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ORIGINAL RESEARCH

SPIRIT: Assessing Clinical Parameters Associated with Using IDegLira in Patients with Type 2 Diabetes in a Real-World Setting in Colombia

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ABSTRACT

Introduction: Insulin degludec/liraglutide (IDegLira) is a fixed-ratio combination of insulin degludec (a basal insulin) and liraglutide (a glucagon-like peptide-1 receptor agonist [GLP-1RA]). This study aimed to investigate clinical outcomes in people with type 2 diabetes mellitus (T2DM) after initiating IDegLira treatment in a real-world setting in Colombia.

Methods: SPIRIT is a non-interventional, single-arm, retrospective chart review study to assess clinical outcomes in people with T2DM. Participating patients were switched from a treatment regimen of basal insulin (with or without oral antidiabetics [OADs]) and started on treatment with IDegLira a minimum of 26±6 weeks before the data collection start date. Data were collected from the medical records of 175 patients in ten clinical centers across Colombia.

Results: Compared with baseline, there was a significant reduction in glycated hemoglobin (HbA1c) (1.3%; 95% confidence interval [CI] − 1.6 to − 1.0; $p<0.0001$) after 26±6 weeks of follow-up. The mean HbA1c at baseline and at the end of the study was 9.1% and 7.8%, respectively. In addition, IDegLira significantly reduced absolute body weight by 1 kg (95% CI − 1.5 to − 0.5; $p<0.0001$), from a mean of 76.1 kg at baseline to 75.1 kg after follow-up. The mean IDegLira dose at the end of the study was 21.3 U, and no severe hypoglycemic events were observed during the follow-up period.

Conclusion: In real-world practice, initiating IDegLira in patients with T2DM previously treated with basal insulin (±OAD) was associated with improved glycemic control, reduced body weight and reduced risk of hypoglycemia.

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Keywords: Body weight; Evidence-based practice; Glycemic control; Hypoglycemia; IDegLira; Type 2 diabetes mellitus

Key Summary Points
Why carry out this study?
Intensification of insulin treatment is often delayed because of the complexity and fear of adverse events associated with the options proposed by guidelines
The fixed-ratio combination known as IDegLira is recognized in international guidelines as an alternative to basal-bolus therapy for intensification of type 2 diabetes mellitus (T2DM) treatment
As the Latino population, and specifically Colombians, are underrepresented in clinical trials, there is a need to generate real-world evidence to understand how this medication works in this population
Although there is some real-world evidence on the use of IDegLira in Colombia, SPIRIT, a retrospective chart review study, has the largest sample size to date, with centers across the country participating; it is also aligned with the requirements for reimbursement of the therapy proposed by insurance companies
What was learned from this study?
After approximately 26 weeks, IDegLira was associated with a significant reduction in glycated hemoglobin (HbA1c), and a high proportion of patients achieved HbA1c < 7%
In this study, the use of IDegLira was associated with modest weight loss and a reduction in insulin dose
No patient experienced a severe hypoglycemic episode during treatment with IDegLira

INTRODUCTION

Current treatment guidelines for type 2 diabetes mellitus (T2DM) currently recommend the use of incretin-based therapies as first-line injectable treatment, but many people with T2DM will require insulin at some point during the course of their disease [1]. Fixed-ratio combinations of basal insulin with a glucagon-like peptide-1 receptor agonist (GLP-1RA) minimize injection burden while balancing the risk of hypoglycemia and weight gain [1, 2]. Xultophy® (Novo Nordisk A/C, Bagsværd, Denmark), a fixed-ratio combination of insulin degludec and liraglutide (IDegLira), is an alternative to traditional treatment intensification options in T2DM. This combination achieves the complementary effects of insulin degludec and liraglutide on fasting and postprandial glycemic control. Additionally, although the current approach to T2DM management states that incretin-based therapies should be initiated prior to insulin therapy, the reality is that many patients are treated with insulin prior to starting on GLP-1RAs, in which case current guidelines recognize the fixed-ratio combination as an alternative to intensification in patients with T2DM and avoid the complexity of multiple daily injections [1, 3].

