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IDegLira for the real-world treatment of type 2 diabetes in Italy. Final results from the REX observational study

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Abstract

Aim: The study was designed to generate real-world evidence on IDegLira in the Italian clinical practice in two groups of patients with type 2 diabetes (T2D), switching to IDegLira either from a basal only (basal group) or basal-bolus insulin regimen (BB group).

Materials and Methods: This was a non-interventional, multicentre, single-cohort, prospective study assessing the long-term glycaemic control in patients with T2D, who switched to IDegLira from a basal insulin ± glucose-lowering medication regimen with or without a bolus insulin component for approximately 18 months, conducted in 28 Italian diabetes centres. The primary endpoint was the change in glycated haemoglobin (HbA1c) levels from baseline to 6 months after IDegLira initiation.

Results: The study included 358 patients with a mean age 67.2 years and diabetes duration of 15.7 years. HbA1c significantly decreased from IDegLira start to all study time points in the overall population (basal group −1.19%; BB group −0.60% at the end of observation). Patients achieving HbA1c <7% levels increased from 12.9% (n = 43) to 40.3% (n = 110) at 18 months. Fasting blood glucose and body weight also significantly decreased in both groups, although more in the BB group. Overall, 14.3% of completed patients had an intensification of treatment (mainly in the basal group) and 48.6% had a simplification of treatment (mainly in the BB group).

Conclusions: Switching to IDegLira in a real-world clinical setting is a valid therapeutic option for patients with T2D with inadequate glycaemic control on basal or BB insulin regimen and/or need to simplify their insulin therapy, with specific reasons and therapeutic goals according to different T2D management trajectories.

KEYWORDS
glycaemic control, basal insulin, real-world evidence, type 2 diabetes

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1 | INTRODUCTION

In type 2 diabetes (T2D), insulin may be the initial treatment in patients with severe hyperglycaemia or may need to be introduced in those whose disease is not adequately controlled by non-insulin glucose-lowering medications (GLMs).[1] However, given the progressiveness of T2D, basal insulin-based regimens may require overtime intensification either by increasing the dose or adding bolus insulin injections, which carries a high risk of hypoglycaemic episodes and weight gain and the burden of a complex regimen.

Glucagon-like peptide-1 receptor agonists (GLP-1RA) have been shown in several randomized controlled trials to be effective in achieving glycaemic control with a low hypoglycaemia risk and promoting weight loss.[2] The combination of long-acting basal insulin and GLP-1RA, which have complementary actions, was shown to be as effective as basal-bolus (BB) insulin in achieving glycaemic control but with a lower risk of hypoglycaemia and weight gain, while also allowing for a lower insulin dose.[3] This combination is recommended by the American Diabetes Association and the European Association for the Study of Diabetes as a valid therapeutic alternative.[4]

IDegLira is the combination of a second-generation long-acting insulin analogue (Degludec) with a GLP-1RA (Liraglutide), whose objective is to enhance the effectiveness of insulin by adding the benefits of GLP-1RA with a decrease in glycated haemoglobin (HbA1c) and weight.[5,6] The safety and efficacy of this drug in patients with T2D were extensively evaluated in the DUAL trial programme.[7–12] IDegLira showed greater HbA1c reduction versus placebo,[8] GLP-1RAs and basal insulins alone,[6,7,10] and non-inferiority versus BB treatment,[11] suggesting that it is a more effective option than basal insulin alone in targeting the multiple aspects of glycaemic control in T2D.[13]

Data from several real-world studies support the results obtained in the IDegLira DUAL programme, highlighting the generalizability of the clinical trial results to routine practice and providing important, country-specific clinical evidence.[14–22] The European multicentre real-world retrospective study EXTRA showed significant reductions in HbA1c and body weight after ≥6 months of treatment with IDegLira in patients coming from a multiple daily-dose insulin injection regimen.[23]

The scientific community and regulatory agencies are interestingly appreciating the potential of real-world studies as a source to support decision-making on the benefits and risks associated with clinical interventions.[24] Most real-world studies on IDegLira were small, short, and/or based on retrospective chart review/data collection, which often make data quality and completeness an issue. Therefore, to complement or challenge trial findings, more high-quality real-world data are needed, such as those that can be gathered from prospective studies.

