ORIGINAL ARTICLE

Journal of the ASEAN Federation of Endocrine Societies

Initiating or Switching to Insulin Degludec/Insulin Aspart in Adults With Type 2 Diabetes in the Philippines: Results from a Prospective, Non-interventional, Real-World Study

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Abstract

Objectives. Blood glucose levels of the majority of Filipino patients with type 2 diabetes (T2D) remain uncontrolled. Insulin degludec/insulin aspart (IDegAsp) is a fixed-ratio co-formulation of the long-acting basal insulin degludec and the rapid-acting prandial insulin aspart. The real-world ARISE (A Ryzodeg® Initiation and Switch Effectiveness) study investigated clinical outcomes across six countries in people with T2D who initiated IDegAsp. This publication presents the clinical outcomes of the Filipino cohort from a subgroup analysis of the ARISE study.

Methodology. This 26-week, open-label, non-interventional study examined outcomes in adults with T2D initiating or switching to IDegAsp (N=185) from other antidiabetic treatments per local clinical guidance.

Results. Compared with the baseline, there was a significant improvement in glycated hemoglobin at the end of the study (EOS) (estimated difference [ED] −1.4% [95% confidence interval −1.7, −1.1]; *P*<0.0001). Fasting plasma glucose (ED −46.1 mg/dL [−58.2, −34.0]; *P*<0.0001) and body weight (ED −1.0 kg [−2.0, −0.1]; *P*=0.028) were significantly reduced at EOS compared with baseline. IDegAsp was associated with a decrease in the incidence of self-reported healthcare resource utilization. Adverse events were reported in eight (4.3%) participants.

Conclusions. Initiating or switching to IDegAsp was associated with improved glycemic control, lower body weight, and lower HRU for people with T2D in the Philippines. No new, unexpected AEs were reported.

Key words: insulin aspart; insulin degludec, insulin aspart drug combination; type 2 diabetes

INTRODUCTION

It is estimated that 6.3% of the global population is affected by type 2 diabetes (T2D).[1] In the Philippines, there are an estimated 4.3 million adults aged 20–79 years with diabetes, which equates to a prevalence of 7.1%.[2] Amid a background of increasing overweight, obesity[3] and a genetic predisposition among the Asian population,[4] T2D represents a major cause of morbidity and mortality in the Philippines.[5–7] The increasing prevalence and incidence of T2D poses a significant challenge for the region's healthcare system.[8]

A 2008 study of people with T2D in the Philippines found that mean glycated hemoglobin (HbA1c) levels were 8.0%, and a few individuals (15%) achieved the American Diabetes Association target of HbA1c <7.0%, indicating suboptimal management.[9] As a consequence, healthcare

eISSN 2308-118x (Online)
Printed in the Philippines

Received: August 24, 2023. October 28, 2023.
Published online first: August 5, 2024.
https://doi.org/10.15605/jafes.039.02.02

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resource utilization (HRU) is increased, as people with T2D-related complications are more likely to be hospitalized and have extended hospital stays compared to those without complications.[10]

Efforts to improve access to affordable insulin are ongoing. The Philippine Department of Health (DOH) launched the Insulin Medicine Access Program in 2009.[11,12] This public-private partnership provides insulin to 22 hospitals nationwide. However, as these are mainly city-based hospitals, access remains limited for people living in rural or deprived areas who are unable to travel.[11]

In 2014, the national healthcare insurance company in the Philippines, PhilHealth, implemented new guidelines to improve access to medication for non-communicable diseases, including diabetes.[8] Insurance coverage has been limited to oral antidiabetic (OAD) medication only. Consequently, many people with low to middle income face continued challenges in accessing vital medication when a single insulin pen costs three days' minimum wage.[8,11] The 2019 Universal Health Care Act established the Health Technology Assessment Council, an advisory body to provide recommendations on medicines for government funding. Although there are barriers to including new medications in the Philippine National Formulary (PNF), insulin glargine has recently been included based on a recommendation by the Health Technology Assessment Council.[13,14] The availability of biosimilars will facilitate competitive bidding and help reduce costs.[13] However, research suggests that the availability of diabetes medicines, including those in the PNF, is often low in both public and private medicine outlets,[15] and access to medication may remain an issue for people with T2D.

Disease management is often suboptimal, even among people receiving insulin, and many struggle to maintain blood glucose control.[5,9] Using a co-formulation that simplifies the insulin regimen and improves medication management could promote better glycemic control and improve individuals' health-related quality of life. Early and effective glycemic control is crucial in minimizing the burden of T2D. Therefore, there is an urgent need to overcome the current barriers preventing people with T2D in the Philippines from accessing essential care and medication.