The safety and efficacy of IDegLira for managing adult patients with T2DM have been established in various phase 3 clinical trials [2, 4–8] that have examined the use of IDegLira in different background populations with T2DM, and in combination with a range of oral antidiabetic drugs (OADs). A number of real-world studies have analyzed types of populations and outcomes not normally included in randomized clinical trials (RCTs) [9, 10]. For example, IDegLira therapy has a significant impact on both gastrointestinal microbes and cognitive function, including depression, cognitive function and markers of inflammation in very elderly subjects with T2DM [11]. Additionally, an observational study on real-world evidence (RWE) was conducted in Colombia, which demonstrated the effectiveness of IDegLira in glycemic control in patients with T2DM [12]. However, this study evaluated patients in only two centers dedicated

to specialized diabetes care. Hence, further evidence is needed with greater representativeness in the population across Colombia. Real-world/non-interventional studies reflect how a product is used and performed in routine clinical practice. Such studies contribute to scientific and clinical knowledge and complement RCT findings by providing evidence of the generalizability of results to a broader population of patients [13].

We designed the non-interventional study (NIS) reported here to generate RWE of IDegLira usage in Colombia by investigating clinical parameters associated with using IDegLira initiated within routine clinical practice in adult patients with T2DM previously treated with basal insulin, with or without OADs. The data generated from this study will add to the body of evidence on glycemic control from RCTs and provide clinical insight into the initiation and intensification of IDegLira in a real-world setting in Colombia.

METHODS

This was a single-arm, retrospective, chart review study in which data reported in the medical records of adult patients with T2DM who had initiated treatment with IDegLira a minimum of 26 ± 6 weeks before the data collection start date were studied . All patients were receiving treatment according to current clinical practice and applicable local labels at physicians' discretion.

All patients who had initiated treatment with IDegLira were eligible for consideration to participate in the study, including those who, at the time of inclusion in this study, had discontinued IDegLira. Information was collected for at least 26 ± 6 weeks after treatment initiation. The eligible patients were selected consecutively, beginning with those who attended the clinic most recently and working backward until the predetermined number of patients per study site was reached. We extracted relevant baseline and follow-up data from medical records of each patient and transferred these data into an electronic case report form. For this study, eligible participants were: (1) adults with T2DM who had switched to IDegLira from basal insulin (± OADs) at least 26 + 6 weeks before the enrollment date and (2) adult patients with available and documented glycated hemoglobin (HbA1c) measurements ≤ 12 weeks before IDegLira initiation.

The exclusion criteria were: mental incapacity, an unwillingness or language barriers precluding adequate understanding or cooperation; a diagnosis of type 1 diabetes mellitus (T1DM), maturity-onset diabetes of the young, latent autoimmune diabetes in adults, gestational diabetes, or any hyperglycemic state other than T2DM; pregnancy or breastfeeding during the study; treatment with basal-bolus insulin before IDegLira initiation; and participation in another T2DM clinical study involving any clinical intervention or administration of an investigational drug within 3 months before initiating IDegLira.

The latest HbA1c measurements recorded (≤ 12 weeks) before the initiation of IDegLira were collected (we used the value closet to week 0), as were as all available HbA1c values in the follow-up period; these values were used to calculate the mean change in HbA1c from baseline to week 26 after IDegLira initiation. We defined the baseline as week 0, the time of IDegLira initiation. If the endpoint variable (e.g. HbA1c, body weight) was unavailable at baseline, the most recent value within ≤ 12 weeks before IDegLira initiation was used. Data on severe hypoglycemic episodes were also collected in the follow-up period if available in the medical records. A severe hypoglycemic episode was defined as an episode of hypoglycemia requiring the assistance of another person to administer carbohydrates or glucagon, or to actively take other corrective actions [11]. The end of the study was 26 weeks after initiation of IDegLira treatment with a window of +6 weeks. If multiple values were available for the specific endpoints within the window, the value closest to week 26 was used.