The REX (Real-world Evidence Xultophy®) study is an Italian multicentre prospective real-world study aimed at investigating long-term glycaemic control, alongside other relevant clinical parameters and prescription patterns, in adult patients with T2D previously treated either with basal insulin ± GLMs (basal group) or with basal insulin ± GLMs plus bolus insulin (BB group), who switched to IDegLira; objectives, methods and baseline patient characteristics have been previously reported.[25] This paper presents the final results of the REX study.

2 | MATERIALS AND METHODS

The study protocol and the statistical methods have been described previously.[25]

2.1 | Study design and population

This was a non-interventional, prospective study investigating long-term glycaemic control in a single cohort of patients with T2D initiating IDegLira in a real-world setting in 28 centres across Italy. The study consisted of both primary data collection (during an 18-month prospective observation period after the enrolment visit) and secondary use of pre-existing data (during the retrospective observation period), from IDegLira initiation to the enrolment visit. The results of the retrospective part have been published before, along with the study protocol.[25] Patients were eligible if they had started IDegLira according to label indications before the enrolment visit, regardless of the physician's willingness to enrol the patient and the patient's decision to participate in the study. Other main eligibility criteria were age ≥18 years, T2D diagnosed ≥12 months before enrolment, treatment either with basal insulin ± other GLMs or with BB ± other GLMs, and one documented HbA1c measurement <3 months before IDegLira initiation. Patients on the BB regimen were eligible provided that the bolus insulin was stopped before IDegLira was started, in compliance with the IDegLira label. According to the interim report,[25] it was expected that the proportion of patients on basal-only insulin versus those on BB insulin was about 3:1. This proportion was not predetermined by the protocol but reflected the use of IDegLira under routine care at the time the study was conducted. Although we are presenting outcome data separately for these two groups, the study did not aim to compare them.

The main exclusion criteria were type 1 diabetes, maturity-onset diabetes of the young, latent autoimmune diabetes in adults, gestational diabetes, or any hyperglycaemic state other than T2D. All patients were prospectively followed up for 18 months, even if they stopped taking IDegLira; data were collected during routine clinical visits without additional diagnostic or monitoring procedures.

All participating patients provided their written informed consent before data collection. The study was approved by the ethics committees of all participating institutions before the start of data collection and conducted in accordance with the Helsinki Declaration.

2.2 | Study objectives

The primary objective was to investigate the change in glycaemic levels after the initiation of IDeglira. Secondary objectives were to describe the rationale provided by the physician for initiating IDegLira;

to evaluate changes in other clinical parameters of glycaemic control and in treatment patterns associated with long-term IDegLira treatment; and to describe the outcomes of interest in the basal and BB groups. Exploratory objectives were to describe changes in other metabolic parameters and in the number and type of concomitant T2D medications after IDegLira initiation.

2.3 | Evaluation measures

The primary endpoint of the study was the change in HbA1c value from baseline to 6 months after IDegLira treatment initiation. Secondary endpoints to be evaluated were the change in HbA1c value at 12 and 18 months, percentage of patients with HbA1c <7%, change in IDegLira daily dose, number and severity of self-reported hypoglycaemic episodes during observation, and percentage of patients with treatment intensification or simplification at the end of observation. Other evaluations were the reasons for switching to IDegLira and the changes over time in fasting blood glucose (FBG), body weight, and the number and type of concomitant diabetes medications. All measures were evaluated in the overall study population and separately in the basal and BB groups. The real-world safety and tolerability of IDegLira during observation were also described.

2.4 | Statistical analysis

2.4.1 | Sample size

The sample size was defined according to the primary endpoint. Further information can be found in the Supplementary Appendix.

2.4.2 | Data analysis

For the primary endpoint and for some secondary and explorative endpoints, a mixed model for repeated measurements (MMRM) was performed. Both crude and adjusted estimates of the change in the analysed variables are presented. The effect evaluated by statistical analysis was the change from baseline to selected time points: 6, 12 and 18 months after treatment initiation. For all binary outcomes, mixed effects logistic regression was used. In addition, sensitivity analyses were performed to assess the robustness of primary and some secondary HbA1c analyses, involving patients 'on treatment' with IDegLira at the time points of interest after treatment initiation. Further details can be found in the Supplementary Appendix.

