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Safety and effectiveness of insulin aspart in type 2 diabetic patients: Results from the ASEAN cohort of the A_1chieve 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_1chieve 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_1chieve 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_1chieve study and to characterize the current status of T2D management in this region.

2. Methods

2.1. Study design

The A_1chieve 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_1chieve 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_1chieve 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_1chieve 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_1chieve 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_1chieve 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.

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