Insulin degludec/insulin aspart (IDegAsp) is a fixed-ratio co-formulation of the long-acting basal insulin degludec and the rapid-acting prandial insulin aspart.[16] The BOOST clinical trial program assessed the efficacy and safety of IDegAsp in participants with T2D. This program has demonstrated the potential for IDegAsp to be used for both insulin initiation and treatment intensification.[17–19] Long-term glycemic control was improved, and non-inferiority was demonstrated with IDegAsp versus biphasic insulin aspart 30 in adults with T2D who were insulin-naïve or inadequately controlled on once- or twice-daily basal, premixed, or self-mixed insulin.[17,18] Improved glucose control was also observed in Japanese adults inadequately controlled with OADs and treated with IDegAsp compared with once-daily insulin glargine.[20] Additionally, the IDegAsp co-formulation yielded similar improvements in glycemic control versus a basal-bolus regimen of separate insulin degludec (IDeg) and insulin aspart (IAsp) injections. This indicates the potential of the IDegAsp co-formulation to provide a simplified alternative to a basal-bolus approach to treatment intensification.[19]

Supporting these clinical trial data are two real-world studies in which switching to IDegAsp from twice-daily premixed insulin (N = 55), intensive insulin therapy (N = 60), or insulin glargine ± prandial insulin (N = 236) was associated with improvement in, or maintenance of, glycemic control and fasting plasma glucose (FPG), and lower daily basal and/or total insulin requirement.[21,22]

The ARISE study investigated glycemic control and other clinical outcomes in a real-world clinical setting across six countries in people with T2D who initiated IDegAsp or switched to IDegAsp from alternative antidiabetic treatment according to local clinical practice (Supplementary Figure S1).[23] The ARISE study has provided the first real-world evidence from the Philippines on the IDegAsp co-formulation. This individual country analysis aims to assess the potential impact of IDegAsp on diabetes management in the Philippines.

METHODOLOGY

Study design and population

Study details have been published previously, but in summary, this was a 26-week, real-world, multi-center, open-label, prospective, non-interventional study examining outcomes in adults with T2D treated with IDegAsp at the discretion of their physician (Supplementary Figure S1).[23–25]

Informed consent was obtained prior to study initiation at the baseline visit. The study consisted of intermediate observational visits in accordance with local clinical practice and an end-of-study (EOS) visit, the first visit within the window from weeks 26–36. The decision to initiate or switch to IDegAsp treatment was taken before study initiation and was independent of the decision to include an individual in the study.

Patients with T2D, fulfilling the inclusion and exclusion criteria of the study, were enrolled in the clinics of participating physicians. Data collection was done between September 2019 and December 2020 from 12 sites across the Philippines.

The study was conducted in accordance with the Declaration of Helsinki 2013. A list of independent ethics committees and institutional review boards that approved the study has been published previously.[23]

Study objectives and endpoints

The primary objectives and endpoints of the ARISE study were published previously.[23] The main objective of this analysis was to evaluate glycemic control and other clinical and safety outcomes after initiating or switching to IDegAsp in the subset of the Filipino population (n = 156 completers, n = 298 recruited initially). The sampling methodology was purposive, with patients recruited at the discretion of their clinician. Assuming a mean change in HbA1c of 0.5% (standard deviation [SD], 1.8%) and a missing HbA1c value at EOS in 25% of participants, a minimum of 139 participants were required to detect an HbA1c difference at 90% power.[23] Descriptive statistics (mean, SD, median and range for continuous variables and proportion for categorical variables) were used to describe participants' baseline characteristics.

The primary endpoint was the change in laboratory-measured HbA1c levels from baseline to EOS. Secondary endpoints included the proportion of participants achieving HbA1c levels <7% at EOS, the proportion of participants achieving HbA1c levels below a predefined individualized treatment target at EOS and change from baseline to EOS in FPG, body weight, and total, basal and prandial insulin dose. Additional endpoints included participant-reported non-severe hypoglycemic episodes (nocturnal and total) occurring within four weeks before IDegAsp initiation and within four weeks before EOS and severe hypoglycemic episodes occurring within 26 weeks before IDegAsp initiation and during the 26-week study period, as defined previously.[23]

Secondary objectives were designed to describe the clinical use of IDegAsp in a real-world setting, including physicians' reasons for initiating or discontinuing treatment. HRU associated with the T2D management and related complications was included as an exploratory endpoint.

Statistical methods

The Philippines full analysis set (FAS) included all eligible participants who gave informed consent and initiated treatment with IDegAsp. The in-study observation period was from the informed consent and treatment initiation visit to study completion (first visit within weeks 26–36). Reasons for not completing the study included withdrawal of informed consent and participant lost to follow-up, deceased, or uncontactable (e.g., closure of study site). The on-treatment observation period was the period in which participants were treated with IDegAsp. Values measured after treatment discontinuation were disregarded.

