larsen J, Koenen C, Schernthaner G. A randomised, 52-week, treat-to-target trial comparing insulin detemir with insulin glargine when administered as add-on to glucose-lowering drugs in insulin-naive people with type 2 diabetes. Diabetologia 2008;51(3):408–16.
[21] Sprague JE, Arbeláez AM. Glucose counterregulatory responses to hypoglycemia. Pediatr Endocrinol Rev 2011;9(1):463–73.
[22] Panicker GK, Karnad DR, Salvi V, Kothari S. Cardiovascular risk of oral antidiabetic drugs: current evidence and regulatory requirements for new drugs. J Assoc Physicians India 2012;60:56–61.
[23] Ligthelm RJ, Kaiser M, Vora J, Yale JF. Insulin use in elderly adults: risk of hypoglycemia and strategies for care. J Am Geriatr Soc 2012;60(8):1564–70.
[24] Chapman TM, Perry CM. Insulin detemir: a review of its use in the management of type 1 and 2 diabetes mellitus. Drugs 2004;64(22):2577–95.
[25] Raslová K, Tamer SC, Clauson P, Karl D. Insulin detemir results in less weight gain than NPH insulin when used in basal–bolus therapy for type 2 diabetes mellitus, and this advantage increases with baseline body mass index. Clin Drug Invest 2007;27(4):279–85.
[26] Rubin RR, Peyrot M. Quality of life and diabetes. Diabetes Metab Res Rev 1999;15(3):205–18.

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# Clinical experience with BIAsp 30: Results from the Indonesian cohort of the international $A_1$chieve 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 $A_1$chieve 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. $A_1$chieve 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

$A_1$chieve 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 $A_1$chieve 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 $A_1$chieve 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.

## REFERENCES

[1] Soegondo S, Widyahening IS, Istantho R, Yunir E. Prevalence of diabetes among suburban population of Ternate – a small remote island in the eastern part of Indonesia. Acta Med Indones 2011;43(2):99–104.
[2] Mayfield JA, White RD. Insulin therapy for type 2 diabetes: rescue, augmentation, and replacement of beta-cell function. Am Fam Physician 2004;70:489–500.
[3] Rodbard HW, Blonde L, Braithwaite SS, Brett EM, Cobin RH, Handelsman Y, et al.; AACE Diabetes Mellitus Clinical Practice Guidelines Task Force. American Association of Clinical Endocrinologists medical guidelines for clinical practice for the management of diabetes mellitus. Endocr Pract 2007;13(Suppl 1):1–68.
[4] Turner RC, Cull CA, Frighi V, Holman RR. Glycemic control with diet, sulfonylurea, metformin, or insulin in patients with type 2 diabetes mellitus: progressive requirement for multiple therapies (UKPDS 49). JAMA 1999;281:2005–12.
[5] Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, et al. Management of hyperglycaemia in type 2 diabetes: a patient-centered approach. Position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetologia 2012;55(6):1577–96.
[6] Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-Year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med 2008;359(15):1577–89.
[7] Rolla AR, Rakel RE. Practical approaches to insulin therapy for type 2 diabetes mellitus with premixed insulin analogues. Clin Ther 2005;27(8):1113–25.
[8] Valensi P. Biphasic insulin aspart 30/70 (BIAsp 30) in the treatment of type 1 and type 2 diabetes. Diabetes Metab Syndr Obes 2009;2:61–71.
[9] Garber AJ, Wahlen J, Wahl T, Bressler P, Braceras R, Allen E. Attainment of glycemic goals in type 2 diabetes with once-, twice-, or thrice-daily dosing with biphasic insulin aspart 70/30 (The 1-2-3 study). Diabetes Obes Metab 2006;8(1):58–66.
[10] Home P, Naggar NE, Khamseh M, Gonzalez-Galvez G, Shen C, Chakkarwar P, et al. An observational non-interventional study of patients with diabetes beginning or changed to insulin analogue therapy in non-Western countries: The $A_1$chieve study. Diabetes Res Clin Pract 2011;94:352–63.
[11] Soewondo P, Soegondo S, Suastika K, Pranoto A, Soeatmadji DW, Tjokroprawiro A. The DiabCare Asia 2008 study – Outcomes on control and complications of type 2 diabetic patients in Indonesia. Med J Indones 2010;19:235–44.
[12] Kann PH, Wascher T, Zackova V, Moeller J, Medding J, Szocs A, et al. Starting insulin therapy in type 2 diabetes: twice-daily biphasic insulin aspart 30 plus metformin versus once-daily insulin glargine plus glimepiride. Exp Clin Endocrinol Diabetes 2006;114(9):527–32.
[13] Valensi P, Benroubi M, Borzi V, Gumprecht J, Kawamori R, Shaban J, et al. Initiating insulin therapy with, or switching existing insulin therapy to, biphasic insulin aspart 30/70 (NovoMix 30) in routine care: safety and effectiveness in patients with type 2 diabetes in the IMPROVE observational study. Int J Clin Pract 2009;63(3):522–31.
[14] Bebakar WM, Chow CC, Kadir KA, Suwanwalaikorn S, Vaz JA, Bech OM. Adding biphasic insulin aspart 30 once or twice daily is more efficacious than optimizing oral antidiabetic treatment in patients with type 2 diabetes. Diabetes Obes Metab 2007;9(5):724–32.
[15] Gao Y, Guo XH. Switching from human insulin to biphasic insulin aspart 30 treatment gets more patients with type 2 diabetes to reach target glycosylated hemoglobin <7%: the results from the China cohort of the PRESENT study. Chin Med J (Engl) 2010;123(9):1107–11.
[16] Khutsoane D, Sharma SK, Almustafa M, Jang HC, Azar ST, Danciulescu R, et al. Biphasic insulin aspart 30 treatment improves glycaemic control in patients with type 2 diabetes in a clinical practice setting: experience from the PRESENT study. Diabetes Obes Metab 2008;10(3):212–22.
[17] Yoshioka N, Kurihara Y, Manda N, Komori K, Kato M, Kijima H, et al. Step-up therapy with biphasic insulin aspart-70/30 – Sapporo 1-2-3 study. Diabetes Res Clin Pract 2009;85(1):47–52.
[18] Raskin P, Allen E, Hollander P, Lewin A, Gabbay RA, Hu P, et al. Initiating insulin therapy in type 2 diabetes: a comparison of biphasic and basal insulin analogs. Diabetes Care 2005;28:260–5.
[19] Esteghamati A, Rajabian R, Amini M, Bahrami A, Khamseh ME, Afkhami-Ardekani M, et al. The safety and efficacy of biphasic insulin aspart 30 (BIAsp 30) in Iranians with type 2 diabetes: an open-label, non-randomised, multi-centre observational study – the Iran subgroup of the IMPROVE™ study. Endokrynol Pol 2010;61(4):364–70.