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ARTICLE

Initiating or switching to IDegAsp in a real-world South African population with type 2 diabetes – a cohort analysis from the ARISE study

Adri Kok[1], Hemant Makan[2], Gracjan Piotr Podgorski[3], Shaifali Joshi[4], Verushka Chetty[5]*, Lungisa Nojoko[6], Hajira Bacus[7], Naeem Moosa[8] and Duma Khutsoane[9]

[1]*Netcare Union Alberton Hospital, Alberton, South Africa*
[2]*Centre for Diabetes, Lenasia, South Africa*
[3]*Netcare Greenacres Hospital, Port Elizabeth, South Africa*
[4]*Diabetes Care Centre, Brooklyn, South Africa*
[5]*Novo Nordisk, Johannesburg, South Africa*
[6]*PPMR-Clinical Trial Centre, ProHealth & Wellness Centre for Integrative Medicine, Port Elizabeth, South Africa*
[7]*Lenmed Health Shifa Hospital, Durban, South Africa*
[8]*General Practice, Lenasia, South Africa*
[9]*Bloemfontein Mediclinic, Bloemfontein, South Africa*
**Correspondence: vrcy@novonordisk.com*

Background: The ARISE study was a 26-week, multicentre, prospective, open-label, non-interventional observational study to investigate clinical outcomes in people with T2D treated with IDegAsp in everyday clinical practice.
Objectives: To report results from the South African cohort of the ARISE study and compare them with those from the overall population.
Design: Non-interventional observational study.
Setting: General and specialist private practices.
Subjects: Adults ≥ 18 years of age with a diagnosis of T2D could be included in the study if they had been switched to, or had initiated, IDegAsp at the discretion of the treating physician. The primary endpoint was change in HbA1c from baseline to end of study.
Outcome measures: The primary endpoint was change in HbA1c from baseline to end of study.
Results: Data were available from 179 patients. Prior to starting IDegAsp, the majority of the patients (76%) were already being treated with insulin therapy and the mean duration of follow-up was 210 days. The most commonly reported reasons for switching to IDegAsp were to improve glycaemic control (88.8%) and reduce the risk of hypoglycaemia (39.1%). In comparison with baseline values, mean HbA1c and fasting plasma glucose were significantly lower at end of study (8.4% vs. 9.6%; estimated mean difference −1.3% [95% confidence interval −1.6 to −1.1, $p < 0.0001$]; and 7.3 vs. 10.9 mmol/L; −3.5 mmol/L [−4.5 to −2.5, $p < 0.0001$], respectively). Improvement in glycaemic control after the switch to IDegAsp was achieved with lower daily insulin doses and less hypoglycaemia when compared with the time period prior to switch. Two patients discontinued IDegAsp due to adverse events.
Conclusion: In this South African cohort, initiating or switching to IDegAsp was associated with improved glycaemic control, lower insulin dose requirements among patients already on insulin therapy, and significantly lower rates of non-severe (overall and nocturnal) and severe hypoglycaemia in comparison with previous therapy.

Keywords: glycaemic control, IDegAsp, initiating, type 2 diabetes, switching

Introduction

In people with newly diagnosed diabetes, lifestyle modification and metformin are the recommended first-line treatments.[1,2] However, diabetes is a progressive disease. Pancreatic beta cell function starts to decline long before diagnosis, such that most patients have already lost 50% of beta cell function by the time type 2 diabetes mellitus (T2D) is diagnosed, and, despite treatment, beta cell function continues to decline at approximately 4% per year.[3,4] Eventually, most patients will require insulin therapy.[5–7]

When oral and other non-insulin agents fail to maintain glycaemia, exogenous insulin supplementation is the only effective treatment option to control blood glucose. With appropriate doses, it is able to achieve clinically significant HbA1c reductions.[2] However, there are many barriers, both physician and patient-related, to initiation and appropriate dose escalation with insulin. Some of these include lack of knowledge concerning therapeutic options, failure to identify and set appropriate individualised HbA1c targets, financial and time constraints, fear and risk of hypoglycaemia, weight gain, the burden of daily injections and, especially with basal-bolus therapy, complicated treatment regimens.[8] Consequently many patients fail to receive or escalate therapy that could reduce morbidity and mortality.

