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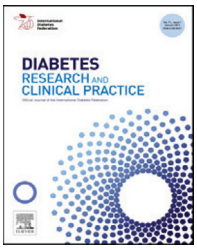

Safety and effectiveness of insulin detemir in type 2 diabetes: Results from the ASEAN cohort of the A$_1$chieve study

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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_1chieve [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_1chieve 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_1chieve [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

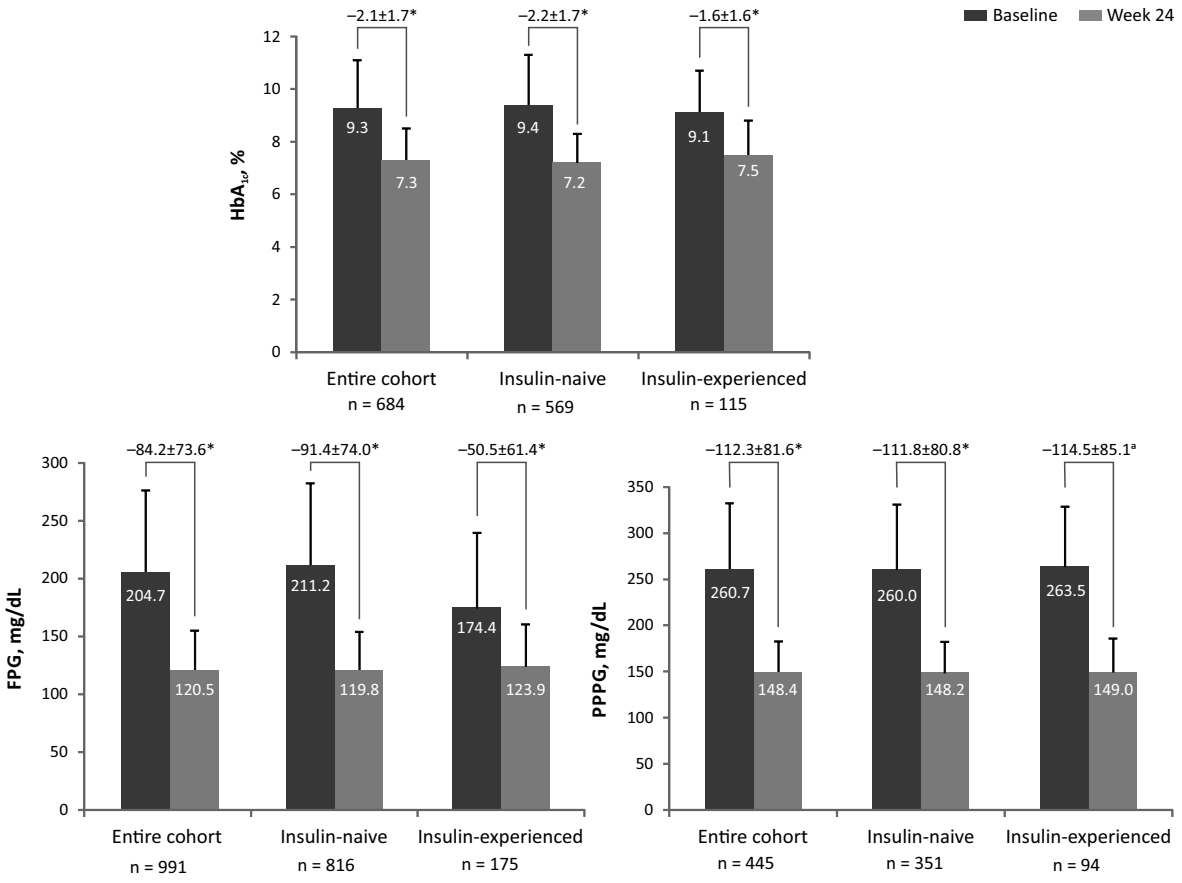

Fig. 1 – Change in glucose control parameters from baseline to Week 24. *p < 0.001.

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_1chieve 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_1chieve 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.

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