Statistical tests for the primary and secondary endpoints were performed as two-sided tests with a significance level of 0.05. The analysis was performed using SAS software. No adjustments were made for multiple comparisons. The primary endpoint analysis was conducted with a mixed model for repeated measurements and based on all participants with at least one post-baseline HbA1c measurement using the 'in-study' observation period. Secondary analyses of the primary endpoint were conducted using 'on-treatment' data only. The crude model included baseline HbA1c and time of HbA1c measurement as covariates. The adjusted model included baseline HbA1c, time of HbA1c measurement, age, sex, body mass index (BMI) and previous antidiabetic treatment regimen as covariates. Covariates were included in the model based on apriori knowledge regarding factors that could potentially influence glycemic control. The incidence rates of non-severe, nocturnal and severe hypoglycemia were analyzed using descriptive statistics. Safety data on adverse events (AEs) were also reported using descriptive statistics. HbA1c and FPG were done in local laboratories at the request of the managing clinician. Per routine practice, body weight and insulin dose were evaluated during site visits. Hypoglycemia was self-reported.

RESULTS

Study population demographics and clinical characteristics

The overall study population results have been reported previously.[23] Of the 298 people recruited for the study in the Philippines, 185 switched to or initiated IDegAsp and were included in the FAS. Of these, 156 participants (84.3%)

Table 1. Demographics and clinical characteristics at baseline

	Philippines N = 185
Age, mean (SD)	58.5 (12.2)
Sex n (%)	
Female	111 (60.0)
Male	74 (40.0)
Duration of diabetes (years), mean (SD)	10.8 (7.3)
Body weight (kg)[a], mean (SD)	67.1 (14.1)
BMI (kg/m^2), mean (SD)	26.0 (5.3)
HbA1c (%)[a], mean (SD)	10.2 (2.1)
FPG (mg/dL)[a], mean (SD)	208.0 (84.1)
Antidiabetic treatment, n (%)	
OADs only	83 (48.0)
Premix insulin ± bolus insulin (± OADs)	18 (10.4)
Basal insulin only (± OADs)	57 (32.9)
Basal–bolus insulin (± OADs)	11 (6.4)
GLP-1 RA ± insulin (± OADs)	4 (2.3)
Dose of previous prandial insulin (U), mean (SD)	24.6 (21.2)
Diabetes complications, n (%)	
Diabetic neuropathy	35 (27.3)
Diabetic nephropathy	24 (18.8)
Cardiovascular disease	12 (9.4)
Diabetic retinopathy	12 (9.4)
Peripheral vascular disease	4 (3.1)

Global ARISE study data were published previously.[25] OADs included sulfonylureas, meglitinides, biguanides, thiazolidinediones, dipeptidyl peptidase 4 inhibitors, sodium glucose co-transporter 2 inhibitors, and α-glucosidase inhibitors.

[a]Baseline assessments from ≤12 weeks prior to signing informed consent and initiating IDegAsp treatment.

BMI: body mass index; FPG: fasting plasma glucose; GLP-1 RA: glucagon-like peptide-1 receptor agonist; HbA1c: glycated hemoglobin; N: number of participants in the full analysis set; OAD: oral antidiabetic drug; SD: standard deviation; U: units.

completed the study. Baseline demographics and clinical characteristics are presented in Table 1. At baseline, the mean (standard deviation [SD]) age was 58.5 (12.2) years, HbA1c was 10.2 (2.1) %, body weight was 67.1 (14.1) kg, BMI was 26.0 (5.3) kg/m^2, and duration of diabetes was 10.8 (7.3) years.

Prior to initiating or switching to IDegAsp, 173 participants had received prior anti-hyperglycemic treatment. Of these, 48.0% were receiving OADs only, and 32.9% were receiving basal insulin, 10.4% premix insulin, 6.4% basal–bolus insulin, and 2.3% glucagon-like peptide-1 receptor agonists with or without insulin, with or without OADs.

At treatment initiation, 132 participants (71.4%) received IDegAsp once daily, and 52 (28.1%) received IDegAsp twice daily. One patient had a regimen listed as "other," i.e., neither once- or twice-daily dosing. The most frequently cited reasons physicians gave for switching people with T2D to IDegAsp were to improve glycemic control (95.7%), promote convenience and flexibility in the dosing regimen (30.3%), have fewer injections compared with basal and bolus therapy (29.7%), and lower the risk for hypoglycemia. (23.3%) (Supplementary Table S1). Physicians could report more than one reason for initiation. For the 13 instances where IDegAsp treatment was discontinued, an unacceptable glycemic profile was cited as a reason for one participant. In the remaining 12 instances, reasons were not specified.