Statistical analyses were performed using SAS Enterprise Guide v. 7.12 and SAS 9.4 (SAS Institute). Study conduct, data monitoring, electronic Case Report Form (eCRF) set-up, and statistical analyses were performed by Medineos SURL, a company subject to the direction and coordination of IQVIA Ltd., on behalf of Novo Nordisk.

3 | RESULTS

3.1 | Patients' demographic and baseline clinical characteristics

In total, 358 patients were enrolled in the study from November 2020 to June 2021. Twenty patients were excluded for ineligibility based on unmet inclusion criteria, leaving 338 patients (94.4%) eligible. At the end, there were 334 patients with at least one post-baseline HbA1c measurement evaluable for the primary analysis (93.3%; full analysis set), 328 of which (98.2%; full analysis set on treatment) were included in the on-treatment sensitivity analysis. Nineteen patients (5.7%) withdrew from the study: 11 were lost to follow-up, five were deceased, one withdrew consent and two had no valid visits before the end of the study. Overall, 315 patients (94.3%) completed the expected 18-month prospective observation period (±3 months of tolerance), with variability in available data at different analysis time points. The mean duration of the observation from the start of IDegLira treatment was 19.6 months (SD 2.0).

At the time of IDegLira initiation, 77.2% (n = 258) of patients were in the basal group and 22.8% (n = 76) in the BB group. Demographics and main baseline clinical characteristics in the overall population and by patient groups are reported in Table 1. Patients in the BB group had a longer duration of diabetes, a slightly higher HbA1c, more diabetes complications and concomitant conditions.

3.2 | Previous diabetes medications

The median (interquartile range) time from the first insulin-including regimen to the start of IDegLira was 31.8 (10.7-70.9) months. The mean (SD) prescribed insulin daily dose before IDegLira initiation was 17.6 (8.7) units in the overall population, 16.9 (8.0) units in the basal group, and 43.7 (23.6) total units in the BB group, 20.2 (10.2) units of basal and 23.4 (16.4) units of bolus insulin; 93.4% of patients in the BB group were reported to use the traditional multiple dose daily regimen. All medications included in the last diabetes regimen before IDegLira initiation are summarized by patient groups in Table 1.

3.3 | Treatment with IDegLira

The reason most frequently reported by physicians for initiating IDegLira was the inadequate glycaemic control achieved with the previous antidiabetic treatment in the basal group (in 220 patients, 85.3%) and the intent to simplify the antidiabetic regimen in the BB group (52 patients, 68.4%). The main reasons for initiating IDegLira, divided by patient groups, are reported in Figure 1.

IDegLira was started at a mean (SD) of 18.6 (6.3) dose steps and reached a mean maximum during the observation of 24.5 (9.7) dose steps. The mean estimated increase in IDegLira over the observation period was 4.7 dose steps at 6 months, 6.2 dose steps at 12 months, and 6.9 dose steps at 18 months (MMRM crude analysis, n = 268

TABLE 1 Patients' demographics and baseline characteristics in the overall population of evaluable patients and by patient groups.