Premixed insulins, containing fixed doses of short-acting and intermediate- or long-acting insulins, offer a simple and effective approach to escalating therapy.[9] IDegAsp is a co-formulation of two different insulin analogues (70% of the ultra-

long-acting basal insulin degludec [IDeg] and 30% of the short-acting [mealtime] insulin aspart [IAsp]), that is administered in one injection from the same pen device.[10] IDeg has a long duration of action (> 24 hours) with 25% less variability compared with other long-acting basal insulins, providing stable and predictable insulin and plasma glucose concentrations between doses.[11,12] IAsp has peak activity just over an hour after injection followed by a decline in action over 4 hours. With once- or twice-daily injection, IDegAsp provides predictable basal and postprandial glycaemic control.[13] When treatment intensification is necessary, adjusting the dose of IDegAsp is simple and can be based on a single pre-breakfast and pre-evening meal self-monitored plasma glucose measurement.[14]

Clinical trials conducted in patients with T2D have compared glycaemic control and hypoglycaemia rates of IDegAsp with basal insulin, alternative premixed insulins and basal-bolus therapy. In insulin-naive T2D patients, once-daily IDegAsp provided superior reductions in HbA1c with fewer hypoglycaemic and nocturnal hypoglycaemic episodes compared with once-daily U100 insulin glargine.[15] IDegAsp provided better control of fasting plasma glucose (FPG) than biphasic insulin aspart 30/70 in both insulin-naive patients and those inadequately controlled with pre- or self-mixed insulin (with or without oral antidiabetic drugs), with a lower risk of both daytime and nocturnal hypoglycaemia, lower daily insulin doses and less weight gain.[16,17] In comparison with a basal-bolus regimen, a similar proportion of patients treated with IDegAsp achieved HbA1c < 7%, with a lower total daily insulin dose, less weight gain and numerically lower rates of hypoglycaemia and nocturnal hypoglycaemia.[18] Results from the patient-reported outcomes suggested that the lower injection burden associated with IDegAsp posed less interference with day-to-day social activities.

It has previously been shown that improved patient-reported outcomes and reduced regimen complexity are associated with improved adherence and consequently better glucose control.[19,20] Conversely, adverse effects, including hypoglycaemia and weight gain, can significantly reduce adherence to insulin therapy.[21,22]

The ARISE (A Ryzodeg Initiation and Switch Effectiveness) study was a real-world study designed to investigate glycaemic control and other clinical outcomes in people with T2D who initiated or switched to IDegAsp from previous antidiabetic treatment according to local clinical practice. The study was conducted across six different countries (Australia, India, Malaysia, Philippines, Saudi Arabia and South Africa). The results from the global cohort have been reported previously.[23] Here, we report results from the South African cohort and compare them with those from the overall population.

Methods

The design of ARISE has been described in detail elsewhere.[24] Briefly, ARISE was a 26-week, multicentre, prospective, open-label, non-interventional observational study investigating clinical outcomes in people with T2D after initiating or switching to IDegAsp at the discretion of their treating physician. Adults ≥ 18 years of age with a diagnosis of T2D were eligible for inclusion if (1) they had been treated with any antidiabetic medications other than IDegAsp for at least 26 weeks; (2) they had an HbA1c value recorded no more than 12 weeks prior to signing informed consent and initiating treatment; (3) at the discretion of the treating physician, they had been switched to, or had initiated, IDegAsp (independent of the decision to include them in the study). The study consisted of a baseline visit (at which informed consent was obtained and treatment with IDegAsp was initiated). Follow-up visits were scheduled at the discretion of the treating physician, and a final end-of-study (EOS) visit was scheduled within 26–36 weeks from initiation of IDegAsp. The starting dose of IDegAsp, frequency of follow-up visits, dose adjustments and prescription of additional antidiabetic medications were at the discretion of the treating physician. Exclusion criteria included previous treatment with IDegAsp and language barriers that would lead to inadequate understanding or cooperation. The study was conducted in accordance with the Declaration of Helsinki (2010) and the protocol was approved by research ethics boards/institutional review boards for all sites. All patients signed informed consent to participate. Data were collected from eight sites across South Africa between August 2019 and December 2020.