Glycemic control

The observed mean (SD) HbA1c, adjusted for covariates, at baseline was 10.0% (2.1%), and the estimated mean (SD) at EOS was 8.5% (0.2%). HbA1c was statistically significantly lower at EOS compared with baseline (estimated difference −1.4% [95% confidence interval {CI} −1.7, −1.1]; *P*<0.0001; Table 2). Similarly, there was a significant reduction in FPG from baseline to EOS (estimated difference −46.1 mg/dL [95% CI −58.2, −34.0]; *P*<0.0001). The proportion of participants with HbA1c levels <7.0% increased from 2.2% (n=4) at baseline to 17.2% (n=23) at EOS. The proportion of

Table 2. Adjusted mixed model for repeated measurements showing change in HbA1C; FPG; body weight; and total, basal, and prandial insulin dose over 36 weeks of IDEGASP treatment in the Philippines

	In-study observation period, N=185	On-treatment observation period, N=185
Change in HbA1c (%)		
Patients analyzed, n	135	135
Observed mean HbA1c at baseline, % (SD)	10.0 (2.1)	10.0 (2.1)
Estimated mean HbA1c at EOS (week 36), % (SE)	8.5 (0.2)	8.5 (0.2)
Estimated mean change, % (95% CI)	−1.4 (−1.7, −1.1), P<0.0001	−1.4 (−1.7, −1.1), P<0.0001
HbA1c less than 7%		
At baseline, n (%)	4 (2.2)	4 (2.2)
At EOS, n (%)[a]	23 (17.2)	23 (17.2)
HbA1c less than pre-defined individual treatment target[b]		
At baseline, n (%)	4 (2.2)	4 (2.2)
At EOS, n (%)[a]	22 (16.4)	22 (16.4)
Change in FPG (mg/dL)		
Patients analyzed, n	129	125
Observed mean FPG at baseline, mg/dL (SD)	206.8 (82.8)	207.6 (83.0)
Estimated mean FPG at EOS (week 36), mg/dL (SE)	161.2 (6.1)	162.2 (6.3)
Estimated mean change, mg/dL (95% CI)	−46.1 (−58.2, −34.0), P<0.0001	−45.5 (−58.1, −32.9), P<0.0001
Change in body weight (kg)		
Patients analyzed, n	148	148
Observed mean body weight at baseline, kg (SD)	67.3 (14.8)	67.3 (14.8)
Estimated mean body weight at EOS (week 36), kg (SE)	67.5 (0.5)	67.5 (0.5)
Estimated mean change, kg (95% CI)	−1.0 (−2.0, −0.1), P=0.028	−1.0 (−2.0, −0.1), P= 0.028
Change in total insulin dose (U)		
Patients analyzed, n	79	-
Observed mean total insulin dose at baseline, U (SD)	38.2 (29.3)	-
Estimated mean total insulin dose at EOS (week 36), U (SE)	39.1 (2.0)	-
Estimated mean change,U (95% CI)	1.2 (−2.7, 5.1)	-
Change in basal insulin dose		
Patients analyzed, n	79	-
Observed mean basal insulin dose at baseline, U (SD)	30.0 (15.7)	-
Estimated mean basal insulin dose at EOS (week 36), U (SE)	26.3 (1.2)	-
Estimated mean change,U (95% CI)	−3.3 (−5.6, −1.0)	-
Change in prandial insulin dose		
Patients analyzed, n	79	-
Observed mean prandial insulin dose at baseline, U (SD)	8.2 (16.8)	-
Estimated mean prandial insulin dose at EOS (week 36), U (SE)	12.9 (1.0)	-
Estimated mean change,U (95% CI)	4.6 (2.6, 6.6)	-

The adjusted model included age, sex, body mass index, and previous anti-hyperglycemic treatment regimen as baseline covariates.

[a] n=134; [b] Categories of pre-defined individual treatment target ranges for HbA1c (%) levels were <6.5, 6.5 to <7.0, 7.0 to <7.5, 7.5 to <8.0, and ≥8.

CI: confidence interval; EOS: end of study; FPG: fasting plasma glucose; HbA1c: glycated hemoglobin; IDegAsp: insulin degludec/insulin aspart; N: number of participants in the Philippines full analysis set; n: number of participants; SD: standard deviation; SE: standard error.

participants achieving HbA1c levels below their predefined individual treatment target increased from 2.2% at baseline (n=4) to 16.4% (n=22) at EOS (Table 2).

