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

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Abstract

Objectives. Insulin degludec (IDeg)/insulin aspart (IAsp; IDegAsp) is a co-formulation of 70% IDeg and 30% IAsp. According to several randomized controlled trials, IDegAsp is effective and safe for patients with type 2 diabetes mellitus (T2DM). A subgroup analysis of the ARISE study was conducted to explore the safety and efficacy of IDegAsp among Malaysian patients with T2DM in real-world settings.

Methodology. ARISE, an open-label, multicenter, non-interventional, prospective study was conducted between August 2019 and December 2020. Adult Malaysian patients with T2DM who were enrolled from 14 sites received IDegAsp as per the local label for 26 weeks. The primary endpoint was change in glycated hemoglobin (HbA1c) levels from baseline to end of study (EOS).

Results. Of the 182 patients included in the full analysis set, 159 (87.4%) completed the study. From baseline to EOS, HbA1c (estimated difference [ED]: –1.3% [95% CI: –1.61 to –0.90]) and fasting plasma glucose levels (ED: –1.8 mmol/L [95% CI: –2.49 to –1.13]) were significantly reduced (p<0.0001). The patient-reported reduced hypoglycemic episodes (overall and nocturnal) during treatment. Overall, 37 adverse events were observed in 23 (12.6%) patients.

Conclusion. Switching or initiating IDegAsp treatment resulted in significant improvements in glycemic control and a reduction in hypoglycemic episodes.

Key words: type 2 diabetes mellitus, insulin degludec, insulin aspart, Malaysia, hypoglycemia

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INTRODUCTION

There has been a steady increase in the global prevalence of diabetes in the last few years. In 2021, over 537 million (1 in 10) adults aged 20 to 79 years had diabetes, while 541 million adults were at a high risk of developing type 2 diabetes mellitus (T2DM).[1] According to the National Health and Morbidity Survey, the overall prevalence of T2DM in Malaysia is estimated to be 18.3%, with roughly one in five adults having T2DM.[2] However, diabetes management is suboptimal in Malaysia.[3]

The Malaysian Clinical Practice Guidelines (CPGs) for the "Management of Type 2 Diabetes Mellitus," recommends the use of glucose-lowering drugs (GLDs; oral or injectable) as monotherapy or in combination, along with lifestyle modifications for the management of T2DM patients with glycated hemoglobin (HbA1c) ≥6.5% or fasting plasma glucose (FPG) ≥6.0 mmol/L.[4] Further, in patients with inadequate glycemic control on maximum doses of oral GLD (OGLD) ± glucagon-like peptide receptor agonist (GLP-1RA), CPGs recommend initiation of once-daily (OD) co-formulation (insulin degludec/insulin aspart; IDegAsp), basal insulin or premixed insulin.[4] The prolonged use of insulin may have associated challenges, including adverse effects such as hypoglycemia and the inconvenience associated with multiple daily injections. Therefore, many patients consider insulin therapy as burdensome and eventually become non-compliant to treatment.[5] To overcome some of these barriers, it is essential to develop a convenient and effective insulin therapy for patients with T2DM.

IDegAsp (Ryzodeg®, Novo Nordisk A/S, Søborg, Denmark), a soluble co-formulation of 70% insulin degludec (IDeg) and 30% insulin aspart (IAsp) is easy to use with its convenient once daily dosing.[6,7] IDegAsp became available in Malaysia in 2018. Effective glycemic control of IDegAsp is due to its unique pharmacodynamic profile. It provides stable basal insulin coverage for 24 hours by the ultra-long-acting IDeg and postprandial control by rapid-acting IAsp. [8] Treatment with IDegAsp is convenient as it requires minimal injections without resuspension and facilitates accurate dosing.[9] Multiple randomized controlled trials (RCTs) have shown the efficacy and safety of IDegAsp,[6,10] as seen in the BOOST clinical trial program.[11-14] A post hoc pooled investigation of five phase 3, open-label, treat-to-target, 26-week RCTs comparing twice-daily (BID) IDegAsp with premixed insulin BID regimen or IDeg OD +IAsp confirmed the safety and efficacy of IDegAsp in a broad patient population with varying characteristics.[15]

However, real-world evidence on the use of IDegAsp is limited. ARISE (A Ryzodeg Initiation and Switch Effectiveness) was an open-label, prospective, single-arm, non-interventional study for 26 weeks, which assessed glycemic control along with other clinical parameters related to the use of IDegAsp in patients with T2DM. This study included patients in Malaysia, South Africa, India, Saudi Arabia, Australia and the Philippines who were either initiated or switched to IDegAsp.[9] We present the results from the Malaysian cohort from a subgroup analysis of the ARISE study.