	Overall population (N = 334)	Basal group (N = 258)	BB group (N = 76)
Gender, n (%)			
Male	195 (58.4)	158 (61.2)	37 (48.7)
Female	139 (41.6)	100 (38.8)	39 (51.3)
Age at the start of IDegLira, years; mean (SD)	67.2 (10.2)	67.0 (10.1)	67.8 (10.5)
BMI, kg/m^2; mean (SD)	30.3 (5.4)	30.1 (5.3)	30.9 (5.9)
Normal weight (18.5-25.0), n (%)	39 (14.1)	30 (14.5)	9 (13.0)
Overweight (25.9-30.0), n (%)	106 (38.4)	85 (41.1)	21 (30.4)
Obese (≥30.0)	131 (47.5)	92 (44.4)	39 (56.5)
Missing	58	51	7
Blood pressure, mmHg; median (IQR)			
Systolic	140 (130-150)	139 (130-150)	140 (130-148)
Diastolic	80 (77-85)	80 (76-85)	80 (80-81)
Missing, n	108	84	24
Diabetes characteristics			
Age at diagnosis, years; mean (SD)	51.4 (11.2)	51.6 (11.0)	50.4 (11.9)
Duration from first diagnosis, years; mean (SD)	15.7 (9.6)	15.2 (9.6)	17.2 (9.8)
HbA1c, %, mean (SD)	8.5 (1.5)	8.6 (1.4)	8.2 (1.7)
FBG, mmol/L, mean (SD)	9.2 (3.2)	9.1 (3.3)	9.4 (3.2)
Major diabetic complications at the start of IDegLira, n (%)			
None	164 (49.1)	134 (51.9)	30 (39.5)
Diabetic macroangiopathy	88 (26.3)	62 (24.0)	26 (34.2)
Diabetic nephropathy	68 (20.4)	46 (17.8)	22 (28.9)
Diabetic retinopathy	58 (17.4)	42 (16.3)	16 (21.1)
Diabetic neuropathy	37 (11.1)	20 (7.8)	17 (22.4)
Number of T2D major complications at the start of IDegLira, n (%)			
1	111 (33.2)	88 (34.1)	23 (30.3)
2	40 (12.0)	26 (10.1)	14 (18.4)
3	16 (4.8)	10 (3.9)	6 (7.9)
4	3 (0.9)	0	3 (3.9)
With clinical conditions in the medical history, n (%)	284 (85.0)	214 (82.9)	70 (92.1)
Concomitant conditions (specification), n (%)			
Hypertension	211 (74.3)	160 (74.8)	51 (72.9)
Dyslipidaemia	173 (60.9)	129 (60.3)	44 (62.9)
Peripheral vascular disease	33 (11.6)	27 (12.6)	6 (8.6)
Symptomatic coronary heart disease	19 (6.7)	14 (6.5)	5 (7.1)
Symptomatic heart failure	8 (2.8)	5 (2.3)	3 (4.3)
Stroke	4 (1.4)	3 (1.4)	1 (1.4)
Other	81 (24.5)	52 (24.3)	29 (41.4)
Medications included in the last diabetes regimen before IDegLira initiation			
Insulin, n (%)			
Basal			
Glargine U100	161 (48.2)	125 (48.4)	36 (47.4)
Glargine U300	99 (29.6)	78 (30.2)	21 (27.6)
Degludec	56 (16.8)	41 (15.9)	15 (19.7)
Detemir	10 (3.0)	9 (3.5)	1 (1.3)
IGlarLixi	5 (1.5)	5 (1.9)	
Insulin NPH	2 (0.6)		2 (2.6)

(Continues)

TABLE 1 (Continued)

	Overall population (N = 334)	Basal group (N = 258)	BB group (N = 76)
Bolus			
Lispro	34 (10.2)		34 (44.7)
Aspart	33 (9.9)		33 (43.4)
Glulisine	7 (2.1)		7 (9.2)
Glulisine + lispro	1 (0.3)		1 (1.3)
GLMs, n (%)			
With GLM treatment	294 (88.0)	252 (97.7)	42 (55.3)
Metformin	236 (70.7)	201 (77.9)	35 (46.1)
Secretagogues	68 (20.4)	67 (26.0)	1 (1.3)
DPP-4 inhibitors	50 (15.0)	48 (18.6)	2 (2.6)
SGLT2 inhibitors	41 (12.3)	37 (14.3)	4 (5.3)
GLP-1 analogues	17 (5.1)	17 (6.6)	
Metformin + DPP-4 inhibitors	14 (4.2)	13 (5.0)	1 (1.3)
Glitazones	12 (3.6)	10 (3.9)	2 (2.6)
Metformin + SGLT2 inhibitors	6 (1.8)	6 (2.3)	
Metformin + secretagogues	4 (1.2)	4 (1.6)	
Alpha-glucosidase inhibitors	3 (0.9)	2 (0.8)	1 (1.3)
Metformin + glitazones	2 (0.6)	2 (0.8)	
Secretagogues + glitazones	3 (0.9)	2 (0.8)	1 (1.3)
DPP-4 inhibitors + SGLT2 inhibitors	1 (0.3)		1 (1.3)
Specific combinations of basal insulin and GLMs, n (%)			
Basal insulin only	6 (1.8)	6 (2.3)	
Basal insulin + 1 GLM	121 (36.2)	121 (46.9)	
Basal insulin + 2 GLMs	108 (32.3)	108 (41.9)	
Basal insulin + 3 GLMs	20 (6.0)	20 (7.8)	
Basal insulin + 4 GLMs	3 (0.9)	3 (1.2)	

Abbreviations: basal group, basal insulin ± GLMs; BB group, basal insulin + bolus insulin ± GLMs; BMI, body mass index; DPP4, dipeptidyl peptidase 4; FBG, fasting blood glucose; GLM, non-insulin glucose-lowering medication; GLP-1, glucagon-like peptide-1; HbA1c, glycated haemoglobin; IQR, interquartile range; NPH, neutral protamine Hagedorn; SGLT2, sodium-glucose cotransporter 2; SD, standard deviation; T2D, type 2 diabetes; U, units/ml.