Body weight

There was a significant reduction in body weight in the overall study population at EOS compared with baseline (estimated difference −1.0 kg [95% CI −2.0, −0.1]; *P*=0.028; Table 2).

Insulin dose

In insulin-experienced participants, the observed mean total daily insulin dose at baseline was 38.2 (SD 29.25) units (U), and the estimated total daily insulin dose at EOS was 39.1 (SD 17.51) U. There was a significant increase in the observed mean daily prandial insulin dose from 8.2 (SD 16.81) U at baseline to 12.9 (SD 8.98) U at EOS, *P*<0.0001. The mean daily basal insulin dose decreased from 30 (SD 15.66) U at baseline to 26.3 (SD 10.40) U at EOS, *P*<0.05.

Hypoglycemia

The estimated incidence of non-severe, nocturnal and severe hypoglycemic episodes were reduced numerically after treatment initiation (Table 3). Due to the small sample size, these data were not analyzed statistically.

Healthcare resource utilization

For HRU associated with diabetes and its complications, initiating or switching to IDegAsp resulted in a decrease in the incidence of self-reported outpatient visits (26 vs. 7) and inpatient hospitalizations (8 vs. 1) in the 12 weeks prior to baseline versus the 12 weeks prior to EOS or IDegAsp discontinuation. The number of workdays missed in the Philippines cohort decreased from 3 to 0 over the same time period (Table 4 and Supplementary Table S2).

Adverse events

AEs were reported in eight (4.3%) participants in the Philippines cohort. This included four serious AEs in three (1.6%) participants (cerebrovascular disorder, community-acquired pneumonia, COVID-19 and death) and eight nonserious AEs in five (2.7%) participants (abdominal pain, body weakness, abdominal discomfort, paronychia, neck abscess, scrotum abscess, dyslipidemia, hyperuricemia) (Table 5). Three serious AEs and six nonserious AEs were judged as unlikely to be caused by IDegAsp treatment. The remaining two nonserious AEs (abdominal pain and body

Table 3. Summary of hypoglycemic events occurring prior to initiation of idegasp (baseline) and prior to EOS or discontinuation in the Philippines

Hypoglycemic events	Number of events	Number of patients, n (%)
Non-severe	73	16
Within 4 weeks prior to initiation	40	13 (81.3)
Within 4 weeks prior to EOS or discontinuation	33	3 (18.8)
Nocturnal non-severe	12	6
Within 4 weeks prior to initiation	10	5 (83.3)
Within 4 weeks prior to EOS or discontinuation	2	1 (16.7)
Severe	3	2
Within 26 weeks prior to initiation	3	2 (100.0)
Within 26 weeks prior to EOS or discontinuation	0	0

Data based on the full Philippines analysis set.

EOS: end of study; IDegAsp: insulin degludec/insulin aspart; n: number of participants with a response.

Table 4. Summary of HRU prior to initiation of IDEGASP (baseline) and prior to EOS in the Philippines

HRU associated with diabetes and its complications	n	Number of visits/resources used, mean (SD)
Self-reported outpatient visits		
Within 12 weeks prior to initiation	26	1.8 (1.3)
Within 12 weeks prior to EOS or discontinuation	7	1.7 (1.0)
Self-reported emergency room visits		
Within 12 weeks prior to initiation	4	1.0
Within 12 weeks prior to EOS or discontinuation	0	0
Self-reported other healthcare provider visits and contacts outside of the hospital setting[a]		
Within 12 weeks prior to initiation	0	0
Within 12 weeks prior to EOS or discontinuation	5	2.2 (1.3)
Self-reported workdays missed		
Within 12 weeks prior to initiation	3	12.0 (15.7)
Within 12 weeks prior to EOS or discontinuation	0	0
Self-reported inpatient hospitalizations		
Within 12 weeks prior to initiation	8	1.0
Within 12 weeks prior to EOS or discontinuation	1	1.0

[a] Includes face-to-face, telephone, and email.

EOS: end of study; IDegAsp: insulin degludec/insulin aspart; HRU: healthcare resource utilization; n: number of participants contributing to the analysis; SD: standard deviation.

Table 5. Adverse events in Philippines cohort of ARISE

	Serious			Nonserious			Total		
	n	%	E	n	%	E	n	%	E
Adverse events	3	1.6	4	5	2.7	8	8	4.3	12
Severity									
Mild	1	0.5	1	5	2.7	8	6	3.2	9
Moderate	1	0.5	1	0	-	-	1	0.5	1
Severe	2	1.1	2	0	-	-	2	1.1	2
Causality									
Probable	0	-	-	1	0.5	2	1	0.5	2
Possible	0	-	-	0	-	-	0	-	-
Unlikely	2	1.1	3	4	2.2	6	6	3.2	9

Data based on Philippines FAS.