Objectives and endpoints

The primary endpoint was change in HbA1c from baseline to EOS. Secondary endpoints were (1) the proportion of participants achieving HbA1c < 7.0% at EOS; (2) the proportion of participants achieving HbA1c levels below a pre-defined individualised treatment target at EOS (categories of target ranges were < 6.5%, 6.5% to < 7.0%, 7.0% to < 7.5%, 7.5% to < 8.0%, and ≥ 8.0%); and (3) change from baseline to EOS in FPG, total, basal and prandial insulin dose, and body weight.

Additional endpoints included (1) individual-reported non-severe hypoglycaemic episodes (overall and nocturnal) occurring within 4 weeks prior to IDegAsp initiation and within 4 weeks prior to EOS, and severe hypoglycaemic episodes occurring within 26 weeks prior to IDegAsp initiation and during the 26-week study duration. Non-severe hypoglycaemia was defined as an episode with symptoms and/or self-measured blood glucose value ≤ 3.9 mmol/L that the individual was able to self-treat. A nocturnal hypoglycaemic event was one occurring at night. Severe hypoglycaemia was defined as an episode of hypoglycaemia requiring the assistance of another individual to actively administer carbohydrate or glucagon or take other corrective action to relieve neurocognitive symptoms associated with hypoglycaemia; (2) reasons for initiating IDegAsp treatment at baseline, reasons for discontinuing IDegAsp treatment; and (3) the proportion of individuals discontinuing treatment during the study.

Exploratory endpoints included healthcare resource utilisation (HRU) associated with the management of diabetes and its complications observed within 12 weeks prior to IDegAsp initiation and within 12 weeks prior to EOS or discontinuation, and HRU associated with severe hypoglycaemia observed within 26 weeks prior to IDegAsp initiation, and during the 26 weeks prior to EOS.

Statistical methods

The full analysis set included all eligible individuals who signed the informed consent and initiated treatment with IDegAsp (intention to treat data set). Primary analysis of the primary endpoint was conducted using crude and adjusted mixed models for repeated measurements (MMRM). The analysis was based on all individuals in the full analysis set with at least one post-baseline HbA_{1c} measurement using the "in-study" observation period. This observation period represented the time period during which individuals were considered to be in the study,

regardless of IDegAsp treatment discontinuation. The crude model included baseline HbA_{1c} and time of HbA_{1c} as covariates. The adjusted model included baseline HbA_{1c}, time of HbA_{1c}, age, sex, body mass index (BMI), study site and previous antidiabetic treatment as covariates. Primary and secondary analyses were repeated for change from baseline to EOS in FPG, insulin dose and body weight, with the baseline value of the relevant endpoint included as covariates. The incidence of non-severe (overall and nocturnal) and severe hypoglycaemia was analysed using negative binomial regression models with the log-transformed follow-up time as offset. Here we present the results of the primary analyses of data from South Africa using the adjusted MMRM for the in-study observation period, except for HRU, which was analysed using the on-treatment observation period only.