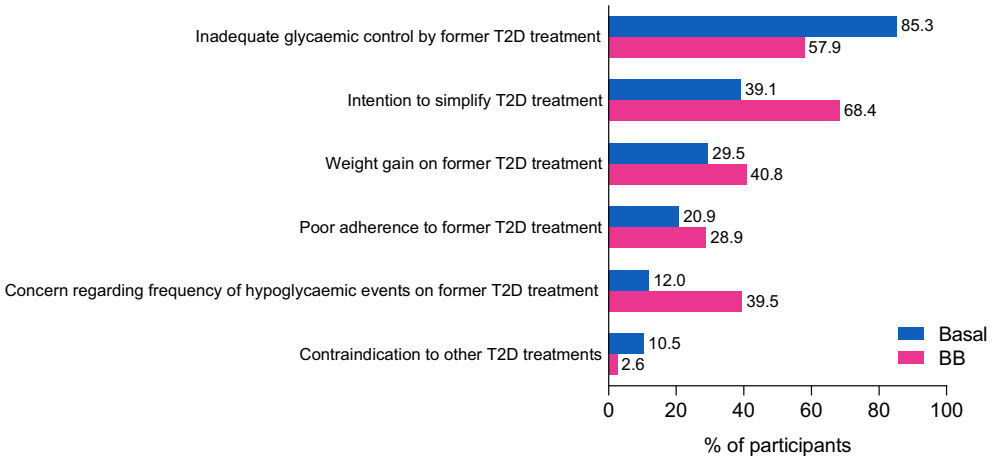

FIGURE 1 Main physician-reported reasons to start the treatment with IDegLira by patient groups. Basal group, basal insulin ± GLMs; BB group, basal insulin + bolus insulin ± GLMs; GLM, non-insulin glucose-lowering medication; T2D, type 2 diabetes.

analysed subjects with 611 observations used). The change from baseline to all time points was statistically significant ($p < .0001$). The mean estimated change in IDegLira dose over time in the overall population and by patient groups is shown in Figure 2A.

The percentage of evaluable patients still on treatment with IDegLira at 18 months of observation was 86.0%. At the end of the observation, we calculated the proportions of patients who experienced 'treatment simplification' (defined as a decrease in total insulin