%: percentage of participants; E: number of events; FAS: full analysis set; n: number of participants.

weakness) were judged to be probably caused by IDegAsp treatment (Table 5).

DISCUSSION

This real-world study demonstrates the potential impact of the IDegAsp co-formulation in a clinical setting in the Philippines, where there is a need to improve glycemic control and reduce the financial burden of medication for people with T2D.

A greater proportion of participants in the Philippines were receiving OAD medication only at baseline compared with the global ARISE study (48% vs. 35.1%).[23] This likely reflects the lack of access to insulin therapy in the region, as well as widespread clinical inertia in diabetes care, resulting in delays in treatment intensification.[26,27] In line with our observation, a real-world study of 1065 participants with T2D in the Western Pacific region found that ~66% had an HbA1c level ≥9.0% at the time of insulin initiation despite receiving two or more OADs.[27]

Initiating or switching to IDegAsp was associated with significant reductions in HbA1c and FPG at EOS compared with baseline for participants in the Philippines. The mean change in HbA1c from baseline to EOS was −1.4% for both the global and Philippines analyses.[23] The significant reduction in FPG from baseline to EOS in both the global study and the Philippines cohort following the initiation of IDegAsp reflects the reduction observed in HbA1c. This Philippines substudy was not statistically powered to analyze treatment effect by prior treatment regimen. However, the global ARISE study found the most significant improvement in glycemic control among people previously receiving OAD therapy only.[23] The proportion of participants with HbA1c levels <7.0% was numerically higher at EOS versus baseline for both the global and Philippines analysis sets.[23]

Using high dosages of basal insulin has been associated with an increased risk of hypoglycemia. An analysis of pooled data from 15 randomized trials in insulin-naïve participants with T2D treated with basal insulin glargine, with or without OADs, for ≥24 weeks found that titration of basal insulin to doses >0.5, >0.7 and >1.0 IU/kg did not improve glycemic control and was associated with an increased risk of hypoglycemia when the dose cut-offs were exceeded.[28] It is therefore important that the global ARISE study and Philippines subanalysis found that initiating or switching to IDegAsp improved glycemic control while leading to significant reductions in daily basal insulin dose. For participants receiving premix or basal–bolus insulin prior to the study, switching to IDegAsp was associated with significant reductions in daily total insulin dose. Reductions in insulin dosage are associated with decreased healthcare costs and the risk of AEs. In this study, all AEs reported were similar to those in previous trials of IDegAsp,[16–22] and no new, unexpected AEs were reported in the ARISE Philippines cohort.

While treatment with premixed insulin analogs offers greater convenience than multiple daily basal–bolus injections, interactions between the basal and bolus components of biphasic formulations can potentially result in delayed postprandial hypoglycemia.[29,30] Accordingly, it is remarkable that the observed improvements in glycemic control were attained without any additional risk of severe, non-severe and nocturnal hypoglycemia. These results are supported by a Phase 3 trial of 296 people with T2D in Japan, in which a significantly higher proportion of participants achieved an HbA1c <7% without hypoglycemia with IDegAsp treatment compared with once-daily insulin glargine (43 vs. 25%; estimated odds ratio [IDegAsp/IGlar] 2.21 [95% CI 1.25, 3.92], P<0.01).[20]

The most frequently cited reason physicians gave for switching people with T2D to IDegAsp was to improve glycemic control, preventing the development or progression of comorbidities arising from inadequate control. Additionally, physicians opted to initiate IDegAsp therapy due to flexibility in the dosing regimen and the need for fewer injections compared with basal–bolus therapy. This highlights the potential of IDegAsp co-formulation to minimize treatment burden and overcome clinical inertia that can delay access to appropriate T2D care.[31]

In the Philippines, approximately 27 million individuals are estimated to be overweight or obese, and the prevalence is rising — overweight and obesity almost doubled between 1998 and 2019, increasing from 20.2% to 36.6%.[3] It is, therefore, crucial that T2D treatments do not contribute to this issue. Insulin and OADs, including sulfonylureas, thiazolidinediones, and meglitinides, are associated with weight gain.[32–34] In the ARISE global cohort and Philippines cohort, improvements in glycemic control were achieved alongside significant reductions in body weight.

The reduction in body weight observed in the Philippines cohort could be related to several factors: discontinuation or dose reduction of OADs that induce weight gain; reduced hypoglycemic episodes may have decreased participants' propensity for '*defensive eating,*' thereby leading to reductions in calorie intake; and treatment adherence may

have been improved in this clinical study setting compared with participants' daily routines.