The primary endpoint was the change in local laboratory-measured HbA1c, from baseline (in week 0) to the end of the study (in week 26 + 6 weeks after IDegLira initiation). Secondary endpoints were the change in absolute body weight and the comparison between the daily dose of basal insulin and IDegLira.

The following clinical data were collected: height, body weight, diabetes complications (neuropathy, retinopathy and nephropathy), cardiovascular risk (smoking, hypertension, dyslipidemia and obesity) and severe hypoglycemic episodes at baseline and follow-up periods where applicable. In addition, we collected data on HbA1c and fasting plasma glucose levels, the date of IDegLira initiation, reasons for initiation, the dose of IDegLira, frequency of insulin(s) administered, and the name(s) of non-insulin antidiabetic medications.

Statistical Analyses

Baseline characteristics and demographics were reported as the mean with the standard deviation (SD) or as the appropriate percentages based on the full analysis set (FAS).

The change in laboratory-measured HbA1c from IDegLira initiation to week 26 (±6 weeks) was analyzed using a mixed model for repeated measurements (MMRM) on the complete analysis set with the 'on treatment' observation period (represents the period in which patients were considered to be treated with IDegLira). The study included all patients initiating IDegLira with at least one post-baseline HbA1c measure during the follow-up. We modeled the change in HbA1c from baseline as a continuous second-order polynomial function of time, with random subject level intercept, slope, and an unstructured covariance matrix for the two random coefficients.

The secondary endpoints were analyzed as baseline-adjusted changes using an analysis of covariance (ANCOVA) model with change from baseline in body weight and basal insulin doses as the dependent variables. Covariates included the baseline HbA1c value. In addition, when the sample size allowed, we considered relevant baseline covariates if found to be significantly important. Possible covariates included age, sex and baseline treatment, among others.

The exploratory endpoints were intended to describe changes in additional clinical parameters/characteristics of interest at 6 months after switching to IDegLira, such as the percentage of patients achieving HbA1c < 7% at week 26 (±6 weeks) and no weight gain, changes in OAD treatment and number of severe hypoglycemic episodes (before and after IDegLira initiation). All analyses were performed using Stata statistical software (version 17; Stata Corp LLC, College Station, TX, USA).

Ethical Approval

The ethical considerations for this protocol are based on the Declaration of Helsinki and the Ethical Guidelines for Health-Related Research with Human Beings prepared by the Council for International Organizations of Medical Sciences (CIOMS) in collaboration with the World Health Organization (WHO). The protocol was approved by the ethics committees or Institution Review Boards (IRBs) of all participating institutions, and by The National Institute of Drug and Food Surveillance (INVIMA) under number NN9068-4884. This study complies with the Colombian Ministry of Health's Resolution 8430 and was considered to be a no risk study that did not require consent from participants. No consent from participants to publish was required because no identifiable information is presented in the results.

The Board approved the clinical trial research protocol on Ethics Research of ten Health Insurers Companies, Hospitals, or Healthcare Centers of Colombia: Institute of Cardiology La Cardio, FRC Ambulatory Unit, Bluecare Research Center, University Hospital San Ignacio, IPS Cabeceras, Funcentra, Integral Diabetes Clinic, EPS Salud Total, Center for Diabetes and Metabolism CEDYM, and Sura diagnostic aids. Details from each center's contribution and IRB approval are provided in the Electronic Supplementary Material.

RESULTS

A total of 175 patients were included in the study (FAS). Baseline demographics and clinical characteristics are presented in Table 1. The patient cohort comprised slight more women than men (57.7% vs. 42.3%), and the mean age was 63.5 years (SD 11.5). The mean body mass

Table 1 Population demographics and baseline characteristics of patients with type 2 diabetes mellitus receiving IDegLira in a real-world evidence setting, Colombia ($N = 175$)