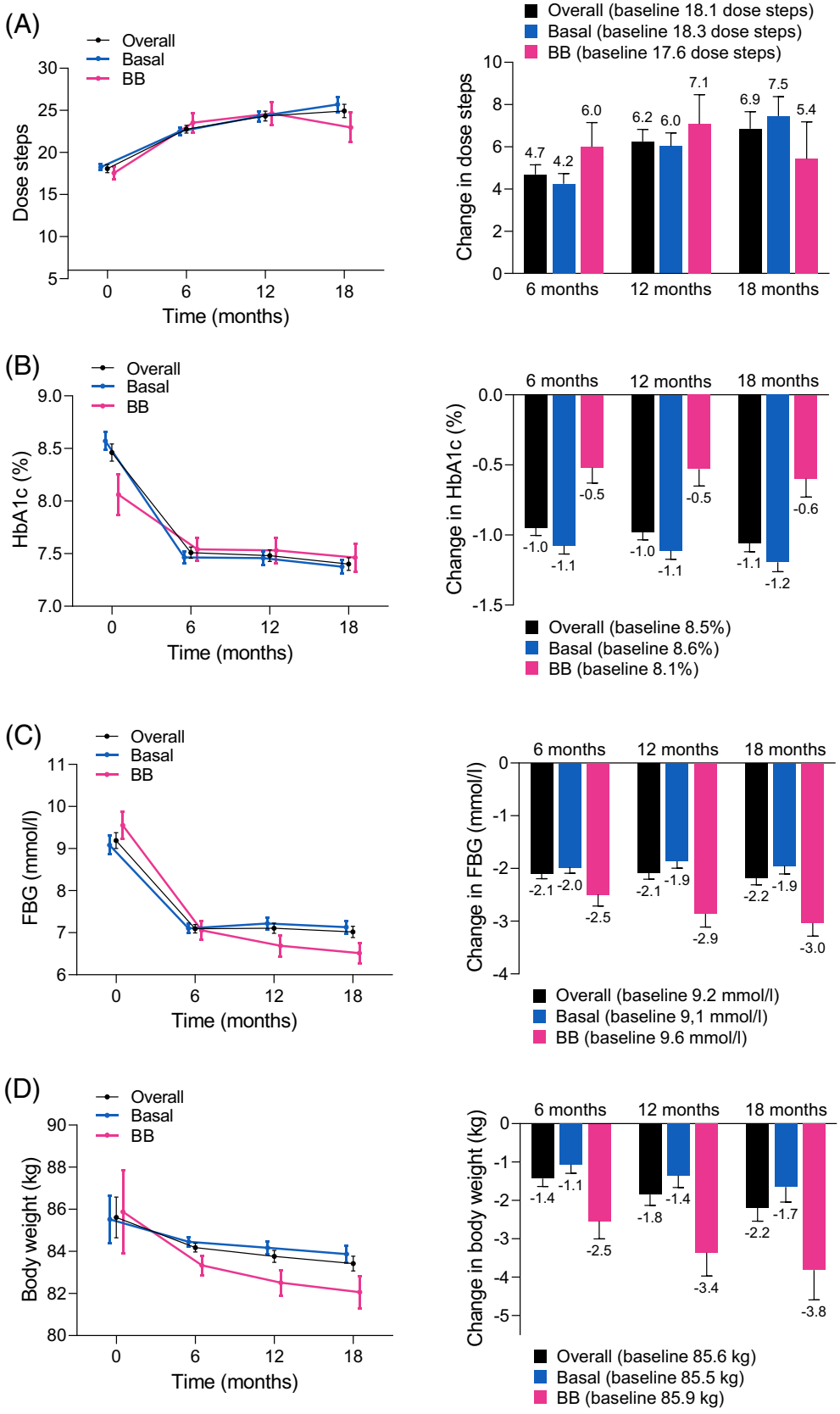

FIGURE 2 Mean estimated change in clinical parameters of interest over time in the overall population of evaluable patients and by patient groups: (A) IDegLira dose; (B) HbA1c levels; (C) FBG levels; (D) body weight. Basal group, basal insulin ± GLMs; BB group, basal insulin + bolus insulin ± GLMs; FBG, fasting blood glucose; GLM, non-insulin glucose-lowering medication; HbA1c, glycated haemoglobin. Error bars refer to the standard error.

dose, including IDegLira if ongoing, or in the number of concomitant GLMs compared with baseline), or 'treatment intensification' (defined as an increase in the number of concomitant GLMs compared with baseline, or the addition of prandial insulin). Overall, 14.3% of patients who completed the study period had an intensification of treatment, and 48.6% (n/N = 153/315) of completed patients had treatment

TABLE 2 Patients with HbA1c <7% during the observation period in the overall population of evaluable patients and by patient groups.

	Overall population (N = 334)	Basal group (N = 258)	BB group (N = 76)
At baseline[a]	43 (12.9)	24 (9.3)	19 (25.0)
At 6 months	76 (35.2)	62 (37.6)	14 (27.5)
At 12 months	55 (27.0)	41 (25.8)	14 (31.1)
At 18 months	110 (40.3)	92 (43.0)	18 (30.5)
At any time during the observation period	171 (51.2)	134 (51.9)	37 (48.7)

Note: Data are presented as n (%).
Abbreviations: basal group, basal insulin ± GLMs; BB group, basal insulin + bolus insulin ± GLMs; GLM, non-insulin glucose-lowering medication.
[a]At the time of IDegLira treatment initiation.

simplification, compared with 73.9% (n/N = 51/69) in the BB group (Supplementary Appendix, Table S1). In the basal group, 79.4% (n/N = 81/102) of patients with treatment simplification at the end of observation had decreased the number of concomitant GLMs from baseline (Supplementary Appendix, Table S2). In the BB group, at the end of observation, 90.1% (n/N = 69/76) of patients were still free of boluses. Evaluable patients persisting with once-daily IDegLira at 18 months were 84.1%.