METHODOLOGY

Study design

The detailed study design has already been published.[9] Briefly, it was an open-label, 26-week multicenter, prospective, non-interventional study conducted from August 2019 through December 2020 in patients with T2DM. Data were collected from 14 sites in Malaysia. The physician decided which patients would be initiated or switched to IDegAsp. Follow-up was for 26 to 36 weeks.

The decision to initiate or switch to IDegAsp was made before baseline and was not dependent on patient inclusion criteria of the current study. Physicians prescribed the initial dose, dose adjustments, dosing frequency of IDegAsp, and discontinued other GLDs. No additional clinical procedures other than the local standard clinical practices were performed.

The study was conducted in accordance with the Declaration of Helsinki. The ethics committee/institutional review board approved the study protocol and patient consent forms for all the sites in Malaysia. The patients were asked to submit written informed consent before study participation. This study is registered in ClinicalTrials.gov (NCT04042441).

Study population

Patients with T2DM (≥18 years of age) who had received anti-diabetic medications other than IDegAsp for at least 26 weeks with an available HbA1c value measured ≤12 weeks before enrolment were included in the study.

Exclusion criteria were patients with mental incapacity, unwillingness to participate, and those who were already on IDegAsp treatment.

Data collection

Data were collected at baseline (visit 1; week 0), at multiple intermediate visits based on the local clinical practice (visit 2×; week 1–25), and at the end of study (EOS) / treatment discontinuation visit (visit 3; the first visit within week 26–36 / at the time of discontinuation).

Study endpoints

The primary endpoint of the study was the change in HbA1c from baseline to EOS. The secondary endpoints were the proportion of patients attaining HbA1c <7.0% at EOS, change in FPG, insulin dose (total, prandial and basal), and body weight from baseline to EOS.

The other endpoints were as follows: patient-reported non-severe hypoglycemic episodes (overall and nocturnal) within four weeks before IDegAsp initiation and within four weeks before EOS, and severe hypoglycemic episodes occurring in the 26 weeks before IDegAsp initiation and during the 26-week study period. Non-severe hypoglycemia was defined as low blood glucose levels at ≤3.9 mmol/L, with or without symptoms, that were managed by the patient without assistance. On the other hand, severe hypoglycemia was a hypoglycemic episode that required assistance from another person to relieve neurocognitive symptoms such as administering carbohydrates or glucagon. A nocturnal event was a hypoglycemic event that occurred during the night. Data on the reasons for starting baseline IDegAsp, the proportion of patients who discontinued treatment during the study period and their reasons for discontinuation were also collected.

Exploratory endpoints included healthcare resource utilization (HRU) in managing diabetes and its complications within 12 weeks before IDegAsp initiation and 12 weeks before EOS or discontinuation.

Statistical analysis

All the patients who signed the informed consent form and initiated IDegAsp treatment were included in the full analysis set (FAS). An enrolment of 1112 patients overall, with a minimum of at least 139 patients in each country, was planned. Statistical basis for determining the number of enrolled patients for the ARISE study has been described previously.[9] The primary endpoint was analyzed via adjusted mixed models for repeated measurements (MMRM). This analysis was conducted using an 'in-study' observation period that included all patients in the FAS with at least one post-baseline HbA1c measurement regardless whether they discontinued IDegAsp or not. The covariates of the adjusted model were baseline HbA1c, HbA1c assessment time, body mass index (BMI), sex, age, study site, and previous GLDs. According to the 'on-treatment' observation period, secondary analyses of the primary endpoint were done. Repeated primary and secondary analyses were conducted to detect the change in FPG, insulin dose and body weight from baseline to EOS and the baseline values of the relevant endpoints were considered as covariates. The primary analysis was conducted via the adjusted MMRM for the in-study observation period for all endpoints, except HRU. The secondary analysis of HRU was conducted using an on-treatment observation period. The on-treatment observation period was a part of the in-study observation period; during this period the patients received IDegAsp and the values measured following the discontinuation of treatment were ignored. Statistical analysis was performed using SAS software version 9.4.