Baseline characteristics	Values
Age, *mean (years)*	63.5 (± 11.5)
Sex, *n (%)*	
Women	101 (57.7%)
Men	74 (42.3%)
Weight, *kg*	76.1 (± 14.8)
BMI, kg/m^2	29.4 (± 4.8)
HbA1c, *%*	9.1% (± 1.6%)
Dose of previous insulin treatment, *U/day*	27.8 (± 13.3)
Glargine U100, *n* (%)	136 (77.7%)
Degludec, *n* (%)	19 (10.9%)
Detemir, *n* (%)	11 (6.3%)
Glargine U300, *n* (%)	5 (2.9%)
Diabetes duration, *years*	10.8 (+ 9.1)
1 year, *n* (%)	3 (1.7%)
2–5 years, *n* (%)	58 (33.1%)
6–10 years, *n* (%)	48 (27.4%)
> 10 years, *n* (%)	66 (37.7%)
Diabetes complications, *n (%)*	29 (16.5%)
Nephropathy	12 (6.8%)
Neuropathy	11 (6.2%)
Retinopathy	6 (3.4%)
Cardiovascular complication, *n (%)*	133 (76%)
Obesity	72 (41.1%)
Hypertension	66 (37.1%)
Dyslipidemia	35 (20%)
Myocardial infarction	19 (10.8%)
Stroke	5 (2.8%)
Peripheral arterial disease	2 (1.1%)
Others	22 (12.5%)

Data are presented as the mean with the standard deviation in parenthesis (± SD) unless stated otherwise, and based on a complete analysis set ($N = 175$); when a complete data set was not available, the number of participants with data available (N) is given in parentheses

BMI Body mass index, *HbA*1c glycated hemoglobin, *T2DM* type 2 diabetes mellitus

index (BMI) was 29.4 (SD 4.8), with > 40% of patients having obesity as a comorbidity. The mean duration of the disease was 10.8 years, and the baseline Hba1c was 9.1 (SD 1.6). Most patients had cardiovascular complications, major risk factors such as dyslipidemia or hypertension or any previous event, such as myocardial infarction or stroke. Before treatment with IDegLira, patients were treated with basal insulin, mainly glargine U100, with an average daily dose of 27.8 U/day (SD 13.3).

The main reason to start IDegLira was the lack of glycemic and metabolic control and hyperglycemia, which are similar causes, representing 63.9% of patients. Weight gain (11.0%) was another reason for initiating IDegLira (Fig. 1).

The change in HbA1c after 26 weeks of receiving IDegLira, the study's primary endpoint, was – 1.3% (median – 1.4%; 95% confidence interval [CI] – 1.0 to – 1.6%). Among all patients, HbA1c decreased in 78.9%, remained in 1.7% and increased in 19.4% (Table 2).

Eight medical records did not report these data regarding the change in weight of patients after 26 weeks of treatment with IDegLira. The remaining 167 patients lost on average 1 kg of body weight (median – 1.1 kg; 95% CI – 1.5 to – 0.5 kg). Overall, weight decreased in 56% of patients, did not change in 22% and increased in 22% (Table 2).

The mean basal insulin dose at the start of the study was 27.8 U, and the mean IDegLira dose at the end of the study was 21.3 U. After 26 weeks of treatment with IDegLira there was