3.4 | Glycated haemoglobin levels

The mean HbA1c level in the overall study population was 8.46% at baseline and significantly decreased by 0.95% after 6 months ($p < .0001$). After 12 months, it had decreased by 0.98% and at 18 months by 1.06% (MMRM crude analysis, n = 334 analysed subjects with 1165 observations used; $p < .0001$ for all time points vs. baseline). The on-treatment sensitivity analysis confirmed the estimated mean changes in HbA1c level: −0.97% (0.05) after 6 months, −1.00% (0.06) after 12 months, and 1.08% (0.06) after 18 months. Figure 2B shows the mean estimated change in HbA1c over time in the two groups. HbA1c levels decreased from baseline to all time points in both groups, but the decrease was almost double in the basal group (−1.19% vs. −0.60% in the BB group at 18 months). At the start of IDegLira treatment, 43 patients overall (12.9%) had HbA1c <7%. During the observation period, the number of patients with HbA1c at target increased, with 51.2% (n = 171) of overall patients achieving at least one HbA1c measurement <7% and 40.3% (n = 110) of patients achieving HbA1c <7% at 18 months (Table 2), mostly without the occurrence of hypoglycaemic episodes (Supplementary Appendix, Tables S3 and S4).

3.5 | Other metabolic parameters

The mean (SD) FBG level at baseline in the overall population (N = 286) was 9.2 (3.2) mmol/L [165.6 (57.6) mg/dl]. The mean estimated decrease in FBG level from baseline was of 2.1 mmol/L (37.8 mg/dl) at 6 months and 12 months and of 2.2 mmol/L (39.6 mg/dl) at 18 months (MMRM crude analysis, n = 272 analysed subjects with 895 observations used; $p < .0001$ for all time points vs. baseline). The mean estimated change in FBG over time by patient groups is reported in Figure 2C. The mean estimated FBG levels significantly decreased from baseline to all time points in both groups, but more in the BB group. The mean estimated decrease in body weight from baseline was 1.4 kg at 6 months, 1.8 kg at 12 months, and 2.2 kg at 18 months in the overall population (MMRM crude analysis, n = 284 analysed subjects with 1025 observations used; $p < .0001$ for all time points vs. baseline); the detailed estimates in the two patient groups are reported in Figure 2D. The mean estimated decrease in body weight from baseline was highly significant at all study time points in both groups, but higher in the BB group.

3.6 | Safety

No self-reported severe hypoglycaemic episodes occurred during IDegLira treatment. Non-severe hypoglycaemic episodes were reported by 10% (n/N = 33/330) of patients with ≥1 assessment of hypoglycaemic episodes available during observation in the overall population, 8.6% (n/N = 22/255) in the basal group, and 14.7% (11/75) in the BB group. Overall, 34 patients (10.1%) reported 50 adverse events, which were serious in 18 patients, all judged to have no suspected relationship with IDegLira, whereas in three patients (0.9%), five adverse drug reactions (ADRs) judged to have a suspected relationship with IDegLira occurred (Table 3).

4 | DISCUSSION

This observational study describes the benefits of IDegLira in the management of T2D in terms of improvement in glycaemic control and therapeutic simplification. The REX study had a special focus on two different groups of patients: those who intensified their regimen with basal-only insulin and those who were stepping back from more complex BB regimens. The baseline clinical characteristics of the study population were previously discussed in the interim results paper.[25] As expected, patients in the BB group were in a more advanced and complicated disease stage compared with those in the basal only group and had an average lower mean HbA1c but were still far from

TABLE 3 Safety events occurred during the observation period among patients eligible for the REX study.