Results

Baseline demographic and clinical characteristics

Of the 386 individuals who were assessed for eligibility in South Africa, 179 were initiated or switched to IDegAsp and were included in the full analysis set (see Supplementary Figure 1). Baseline demographics and clinical characteristics for the South African cohort and overall study population are presented in Table 1. The South African cohort was generally comparable to the overall cohort. The mean age was 56.5 years and mean duration of diabetes was 12.6 years. Notable differences in comparison with the overall cohort were a higher proportion of females (54.2% vs. 46.4%), greater mean body weight (90.5 vs. 79.5 kg) and a higher proportion of subjects receiving a prandial insulin at baseline, either as part of a premix (36.9% vs. 21.8%) or basal-bolus (19.6 vs. 13.0) insulin regimen. Before switch to IDegAsp, the majority of patients (76%) were already being treated with insulin, whereas the remainder (24%) were receiving oral antidiabetic (OAD) medications. At treatment initiation, IDegAsp was most commonly prescribed twice daily (BID) (64.8%), with the remainder receiving once-daily injections (OD) (35.2%). The mean (standard deviation [SD]) initial total daily dose of IDegAsp was 37.7 (22.8) U.

Table 1: Demographic and clinical characteristics at baseline

Factor	Overall *N* = 1 102	South Africa *N* = 179
Age, mean (SD)	58.6 (12.2)	56.5 (11.7)
Male, *n* (%)	591 (53.6)	82 (45.8)
Duration of diabetes (years), mean (SD)	13.3 (8.3)	12.6 (7.2)
Body weight (kg), mean (SD)	79.5 (19.6)	90.5 (20.9)
BMI (kg/m^2), mean (SD)	29.2 (5.9)	32.7 (6.6)
HbA_{1c} (%), mean (SD)	9.8 (2.0)	9.6 (1.9)
HbA_{1c} individualised treatment target, *n* (%)		
< 7.0%	223 (20.2)	31 (17.3)
7.0%–< 7.5%	691 (62.7)	117 (65.4)
7.5%–< 8.0%	112 (10.2)	16 (8.9)
≥ 8.0%	76 (6.9)	15 (8.4%)
FPG (mmol/L), mean (SD)	11.0 (4.2)	11.2 (4.8)
Anti-diabetic treatment, n (%):		
OADs only	371 (35.1)	43 (24.0)
Premix insulin ± bolus insulin (± OADs)	232 (21.8)	66 (36.9)
Basal insulin only (± OADs)	230 (21.8)	24 (13.4)
Basal-bolus insulin (± OADs)	137 (13.0)	35 (19.6)
GLP-1 RA ± insulin (± OADs)	87 (8.2)	11 (6.1)
Dose of previous prandial insulin (U), mean (SD)	25.8 (22.8)	27.9 (30.4)
Diabetes complications, *n* (%):		
Diabetic neuropathy	216 (24.7)	25 (15.7)
Diabetic nephropathy	178 (20.3)	18 (11.3)
Cardiovascular disease	150 (17.1)	24 (15.1)
Diabetic retinopathy	102 (11.6)	13 (8.2)
Peripheral vascular disease	15 (1.7)	0

BMI, body mass index; FPG, full analysis setting plasms glucose; GLP-1 RA, glucagon-like peptide-1 receptor agonist; OAD, oral antidiabetic drug; *N*, number of individuals in the full analysis set; SD, standard deviation; U, unit.

Physicians' reasons for initiating or switching to IDegAsp are summarised in Table 2. The most commonly reported reasons were to improve glycaemic control (88.8%) and to reduce the risk of hypoglycaemia (39.1%). Other reasons included flexibility of the dosing regimen (26.8%), fewer injections than basal-bolus insulin (15.1%) and no reconstitution required (2.2%).

Glycaemic control

The mean and median durations of follow-up were 210 and 225 days, respectively. In comparison with baseline, mean HbA_{1c} was significantly lower at EOS (8.4% vs. 9.6%) with an estimated mean difference of −1.3% (95% CI −1.6;−1.1, $p < 0.0001$) (Table 3). Similarly, FPG values were significantly reduced from baseline to EOS (7.3 vs. 10.9 mmol/L), with an estimated mean difference of −3.5 mmol/L (95% CI −4.5; −2.5, $p < 0.0001$). At EOS, the percentages of subjects achieving HbA1c < 7% or HbA1c level below their pre-defined individualised target were significantly higher than at baseline (18.1% vs. 4.5% and 16.8% vs. 2.2%, respectively).