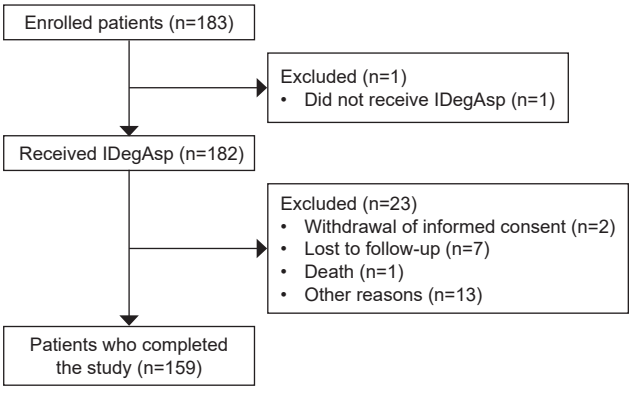

Figure 1. Patient flow through the trial.

RESULTS

Patient demographics and clinical characteristics

Among 1112 eligible patients enrolled in the ARISE study, 205 patients from Malaysia were included. Among them, 187 signed the informed consent, however, only 183 participants attended visit 1. Only 182 patients were initiated or switched to IDegAsp and were included in the FAS (Figure 1). However, only 159 participants (87.4%) completed the study. Nineteen (10.4%) patients discontinued treatment and their reasons for doing so are listed in Supplementary Table 1.

Table 1 represents the baseline demographics and clinical characteristics of the patients. The study enrolled an equal proportion of males and females with a mean age of 56.4 years (standard deviation [SD] 11.88 years). Similar to the population in the global cohort, the Malaysian cohort enrolled those with long-standing diabetes with a mean of 11.2 years (SD 7.99 years), mean BMI of 27.4 kg/m^2 (SD

Table 1. Demographic and clinical characteristics at baseline of patients in Malaysia and for the overall study population (six countries)

	Malaysia N=182[a]	Overall study N=1102[a]
Age, mean (SD)	56.4 (11.88)	58.6 (12.23)
Male, n (%)	95 (52.2)	591 (53.6)
Duration of diabetes (years), mean (SD)	11.2 (7.99)	13.3 (8.33)
Body weight (kg), mean (SD)	71.8 (14.38)	79.5 (19.56)
BMI (kg/m$_2$), mean (SD)	27.4 (4.62)	29.2 (5.86)
HbA1c (%), mean (SD)	10.0 (2.14)	9.8 (1.99)
FPG (mmol/L), mean (SD)	11.0 (4.39)	11.0 (4.22)
Anti-diabetic treatment, n (%)		
OADs only	52 (31.5)	371 (35.1)
Premixed insulin ± bolus insulin (± OADs)	36 (21.8)	232 (21.8)
Basal insulin only (± OADs)	38 (23.0)	230 (21.8)
Basal–bolus insulin (± OADs)	24 (14.5)	137 (13.0)
GLP-RA ± insulin (± OADs)	15 (9.1)	87 (8.2)
Dose of previous prandial insulin (U), mean (SD)	27.0 (22.05)	25.8 (22.84)
Diabetes complications, n (%)		
Diabetic neuropathy	46 (28.8)	216 (24.7)
Diabetic nephropathy	64 (40.0)	178 (20.3)
Cardiovascular disease	27 (16.9)	150 (17.1)
Diabetic retinopathy	20 (12.5)	102 (11.6)
Peripheral vascular disease	1 (0.6)	15 (1.7)

[a] Note that the number of patients differed for the different items.
BMI, body mass index; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; N, number of patients in the full analysis set; n, number of patients in the subcategory; OAD, oral antidiabetic drug; SD, standard deviation; U, unit.