Socioeconomic factors play a major role in the quality and consistency of diabetic care that is accessible in the Philippines.[8,35] A study evaluating access to diabetes care in the Philippines found that people with T2D took their medications intermittently based on their own judgment, selecting some elements of medical advice, and weighing symptoms against medication cost.[35] As highlighted by the results described above, there is a tendency towards delayed insulin initiation in Asia. People with T2D are often receiving multiple OADs when insulin is prescribed.[27] Timely access to insulin therapy is needed to enable optimal glycemic control and prevent comorbidities.[27] The reduction in diabetes-associated HRU observed in those switching to IDegAsp in both the global and Filipino studies demonstrates the potential to reduce the financial burden associated with T2D.[23]

Although efforts have been made to improve care for people with T2D through initiatives such as the Insulin Medicine Access Program, insulin access remains limited for many in the Philippines.[11] Following the enactment of the Universal Health Care act into law in 2019, all Filipinos are automatically enrolled in the national health insurance program.[36] This enables individuals to access health services without increasing their financial burden. While insulin glargine is now included in the PNF, access to medications in the PNF is often low in both public and private medicine outlets.[15] For those who do have access to insulin, management of T2D is often suboptimal.[5,9] Equitable access to treatment options that simplify the insulin regimen and improve medication management could help to improve glycaemic control and quality of life for people living with T2D. We recommend that the HRU data from ARISE be considered by the DOH within this context to assess the impact of IDegAsp on people with T2D.

The limitations of this study have been reported previously.[23] The study design did not allow control over baseline parameter ranges. As an open-label, single-arm study, there was no control group for comparison. Thus, the study effect could not be estimated, and any additional factors, such as changes to other elements of treatment, were not accounted for. Although all participants were recruited prior to the COVID-19 pandemic, follow-up became challenging owing to the strict implementation of health protocols and lockdowns in the country. Several participants were lost to follow-up during this period.

CONCLUSION

Results from this open-label, single-arm, non-interventional study of people with T2D treated with IDegAsp in the Philippines found improved outcomes, including improved glycemic control, lower body weight, and lower HRU following treatment initiation. No new, unexpected AEs were reported.

Acknowledgments
Medical writing and editorial support for the development of this manuscript, under the direction of the authors, was provided by Katie Chruszcz, MSc, and Liz Southey, MSc, of The Salve Health Ltd, UK.

Statement of Authorship
All authors certified fulfillment of ICMJE authorship criteria.

CRediT Author Statement
NNJ: Investigation, Resources, Writing – review and editing; **NAG:** Investigation, Writing – review and editing; **GA:** Investigation, Writing – review and editing; **GJRA:** Conceptualization, Methodology, Validation, Formal analysis, Investigation, Resources, Writing – original draft preparation, Writing – review and editing, Visualization, Supervision, Project administration; **OAD:** Investigation, Writing – review and editing; **REF:** Investigation, Writing – review and editing; **NTF:** Resources, Writing – review and editing, Supervision, Project administration, Funding acquisition; **SK:** Investigation, writing – review and editing; **BM:** Conceptualization, Methodology, Validation, Formal analysis, Investigation, Resources, Writing – original draft preparation, Writing – review and editing, Visualization, Supervision, Project administration; **RM:** Investigation, Writing – review and editing; **AP:** Investigation, Resources, Writing – review and editing; **FP:** Investigation, Writing – review and editing; **MPR:** Resources, Writing – review and editing, Supervision, Project administration, Funding acquisition; **AS:** Conceptualization, Methodology, Validation, Formal analysis, Investigation, Data Curation, Writing – original draft preparation, Writing – review and editing, Visualization, Supervision, Project administration, Funding acquisition; **MT:** Investigation, Resources, Data Curation, Writing – review and editing, Visualization

Author Disclosure
Nicole-Therese Flor, Mercerose Puno-Rocamora, and Ahsan Shoeb are employees of Novo Nordisk Philippines, Taguig City, Philippines and hold stocks in Novo Nordisk.

Data Availability Statement
Datasets generated and analyzed are included in the published article.

Funding Source
This study, medical writing support, and article processing charges were funded by Novo Nordisk.