Insulin dose

Overall, among patients who were treated with insulin at baseline, there was a significant reduction in daily insulin doses across the in-study observation period. At baseline, the mean (SD) total daily insulin dose was 58.1 (36.3) U compared with mean (SE) estimated total daily insulin dose of 48.3 (2.47) U at EOS (estimated change −11.5 U [95% CI −16.39; −6.59], $p < 0.0001$). There was also a significant decrease in estimated mean daily prandial insulin dose (22.4 [29.9] U at baseline vs. 16.4 [1.17] U at EOS; estimated change −6.9 U [95% CI −9.2;

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

Factor	Overall *N* = 1 102	South Africa *N* = 179
To improve the individual's glycaemic control	1 026 (93.1)	159 (88.8)
To lower the risk of hypoglycaemia	291 (26.4)	70 (39.1)
Flexibility in the dosing regimen	286 (26.0)	48 (26.8)
Fewer injections than basal-bolus therapy	277 (25.1)	27 (15.1)
No reconstitution needed	98 (8.9)	4 (2.2)
Change in coverage status favouring IDegAsp	82 (7.4)	0
Other	54 (4.9)	30 (16.8)

Physicians could select more than one reason for each person. Data in (parentheses) are percentage of responses. A change in coverage status favouring IDegAsp refers to a change in healthcare insurance or reimbursement requirements that led to better access to the drug. *N*, number of individuals in the full analysis set.

Table 3: Change in HbA_{1c}, FPG, and body weight with IDegAsp treatment from baseline to end of study (EOS)

	Overall N = 1 102	South Africa N = 179
Overall change in HbA_{1c}		
Subjects with data, n	935	170
Observed mean HbA_{1c} at baseline, % (SD)	9.7 (1.9)	9.6 (1.9)
Estimated mean HbA_{1c} at EOS, % (SE)	8.3 (0.1)	8.4 (0.1)
Estimated mean change, % (95% CI)	-1.4* (-1.5; -1.3)	-1.3* (-1.6; -1.1)
Change in HbA_{1c} according to treatment prior to study, % (95% CI)		Data not available
OADs only		
Observed mean HbA_{1c} at baseline, % (SD)	10.2 (2.0)	
Mean change from baseline to EOS	-2.0* (-2.2; -1.8)	
Premix insulin ± bolus insulin (± OADs)		
Mean change from baseline to EOS	9.4 (1.9) -0.9* (-1.2; -0.6)	
Basal insulin only (± OADs)		
Observed mean HbA_{1c} at baseline, % (SD)	9.7 (1.8)	
Mean change from baseline to EOS	-1.3* (-1.6; -1.1)	
Basal–bolus insulin (± OADs)		
Observed mean HbA_{1c} at baseline, % (SD)	9.3 (1.9)	
Mean change from baseline to EOS	-0.9* (-1.2; -0.5)	
GLP-1 RA ± insulin (± OADs)		
Observed mean HbA_{1c} at baseline, % (SD)	9.2 (1.8)	
Mean change from baseline to EOS	-1.3* (-1.6; -1.0)	
HbA_{1c} < 7.0%, n (%)		
At baseline	4.3	4.5
At EOS	14.9	18.1
HbA_{1c} < pre-defined individual target, n (%)		
At baseline	2.5	2.2
At EOS	14.9	16.8
Change in FPG		
Subjects with data, n	622	85
Observed mean FPG at baseline, mmol/L (SD)	10.9 (4.1)	10.9 (4.5)
Estimated mean FPG at EOS, mmol/L (SE)	8.2 (0.1)	7.3 (0.5)
Estimated mean change, mmol/L (95% CI)	-2.7* (-3.0; -2.5)	-3.5* (-4.5; -2.5)
Change in body weight		
Subjects with data, n	900	169
Observed mean body weight at baseline, kg (SD)	79.6 (19.2)	90.4 (20.8)
Estimated mean body weight at EOS, kg (SE)	79.4 (0.3)	88.8 (0.5)
Estimated mean change, mmol/L (95% CI)	-1.0* (-1.5; -0.5)	-0.2 (-0.8; 1.2)

*$p < 0.0001$ at EOS vs. baseline. *N*, number of individuals in the full analysis set; *n*, number of individuals with a response.