Table 2. Physicians' reasons for initiating or switching to IDegAsp

	Malaysia N=182	Overall study N=1102
To improve the patient's glycemic control	169 (92.9)	1026 (93.1)
To lower the risk of hypoglycemia	37 (20.3)	291 (26.4)
Flexibility in the dosing regimen	58 (31.9)	286 (26.0)
Fewer injections than basal and bolus therapy	43 (23.6)	277 (25.1)
No reconstitution needed	16 (8.8)	98 (8.9)
Change in coverage status favoring IDegAsp	14 (7.7)	82 (7.4)
Other	6 (3.3)	54 (4.9)

Data are number of patients (%). Physicians could select more than one reason for each patient. 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 patients in the full analysis set.

4.62 kg/m^2), and very poor glycemic control with mean HbA1c of 10.0% (SD 2.14%). Before initiating or switching to IDegAsp, 165 (90.7%) patients had received other anti-hyperglycemic therapies. The physicians' reasons for initiating or switching to IDegAsp are summarized in Table 2. The main reason behind initiating or switching to IDegAsp in the Malaysian cohort (92.9%) and the overall study population (93.1%) was to improve glycemic control. A higher proportion of patients (51.1%; n = 93) received OD regimen of IDegAsp versus the BID regimen (48.9%; n = 89) at treatment initiation. The mean (SD) initial total daily dose of IDegAsp was 29.1 (19.7) U.

Glycemic control

The HbA1c and FPG were significantly reduced from baseline to EOS (estimated difference [ED]: –1.3% [95% CI: –1.61 to –0.90]; p<0.0001 and ED: –1.8 mmol/L [95% CI: –2.49 to –1.13]; p<0.0001 respectively). The number of patients with HbA1c levels less than 7.0% increased from 10 (5.5%) at baseline to 25 (17.0%) at EOS.

Insulin dose

There was a reduction in the total daily dose of insulin in insulin-experienced patients (using prior basal insulin only, basal–bolus insulin and premixed insulin) at EOS compared with that at baseline (ED: –1.9 U [95% CI: –7.95 to 4.18]; p=0.5378). Similarly, a reduction in daily prandial insulin dose was observed in these patients (ED: –1.8 U [95% CI: –5.70 to 2.12]; p=0.3648). Likewise, the daily basal insulin dose was also reduced at EOS compared with baseline (ED: –0.6 U [95% CI: –2.90 to 1.67]; p=0.5931). However, these reductions were not statistically significant.

Hypoglycemia

The number of events and number of patients experiencing overall and nocturnal non-severe hypoglycemia and severe hypoglycemia in 4 weeks before IDegAsp initiation reduced from baseline (non-severe, 38; nocturnal, 19; severe, 7) to that within 4 weeks preceding EOS or discontinuation (non-severe, 11; nocturnal, 2; severe, 1; Table 3).

Body weight

A significant reduction in body weight was observed at EOS compared with baseline (ED: –0.9 kg [95% CI: –1.69 to –0.02]; p=0.046) in the Malaysian cohort. The same was also observed in the overall study population at EOS compared with baseline (ED: –1.0 kg [95% CI: –1.51 to –0.52]; p<0.0001).[16] On subgroup analysis of the overall population, a statistically significant reduction in body weight was observed in prior OAD-only users (ED: –1.4 kg [95% CI: –2.32;–0.49]; p=0.0028), basal insulin users (ED: –1.1 kg [95% CI: –2.09;–0.07]; p=0.0362), and basal–bolus insulin users (ED: –1.5 kg [95% CI: –2.70;–0.23]; p=0.0212). In patients who received GLP-1RA ± insulin treatment previously, (ED: 0.3 kg [95% CI: –1.10;1.77]; p=0.6411) a small increase in body weight was observed.[16]

Adverse events

Overall, 37 adverse events (AEs) were observed in 23 (12.6%) patients. Of these, 23 non-serious events were reported in 15 (8.2%) patients and 14 serious events in 11 (6.0%) patients. Further evaluation indicated that 10 serious and 18 non-serious events were unlikely to be caused by IDegAsp treatment. The AEs are shown in Table 4.