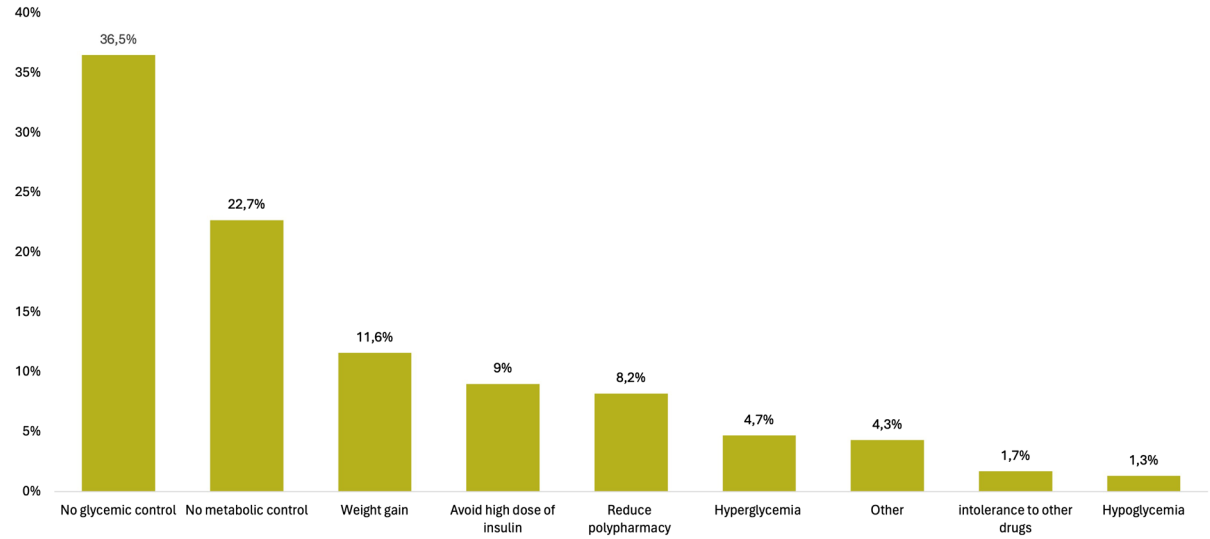

Fig. 1 Reasons for initiating IDegLira in patients with type 2 diabetes mellitus T2DM. *IDegLira* Fixed-ratio combination of insulin degludec and liraglutide

Table 2 Description of change in glycated hemoglobin and weight in patients with type 2 diabetes mellitus 26 weeks after starting treatment with IDegLira, Colombia, 2022

Change in HbA1c and weight	*n*	%
HbA1c change		
HbA1c decrease	138	78.9
0.1–1.0%	42	24.0
1.1– 2.0%	51	29.1
2.1– 5.0%	39	22.3
> 5.0%	6	3.4
No change	3	1.7
HbA1c increase	34	19.4
Weight change		
Weight decrease	93	55
< 1.0 kg	25	15
1.1–3.0 kg	37	12
3.1–6.0 kg	20	12
> 6.0 kg	11	7
No change	37	22

*HbA*1c Glycated hemoglobin, *T2DM* type 2 diabetes mellitus

a statistically significant change in daily insulin dose (- 6.4 U; median — 9 U; 95% CI – 4.7 to – 8.1 U). (Table 3).

Finally, as exploratory objectives, the changes in several clinical parameters were evaluated, as well as the use of OADs as add-on treatment in the patients (Table 4).

DISCUSSION

The current study is the first large, multicenter, observational study in a real-world setting on the initiation of IDegLira for treating T2DM in Colombia. Among the participants, IDegLira lowered HbA1c in 78.9% of patients with T2DM, similar to the results reported in the DUAL V and VII RCTs [7, 14]. One of the advantages of RWE studies is that they include patients more similar to those seen in daily medical practice, as compared to those in clinical trials, so their external validity is greater. In addition, if the results of the RWE studies coincide with those of the RCTs, these results become more robust and generate more confidence in clinical decision-making.

The clinical characteristics of the population at the beginning of the study (Table 1) are

Table 3 Comparison between starting doses of basal insulin and IDegLira

Parameters	Dose of basal insulin	Dose of IDegLira	Change (Δ)
Mean (SD)	27.8 (13.3)	21.3 (8.8)	− 6.4 95% CI: − 4.7 to − 8.1 $p < 0.0001$
Minimum	6	6	
Maximum	90	64	

CI Confidence interval, *SD* standard deviation

Table 4 Change in clinical parameters and oral antidiabetic drugs in patients with type 2 diabetes mellitus after 26 weeks of starting treatment with IDegLira

Clinical parameter	Baseline	End of study	*p*-value
Patients with HbA1C < 7%, *n* (%)	6 (3.4)	43 (24.6)	< 0.0001
Patients achieving HbA1c < 7% at week 26 (± 6 weeks) and no weight gain, *n* (%)	NA	35 (20)	–
Number of severe hypoglycemic episodes, *n*	23	0	–
Number of patients with severe hypoglycemic episodes, *n*	10	0	0.002
Patients using OADs, *n* (%)	167 (95.4)	157 (89.7)	0.006
Patients suspending any OADs (except DPP4i), *n* (%)	–	30 (17.1)	–