−4.6], $p < 0.0001$); and in estimated mean basal daily insulin dose (35.6 [18.2] U at baseline vs. 31.9 [1.27] U at EOS; estimated change −4.2 [95% CI −6.7; −1.7], $p = 0.0012$).

Hypoglycaemia

The percentage of subjects reporting non-severe hypoglycaemia or nocturnal non-severe hypoglycaemia during the 4 weeks prior to EOS was lower than during the 4 weeks prior to initiating IDegAsp (6.7% vs. 16.2% and 2.2% vs. 5.0%, respectively) (Table 4). There were no reported episodes of severe hypoglycaemia during the course of the study.

Body weight

There was no significant change in body weight during the study period (Table 3).

Healthcare resource utilisation

In comparison with the 12 weeks prior to initiating or switching to IDegAsp, self-reported outpatient visits, emergency room visits, in-patient hospitalisations, other healthcare provider visits and workdays missed were less frequent in the 12 weeks prior to EOS (Table 5).

Discontinuation of IDegAsp

The majority of subjects (95.0%) completed the study and only 2 patients discontinued IDegAsp due to adverse events. Other reasons for discontinuation are listed in Table 6.

Discussion

While randomised, controlled clinical trials (RCTs) are the gold standard for evaluating the efficacy and safety of therapeutic agents, strict treatment protocols and inclusion and exclusion

Table 4: Summary of hypoglycaemic episodes occurring prior to initiation of IDegAsp (baseline) and prior to EOS or discontinuation

Factor	Overall *N* = 1 102		South Africa *N* = 179	
	Events, *n*	Individuals with an event, *n* (%)	Events, *n*	Individuals with an event, *n* (%)
Non-severe:				
Within 4 weeks of initiation	364	128 (11.6)	153	29 (16.2)
Within 4 weeks prior to EOS or discontinuation	162	44 (4.0)	43	12 (6.7)
Nocturnal non-severe:				
Within 4 weeks of initiation	142	59 (5.4)	49	9 (5.0)
Within 4 weeks prior to EOS or discontinuation	31	14 (1.3)	12	4 (2.2)
Severe:				
Within 26 weeks of initiation	51	23 (2.1)	9	4 (2.2)
Within 26 weeks prior to EOS	3	3 (0.3)	0	0

Data were based on the full analysis set. Negative binomial regression models specifying a log-transformed follow-up time offset term were used to examine the incidence rate of hypoglycaemic events occurring prior to initiation of IDegAsp and prior to end of study or at discontinuation. *N*, number of individuals in the full analysis set; *n*, number of individuals contributing to the analysis.

Table 5: Summary of healthcare resource utilisation prior to initiation of IDegAsp (baseline) and prior to EOS

	Overall N=1,102	South Africa N=179
Individuals reporting any visit/resource n (%)		
Within 12 weeks of initiation	510 (46.3)	76 (42.5)
Within 12 weeks prior to EOS	307 (27.9)	17 (9.5)
Individuals who self-reported an outpatient visit		
Within 12 weeks of initiation	394 (35.8)	52 (29.1)
Within 12 weeks prior to EOS	195 (17.7)	3 (1.7)
Individuals who self-reported an emergency room visit		
Within 12 weeks of initiation	46 (4.2)	8 (4.5)
Within 12 weeks prior to EOS	8 (0.7)	2 (1.1)
Individuals who self-reported an in-patient hospitalization		
Within 12 weeks of initiation	78 (7.1)	23 (12.8)
Within 12 weeks prior to EOS	12 (1.1)	5 (2.8)
Individuals who self-reported any other healthcare providers visit and contact outside of a hospital setting		
Within 12 weeks of initiation	169 (15.3)	30 (16.8)
Within 12 weeks prior to EOS	155 (14.1)	11 (6.1)
Individuals who self-reported any work-days missed		
Within 12 weeks of initiation	58 (5.3)	14 (7.8)
Within 12 weeks prior to EOS	9 (0.8)	2 (1.1)