Healthcare resource utilization

Healthcare resource utilization in the 12-weeks before baseline and the 12-weeks prior to EOS or discontinuation in both global and Malaysian cohorts is shown in Table 5. The number of self-reported outpatient visits among the Malaysian cohort within the 12 weeks before baseline and within 12 weeks before EOS or discontinuation were 55 and 24, respectively. Within 12 weeks prior to treatment

Table 3. Hypoglycemic episodes occurring during 4 weeks prior to initiation of IDegAsp (baseline) and during 4 weeks prior to EOS or discontinuation (i.e., the last 4 weeks of the on-treatment period) during on-treatment observation period

	Malaysia N=182		Overall study N=1102	
	Number of events	Number of patients, n (%)	Number of events	Number of patients, n (%)
Non-severe hypoglycemic episodes				
Number of events/patients	49	23	526	163
Within 4 weeks prior to treatment initiation	38	21 (91.3)	364	128 (78.5)
Within 4 weeks prior to EOS or at discontinuation	11	3 (13.0)	162	44 (27.0)
Nocturnal non-severe hypoglycemic episodes				
Number of events/patients	21	12	173	72
Within 4 weeks of initiation	19	11 (91.7)	142	59 (81.9)
Within 4 weeks prior to EOS or discontinuation	2	1 (8.3)	31	14 (19.4)
Severe hypoglycemic episodes				
Number of events/patients	8	6	54	26
Within 26 weeks of initiation	7	5 (83.3)	51	23 (88.5)
Within 26 weeks prior to EOS or discontinuation	1	1 (16.7)	3	3 (11.5)

Data based on the FAS, on-treatment observation period; EOS, end of study; N, number of patients in the full analysis set; n, number of patients with response.

Table 4. Solicited serious and non-serious selected significant AEs during in-study observation period

	Malaysia N=182	
	Number of events	Number of patients, n (%)
Non-serious		
Number of events/patients	23	15 (8.2)
Severity		
Mild	17	12 (6.6)
Moderate	6	5 (2.7)
Severe	0	0
Serious		
Number of events/patients	14	11 (6.0)
Severity		
Mild	1	1 (0.5)
Moderate	5	5 (2.7)
Severe	8	6 (3.3)

Data based on the FAS, in-study observation period; N, number of patients in the full analysis set; n, number of patients with response.

initiation, eight patients reported having missed workdays due to diabetes and its complications, while none of the patients reported missed workdays after treatment initiation in the Malaysian cohort.

DISCUSSION

This subgroup analysis of the non-interventional real-world ARISE study was conducted to assess the glycemic control and various clinical outcomes related to the administration of IDegAsp in patients initiated or switched to IDegAsp therapy. IDegAsp resulted in significant improvements in glycemic control in the Malaysian cohort, as evident by a reduction in HbA1c levels from baseline to EOS. In addition, FPG was significantly reduced from baseline to EOS and the number of non-severe and severe hypoglycemic events also reduced from baseline following IDegAsp treatment.

The results from the current subgroup analysis are consistent with those reported in a meta-analysis of 17 studies comparing IDegAsp with insulin analogs. The meta-analysis included 3831 patients with T2DM, where IDegAsp BID significantly reduced FPG and minimized nocturnal hypoglycemia risk in comparison to conventional premixed insulin BID; however, both insulin types had a similar effect on HbA1c levels.[17] In another meta-analysis of six RCTs including 1346 patients with T2DM, a significant decrease in mean HbA1c was reported with IDegAsp OD compared with insulin glargine (IGlar) OD.[18] In another retrospective observational study, IDegAsp OD led to significantly lower HbA1c levels and FPG than basal insulin in 87 patients with T2DM in each treatment group.[19] The reduction in FPG with IDegAsp could be attributed to the long-acting effect of the IDeg analog while HbA1c reduction may be due to the prandial coverage of the IAsp analog.[17]

The doses of total daily, prandial and basal insulin were reduced from baseline to EOS in this study; however, these reductions were not statistically significant. A similar trend was observed in a retrospective real-world study in Japan where there was a significant reduction ($p<0.0001$) in daily basal insulin dose over 26 weeks in patients with T2DM who were administered with IDegAsp.[20] Also, nine studies in the meta-analysis reported a reduction or no difference in total dose requirement for IDegAsp compared to other basal insulins.[17]