DPP4i Dipeptidyl peptidase 4 inhibitors, *HbA1c* glycated hemoglobin, *OADs* oral antidiabetic drugs, *T2DM* type 2 diabetes mellitus

similar to those presented in other RWE studies. The average duration of T2DM was a little over a decade (10.8 years), which increases the risk of developing macro- and microvascular damage. Similarly, the prevalence of obesity in these patients was greater than 40%, twofold higher than the proportion observed in the general population in Colombia [15]. It is essential to highlight that the baseline HbA1c of the patients at the time of starting IDegLira was higher than that observed in the DUAL trials, which makes it more challenging to achieve Hba1c targets [6, 7, 13]. This high level of clinical complexity that these patients had at the beginning of the study highlights the importance of the clinical results identified during the follow-up period.

Most of the patients (77.7%) were receiving insulin glargine U100 and therefore this population is comparable to the patient population of the DUAL V study (duration of diabetes 11.6 years; BMI 31.7 kg/m^2) [6]. The decrease in HbA1c in the DUAL V study was 1.81% vs. 1.3% in the present study. Similarly, the weight decrease in the DUAL V study was 1.4 kg verus 1.1 kg in this study (patients who received insulin glargine in the DUAL V study gained 1.8 kg). Another significant result of our study was weight loss in 55% of the patients. This outcome is important in an RWE study because there was no weight loss intervention other than the treating physician's suggestion in their consultation. Considering that weight gain is one of the main problems faced in treating T2DM [16], obtaining weight loss in more than half of the patients is a significant achievement of treatment with IDegLira. The results of this study are similar to those of other RWE studies performed in different countries, in which the HbA1c decrease

ranged between 0.3% and 1.7%, and the weight decrease was between 0.5 and 3.11 kg [6, 10, 17–19]. These similar results provide consistency and robustness to these clinical outcomes.

Similarly, using a lower dose of IDegLira compared to basal insulin dramatically impacts the quality of life of patients with T2DM because it reduces the risk of developing hypoglycemic events, which did not present in the population of the current study during the time of analysis. The same results were seen in another study involving elderly patients with T2DM treated with iDegLira, where iDegLira simplified treatment while improving quality of life and reducing hypoglycemia [20]. This result is expected as the lower incidence of hypoglycemia has already been proven with a new generation of long-acting insulin analogs versus other therapeutic regimens, such as basal/bolus [16]. However, the fear of hypoglycemia is a problem that patients with T2DM must face because it is a severe adverse event that, unfortunately, has been underestimated, especially by health insurers, but is accompanied by anxiety states and lack of long-term adherence [21]. Therefore, the fear of hypoglycemia affects the quality of life [22] and increases the healthcare costs of patients with T2DM [23]. For this reason, a significant clinical outcome is the finding of the use of fewer IDegLira units and the absence of severe hypoglycemia events during the follow-up period.

It is essential to consider that the baseline HbA1c (9.1% ± 1.6%) was significantly higher than the initial HbA1c in DUAL V and VII trials (8–8.2%), which makes it more challenging to achieve glycemic targets. Similarly, it is essential to consider the average daily dose of IDegLira at the end of this study, which was 21.3 U. The median dose of Ideglira at treatment initiation was 16 U and at week 26 the average dose was 21 U; this may suggest that patients titrated their medication only twice on average—i.e. they did not have an optimal up-titration of IdegLira to ensure significant effectiveness. Some patients used up to 90 U/day of basal insulin before IdegLira initiation (Table 4). These patients started with a median dose of 16 U, which may explain why close to 20% of patients had higher Hba1c at follow-up. This situation is of the most significant interest because there are challenges to insulin titration in a real-life scenario due to the patient's level of education, barriers to access to follow-up and specialist consultation and fear of hypoglycemia.