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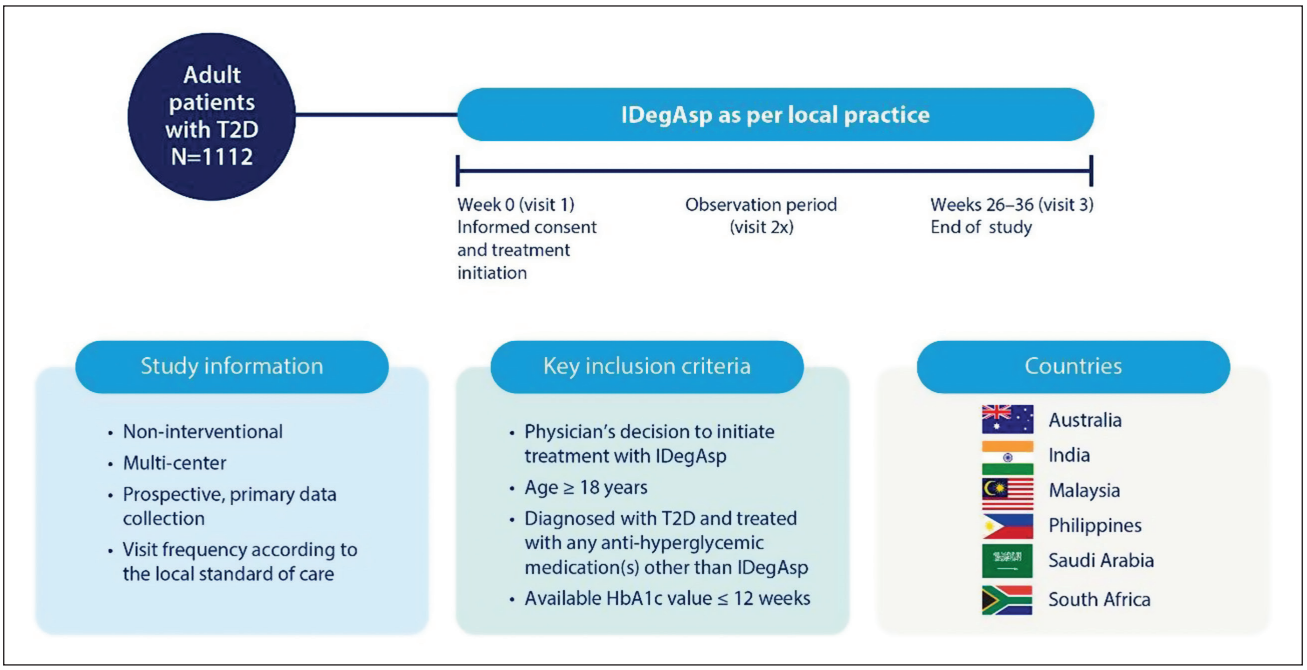
SUPPLEMENTARY MATERIALS



Supplementary Figure S1. Study design.

HbA1c: glycated hemoglobin; IDegAsp: insulin degludec/insulin aspart; N: number of participants enrolled into the full study; T2D: type 2 diabetes.

Supplementary Table S1. Physician explanations for initiating or moving participant to IDEGASP

	n (%) (N=185)
To improve the participant's glycemic control	177 (95.7)
To lower the risk of hypoglycemia	43 (23.2)
Flexibility in the dosing regimen	56 (30.3)
Fewer injections than basal and bolus therapy	55 (29.7)
No reconstitution needed	16 (8.6)
Change in coverage status favoring IDegAsp	12 (6.5)
Other	1 (0.5)

Physicians could select more than one reason for each participant. A change in coverage status favoring IDegAsp refers to a change in healthcare insurance or reimbursement requirements that led to better access to the drug.

IDegAsp: insulin degludec/insulin aspart; n: number of participants; N: number of participants in analysis set.

Supplementary Table S2. Summary of HRU prior to initiation of IDEGASP (baseline) and prior to EOS in the Philippines

HRU associated with severe hypoglycemia	Number of patients reporting visits (%)
Self-reported outpatient visits	
Within 26 weeks prior to initiation	2 (1.1)
Within 26 weeks prior to EOS or discontinuation	1 (0.5)
Self-reported emergency room visits	
Within 26 weeks prior to initiation	1 (0.5)
Within 26 weeks prior to EOS or discontinuation	0
Self-reported inpatient hospitalizations	
Within 26 weeks prior to initiation	0
Within 26 weeks prior to EOS or discontinuation	0
Self-reported episodes requiring assistance from an ambulance	
Within 26 weeks prior to initiation	1 (0.5)
Within 26 weeks prior to EOS or discontinuation	0
Self-reported episodes required administration of glucagon	
Within 26 weeks prior to initiation	0
Within 26 weeks prior to EOS or discontinuation	0
Self-reported workdays missed	
Within 26 weeks prior to initiation	0
Within 26 weeks prior to EOS or discontinuation	0

EOS: end of study; IDegAsp: insulin degludec/insulin aspart; HRU: healthcare resource utilization; n: number of participants contributing to the analysis; SD: standard deviation.