In our study, the incidence of overall and nocturnal non-severe and severe hypoglycemic events was reduced from baseline to EOS. Although the low number of hypoglycemic events did not allow for statistical comparisons, these results suggest that improvement in glycemic control can be achieved with IDegAsp potentially without increased risk of hypoglycemia. In the meta-analysis of studies comparing IDegAsp and IGlar, the rates of confirmed overall hypoglycemia (odds ratio [OR] = 1.59; 95% CI: 0.97 to 2.61; p=0.07; I^2=66%) and nocturnal hypoglycemia (OR=0.54, 95% CI 0.31 to 0.94, p=0.49; I^2=57%) were not significantly different between the treatment groups.[18] Similarly, the risk of confirmed hypoglycemia with IDegAsp, premixed insulin BID (OR 0.52; 95% CI: 0.42 to 0.65; I^2=23.9%) and basal insulin OD (OR 0.51, 95% CI 0.27 to 0.95, I^2=66.0) was comparable. In a meta-analysis, nocturnal hypoglycemia was significantly reduced with IDegAsp.[17]

Table 5. Healthcare resource utilization during on-treatment observation period

HRU associated with diabetes and its complications	Malaysia N=182		Overall study N=1102	
	n	Mean (SD)	n	Mean (SD)
Self-reported outpatient visits				
Within 12 weeks prior to initiation	55	5.0 (16.66)	394	3.2 (6.77)
Within 12 weeks prior to EOS or discontinuation	24	1.7 (1.73)	195	2.5 (2.88)
Self-reported emergency room visits				
Within 12 weeks prior to initiation	8	1.4 (1.06)	46	1.3 (0.66)
Within 12 weeks prior to EOS or discontinuation	4	1.8 (0.50)	8	1.4 (0.52)
Self-reported other healthcare provider visits and contacts outside of the hospital setting (face-to-face, telephone and email)				
Within 12 weeks prior to initiation	5	1.4 (0.55)	69	2.4 (3.32)
Within 12 weeks prior to EOS or discontinuation	2	1.0	12	1.7 (1.72)
Self-reported workdays missed				
Within 12 weeks prior to initiation	8	15.8 (18.58)	58	8.7 (14.90)
Within 12 weeks prior to EOS or discontinuation	0	0	9	3.1 (3.10)
Self-reported in-patient hospitalizations				
Within 12 weeks prior to initiation	14	1.2 (0.58)	78	1.2 (0.43)
Within 12 weeks prior to EOS or discontinuation	4	1.3 (0.50)	12	1.7 (1.72)

Data based on FAS. EOS, end of study; HRU, healthcare resource utilization; N, number of patients in the FAS; n, number of patients with response.

IDegAsp also demonstrated better glycemic control in multinational patients with T2DM before, during and following Ramadan fasting in a randomized treat-to-target trial with a 74% reduction in overall hypoglycemia, 83% reduction in nocturnal hypoglycemia and 44% reduction in severe hypoglycemia compared with the premixed insulin analog, biphasic IAsp 30. These results suggest that IDegAsp could also be an appropriate choice of treatment for patients who fast for 12 to 16 hours daily during Ramadan in countries in Asia, Africa and the Middle East, including Malaysia.[21,22] A multicenter, prospective, post-marketing surveillance study found IDegAsp to have long-term safety, efficacy and tolerability in a Japanese real-world setting.[23] Another prospective real-world study on Japanese patients with T2DM reported similar rates of non-severe hypoglycemia before and after switching to IDegAsp from IGlar U100/U300, suggesting glycemic control, safety and tolerability to IDegAsp.[20]

Severe hypoglycemia is mostly seen in patients with T2DM who are more than 75 years of age.[23] In addition, hypoglycemic episodes are major concerns in insulin initiation and treatment intensification among patients and physicians.[5] Hence, hypoglycemic episodes can be a limiting factor for insulin intensification, particularly in elderly patients.[23] However, post hoc analysis of the 26-week BOOST clinical trial program which enrolled 756 patients from several countries including Malaysia, reported that IDegAsp BID was effective in improving glycemic control with reduced incidence of hypoglycemia in elderly patients with T2DM.[24]

In our study, a decrease in body weight from baseline to EOS (ED: –0.9 kg [95% CI –1.69 to –0.02], p=0.046) was observed, similar to that in the overall study population. Likewise, a 52-week trial on patients with T2DM reported a reduction in mean body weight by 0.78 kg in patients administered IDegAsp.[25] Weight loss and a significant decrease in BMI were also observed in patients on IDegAsp treatment for 12 months.[26] Taken together, all these studies have reported similar body weight changes with IDegAsp, as in this study.