Data based on the full analysis set, on-treatment observation period. EOS, end of study.

criteria dictate management strategies and select for trial populations that are not necessarily representative of those in everyday clinical practice. In contrast, real-world studies complement the results from RCTs by providing insight into current management practices and the effects of medicines in the heterogeneous patient population seen in clinical practice.[25]

In the ARISE study, patients with T2D who initiated or were switched to IDegAsp in private medical practices in South Africa were followed up for 26–36 weeks. Treatment with IDegAsp was associated with significant improvements in mean HbA1c, FPG and the percentage of patients who achieved their glycaemic target. Approximately three-quarters of the patients were switched to IDegAsp from another insulin regimen, and more than half of those were using prandial insulin, either as a premix or as basal-bolus therapy. In these patients, switching to IDegAsp was associated with a significant reduction in the total daily, prandial and basal doses of insulin. The improvement in glycaemic control was achieved without an increase in hypoglycaemic episodes. Conversely, in comparison with the 4 weeks prior to initiating IDegAsp, in the 4 weeks before EOS, both the number of patients reporting hypoglycaemic episodes and the frequency of episodes were substantially reduced. In analysis of the full analysis set, no episodes of severe hypoglycaemia were reported after switch to IDegAsp. Exploratory analysis suggested that these improvements in outcomes were associated with lower utilisation of healthcare resources, including use of outpatient facilities and admissions to hospital, and number of workdays missed.

In general, the results in the South African cohort of ARISE were similar to the pooled overall results. At baseline, more patients in the South African cohort were receiving insulin, and 4.5% were meeting a target of HbA1c < 7%. These observations are commensurate with the higher percentage of South African physicians reporting "to lower risk of hypoglycaemia" as the reason for switching to IDegAsp. Also, in the South African cohort, IDegAsp treatment was associated with a significant

Table 6: Reasons for individuals discontinuing IDegAsp during the study period

Factor	Overall *N* = 1 102	South Africa *N* = 179
Discontinued treatment during the treatment period, *n* (%)	59 (5.4)	9 (5.0)
Change in coverage status disfavouring IDegAsp	10 (16.9)	4 (44.4)
Adverse event	5 (8.5)	2 (22.2)
Unacceptable hypoglycaemia profile/ pattern	2 (3.4)	0
Lack of convenience	2 (3.4)	1 (11.1)
Insufficient effect on glycaemic control	2 (3.4)	0
Pregnancy or intentions to become pregnant	2 (3.4)	0
Weight gain	0	0
Other	32 (54.2)	2 (22.2)
Unknown	4 (6.8)	0

Data are the number of individuals (%). Analysed using the on-treatment observation period. A change in coverage status disfavouring IDegAsp refers to a change in healthcare insurance or reimbursement requirements that led to worse access to the drug. *N*, number of individuals in the full analysis set; *n*, number of individuals with a response.

reduction in daily prandial insulin dose, whereas the overall study population reported a significant increase.[23] This disparity might be explained by a greater use of prandial insulin at baseline in the South African cohort. However, in the South African cohort, it is also possible that a reduction in prandial insulin might have contributed to higher postprandial glucose levels, which, in turn, would increase HbA1c.

It is notable that, despite improvement in glycaemia and the number of patients achieving HbA1c target, at EOS the percentage of patients who did achieve target HbA1c was still very low (approximately 18% for HbA1c < 7% and 17% for HbA1c < predefined target). More than 80% of patients were aiming for HbA1c < 7.5%, and although this target was generally not achieved, for patients switched from another insulin regimen, the mean total daily dose of insulin was lower after initiation of IDegAsp. This suggests that patients are not being sufficiently monitored and treatment is not being adequately and timeously adjusted. Indeed, the large proportion of patients still being treated with OADs (24%) at baseline despite lack of control and an average duration of almost 13 years since diagnosis suggests therapeutic inertia and hesitancy to escalate therapy. The same observation was made in another recent observational study of diabetes management in South African private practice.[26] In that study, despite failing to meet glycaemic targets, over a 24-month period only 5% of patients had adjustments made to their diabetes medication.