This study provides important insights into the clinical outcomes of initiating IDegLira in a real-world setting in Colombia. By including patients from ten different centers in Colombia and establishing broad inclusion and exclusion criteria, the results are more generalizable to a vast population of people with T2DM compared to RCTs [24]. Also, SPIRIT improves our understanding of clinical outcomes from the use of one of the most highly used therapies for the treatment of T2DM in Colombia, which is also reimbursed by National Health Care System in patients previously treated with insulin. For this reason, RWE studies have the highest external validity when compared to other study designs since this study model has the lowest risk of selection bias by representing the clinical and demographic characteristics of most patients, which is very important in clinical studies for T2DM.

Evaluation of the effect of a therapy as IDegLira is important because this therapy is an alternative to avoid complex insulin regimens, and even when guidelines recommend the early use of GLP-1RA, access to treatments with GLP-1RA is difficult in some scenarios. As such, IDegLira may be an option that provides some of the benefits of a GLP-1RA to patients with T2DM. There is accumulating evidence on this formulation that implies it is still a valuable tool for treatment of T2D, especially in older patients, as included in SPIRIT study. In addition, SPIRIT results may be of value in the context of the situation in Colombia in terms of access to antidiabetic medications and costs.

There are several limitations to this study, including those typical for observational studies, such as, for example, it is a single-arm study with no comparator arm, missing data in medical records may impact results, recording bias from the patients related to specific outcomes such as hypoglycemia and the variability in the selection and extraction of data. In addition, one of the main weaknesses of RWE studies is that they do not have strict exposure control

(IDegLira and basal insulin, in this case), so they will always have some level of risk of information bias. However, in the case of the present study, considering that the average duration of the disease was > 10 years, we can assume that this risk is much lower. We base this assumption on the premise that when patients have had T2DM for a long time, they are more accurate in measuring the medication prescribed by their treating physician.

CONCLUSION

Initiating IDegLira in patients with T2DM previously treated with basal insulin (±OAD) was associated with improved glycemic control, reduced body weight and reduced risk of hypoglycemia, which generates greater robustness to clinical outcomes and more confidence for clinical and administrative decision-makers. These results support previously published data showing that IDegLira data are generalizable to a broad population of patients with T2DM in routine clinical practice in Colombia.

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Author Contributions. Maria Alejandra Alzate and Preethy Prasad are responsible for the concept and design of the study. Alex Ramirez-Rincon, Diana Henao-Carrillo, Miguel Omeara, Julio Oliveros and Jose Assaf participated in data collection, data analysis, reviewing and editing the manuscript. Maria Alejandra Alzate and Jaime Ordoñez contributed to data analysis and writing the manuscript. All authors approved the final draft of the manuscript.

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Data Availability. The datasets generated or analyzed for the current study are available from the sponsor institution upon reasonable request.

Declarations

Conflict of Interest. María Alejandra Alzate and Preethy Prasad are employees of Novo Nordisk. Alex Ramírez-Rincón, Diana Henao-Carrillo, Miguel Omeara, Julio Oliveros, José Assaf and Jaime E. Ordóñez have no conflicts of interest to declare.

Ethical Approval. The ethical considerations for this protocol are based on the Declaration of Helsinki and the Ethical Guidelines for Health-Related Research with Human Beings prepared by the Council for International Organizations of Medical Sciences (CIOMS) in collaboration with the World Health Organization (WHO). The protocol was approved by the ethics committees or Institution Review Boards (IRBs) of all participating institutions, and by The National Institute of Drug and Food Surveillance (INVIMA) under number NN9068-4884. This study complies with the Colombian Ministry of Health's Resolution 8430 and was

considered to be a no risk study that did not require consent from participants. No consent from participants to publish was required because no identifiable information is presented in the results. The Board approved the clinical trial research protocol on Ethics Research of ten Health Insurers Companies, Hospitals, or Healthcare Centers of Colombia: Institute of Cardiology La Cardio, FRC Ambulatory Unit, Bluecare Research Center, University Hospital San Ignacio, IPS Cabeceras, Funcentra, Integral Diabetes Clinic, EPS Salud Total, Center for Diabetes and Metabolism CEDYM, and Sura diagnostic aids. Details of each center's contribution and IRB approval are provided in the Electronic Supplementary Material.

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