Several studies have reported lower rates of AEs in patients on IDegAsp treatment regimen with hypoglycemia as the most frequent AE reported.[20,23] Although 37 AEs were recorded across 23 patients in the Malaysian cohort, most of them were judged unlikely to be caused by IDegAsp treatment. There were fewer HRU in terms of self-reported outpatient visits, visits to the emergency room and other healthcare providers, in-patient hospitalizations and missed workdays during the 12 weeks prior to EOS or discontinuation compared to 12 weeks before IDegAsp treatment initiation. However, the numbers were too small to draw firm conclusions.

This study provided insights into diabetes management in a real-world setting. A high number of patients completing the study, a larger cohort, and a multicenter study design revealed a robust dataset. The prospective study design with broad inclusion and exclusion criteria facilitated data collection from an optimal study cohort. However, the study findings might not be generalizable as only the Malaysian population was analyzed. Moreover, this was a single-arm, open-label study without a comparator group. Additionally, patients expected to benefit from a change of regimen to IDegAsp were selected by their physicians for the study, which could have led to potential selection bias.

CONCLUSION

The results from this analysis of a Malaysian cohort with T2DM who initiated or switched to IDegAsp in the real-world setting demonstrated improved glycemic control, reduced mean insulin dose in insulin-experienced patients and reduced frequencies of non-severe and severe hypoglycemic events. The findings from this study support the real-world use of IDegAsp in patients with T2DM who are not adequately controlled with non-insulin anti-hyperglycemic therapies.

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

CRediT Author Statement
MM: Investigation, resources, writing – review and editing, visualization, supervision; **SCL:** Investigation, resources, writing – review and editing, visualization; **MM:** Investigation, resources, writing – review and editing, visualization, supervision; **SU:** Conceptualization, investigation, resources, writing – original draft preparation; writing – review and editing, visualization, project administration, funding acquisition; **DM:** Writing – original draft preparation, writing – review and editing, project administration, funding acquisition; **MSMK:** Investigation, resources, writing – review and editing, visualization; **SS:** Investigation, resources, writing – review and editing, visualization; **AMD:** Investigation, resources, writing – review and editing, visualization; **KMC:** Investigation, resources, writing – review and editing, visualization; **LYT:** Investigation, resources, writing – review and editing, visualization; **SBN:** Investigation, resources, writing – review and editing, visualization; **JHGL:** Investigation, resources, writing – review and editing, visualization; **ZH:** Investigation, resources, writing – review and editing, visualization; **KBTSAK:** Investigation, resources, writing – review and editing, visualization; **BKL:** Investigation, resources, writing – review and editing, visualization; **SPC:** Investigation, resources, writing – review and editing, visualization.

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SUPPLEMENT

Supplementary Table 1. Reasons for discontinuing IDegAsp treatment during the study period

	Overall n=19
Insufficient effect on glycemic control	1 (5.3)
Unacceptable hypoglycemia profile/pattern	0
Lack of convenience	1 (5.3)
Adverse event	1 (5.3)
Change in coverage status disfavoring IDegAsp	6 (31.6)
Pregnancy or intentions to become pregnant	1 (5.3)
Weight gain	0
Other	9 (47.4)
Unknown	0

Footnote: Data are number of patients (%). Analyzed using the on-treatment observation period. A change in coverage status disfavoring IDegAsp refers to a change in healthcare insurance or reimbursement requirements that led to worse access to the drug. n, number of patients with response. 'Other' includes various reasons such as financial constraints, inter-district travel bans due to COVID-19, restrictions and concerns related to COVID-19 etc.