Although the results of ARISE are consistent with randomised controlled trials of IDegAsp, the decrease in HbA1c was considerably less than that observed in those studies in which physicians and patients were mandated to adhere to regular follow-ups and strict titration algorithms. Therefore, it may be beneficial to consider stricter titration algorithms in routine care. This could be facilitated by titration schedules, which can be implemented by the patient based on home monitoring without the necessity to consult the physician.

IDegAsp has a number of features that might improve confidence to escalate therapy. The basal component of IDegAsp has low pharmacokinetic/pharmacodynamic (PK/PD) variability, which simplifies dose titration and reduces risk of hypoglycaemia.[12,14] Due to a clearer PK/PD separation of the basal and prandial components in IDegAsp compared with other insulins, the prandial effect is better able to match the physiological need following a large meal, with less risk of late postprandial hypoglycaemia. Unlike other premix insulins, IDegAsp does not require resuspension before each injection. Consequently, IDegAsp offers a simple treatment regimen (once or twice daily) that offers flexibility in timing of injections, as long as IDegAsp is dosed with the largest meal of the day and the time interval between injections is longer than 4 hours.[13,27,28] These are important considerations, considering that hypoglycaemia and flexibility of dosing regimen were the second and third most frequent reasons for switching to IDegAsp in this study.

The multicentre design and broad, true-to-life inclusion and exclusion criteria of ARISE make the results generalisable to an extensive population of people with T2D. However, there are a number of limitations of the study that might confound interpretation of the results.

First, the duration of observation was limited to 36 weeks. Observing treatment over a longer period allows for further adjustments to therapy, which might increase the number of patients who achieve their glycaemic targets. In patients who were already receiving insulin, the total dose of insulin was lower after the switch to IDegAsp. However, although a larger proportion of patients did achieve their targets after the switch, most patients did not, and higher doses might have been appropriate for this latter group. Furthermore, as mentioned, a lower prandial insulin dose may increase post-prandial glycaemia and HbA1c. Because the data for post-prandial glucose levels are not available, we cannot comment further on that. Due to the non-interventional study design, insulin titration methods and frequency of injecting were left to the discretion of the treating physician. Suboptimal doses may lead to underestimation of the potential efficacy of IDegAsp, but also to the risk of hypoglycaemia, which may increase with higher doses of IDegAsp.

Second, adherence to therapy was not recorded. Previous studies have shown that adherence to insulin therapy is poor.[29–32] Reasons for this include fear of hypoglycaemia, aversion to injections and the complexity of treatment regimens.[22,32] Furthermore, the study was conducted during the initial months of the COVID-19 pandemic, when access to routine medical care appointments and medication was restricted. This would have impacted the standard of care and adjustments to medications and doses. Although overall mean body weight did not increase in the South African cohort, restrictions in physical activity and increased snacking during isolation were associated with weight increase and are likely to have adversely affected glycaemic control in those with T2D.[33]

Third, ARISE had an open-label design and participants were empirically selected with the expectation that they would benefit from initiating or switching to IDegAsp. Therefore, there is potential for selection bias, and placebo and Hawthorne effects also cannot be excluded. These may potentially lead to an overestimation of efficacy.

Conclusions

In this real-world, prospective, non-interventional study in South Africans with T2D, initiating or switching to IDegAsp was associated with improved glycaemic control, lower insulin dose requirements among patients already on insulin therapy, and significantly lower rates of non-severe (overall and nocturnal) and severe hypoglycaemia in comparison with previous therapy. However, the results from this study add to existing literature indicating that the overall standard of care for patients with T2D in South Africa is suboptimal.

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