	Eligible patients (N = 338)
Patients with at least one AE, n (%)	34 (10.1)
Patients with at least one SAE, n (%)	18 (5.3)
Patients with at least one ADR to IDegLira	3 (0.9)
AEs with no suspected causal relationship with IDegLira	
Total number of AEs with no suspected causal relationship with IDegLira	45
Severity, n (%)	
Mild	28 (62.2)
Moderate	7 (15.6)
Severe	10 (22.2)
Seriousness, n (%)	
Yes	18 (40.0)
Action taken to IDegLira, n (%)	
Drug interrupted	4 (8.9)
Drug withdrawn	8 (17.8)
Dose reduced	2 (4.4)
Dose increased	2 (4.4)
Dose not changed	22 (48.9)
Not applicable	7 (15.6)
Unknown	1 (2.2)
Outcome, n (%)	
Recovered/resolved	29 (67.4)
Recovering/resolving	3 (7.0)
Not recovered/not resolved	6 (14.0)
Fatal	5 (11.6)
Unknown	2
ADRs to IDegLira	
Total number of ADRs to IDegLira	5
Type, n (%)	
Hypoglycaemia	2 (40.0)
Minor stroke (ischaemic stroke)	1 (20.0)
Nausea	1 (20.0)
Vomiting	1 (20.0)
Severity, n (%)	
Mild	1 (20.0)
Moderate	3 (60.0)
Severe	1 (20.0)
Seriousness, n (%)	
Yes	1 (20.0)
Action taken to IDegLira, n (%)	
Drug interrupted	4 (80.0)
Drug withdrawn	1 (20.0)
Outcome, n (%)	
Recovered/resolved	4 (80.0)
Recovered/resolved with sequelae	1 (20.0)

Abbreviations: ADR, adverse drug reaction; AE, adverse event; SAE, serious adverse event.

the target value of 7%. These data confirm that adequate glycaemic control is still not enough pursued under routine care, and treatment intensification tends to be implemented with delay.

The most important finding of the REX study was the significant improvement in glycaemic control following the switch to IDegLira observed at 6, 12 and 18 months of follow-up. After the start of IDegLira, HbA1c significantly decreased from baseline at all time points in the overall population, with the reductions being twice as large in the basal group compared with the BB group (−1.08% vs. −0.52% at 6 months; −1.11% vs. −0.53% at 12 months; −1.19% vs. −0.58% at 18 months). Overall, the percentage of patients achieving HbA1c <7% increased from 12.9% (N = 43) at baseline to 51.2% (N = 171) at any time during the observation period in the whole cohort. FBG and body weight also significantly decreased from baseline to all study time points in both groups, although more in the BB group. Overall, 14.3% needed an intensification of treatment during the course of IDegLira treatment, mainly in the basal group, and 48.6% had a simplification of treatment, mainly in the BB group.

As already highlighted in the interim results paper,[25] patients in the basal group switched to IDegLira mainly because they had not achieved satisfactory glycaemic control with the previous therapy. This is consistent with the fact that in these patients, the switch to IDegLira was associated with a reduction in HbA1c of 1.19% at the end of observation. However, it is noteworthy that even the patients in the BB group, who stopped boluses and were switched to IDegLira mainly to simplify the previous therapeutic regimen, had an average HbA1c level far from target, and they achieved a significant reduction in HbA1c during observation. Therefore, in the BB group, therapeutic simplification was accompanied by a significant decrease in HbA1c. In a study conducted among participants with T2D on basal plus prandial insulin, the addition of a once-weekly GLP-1RA was able to substitute fully for prandial insulin in 54% of people at 26 weeks.[26] In the BEYOND trial, switching to a fixed-ratio combination of basal insulin and GLP-1RA led to a similar degree of glucose control at 6 months as did the intensification of BB insulin, but with fewer insulin doses, fewer injections, and hypoglycaemia.[27] This should be considered a major achievement in the management of patients on complex insulin therapy, repositioning them in a more appropriate regimen according to the recommended international standards. The reduction in body weight is an incremental value of this approach. When intensifying a basal-only regimen, IDegLira can limit body weight increase or lead to modest weight loss. Most importantly, when switching from BB therapy, IDegLira resulted in a more meaningful weight loss of almost 4 kg. The proportion of patients on target (HbA1c <7%) at 18 months more than tripled in the overall population and more than quadrupled in the basal group, mostly without the occurrence of hypoglycaemic episodes. These favourable results obtained in the basal-only group were expected, as they confirm and reinforce published data showing that adding a free or fixed-dose of GLP-1RA to basal insulin achieves better glycaemic control with reductions in weight and hypoglycaemia rates.[28,29] The REX study shows that IDegLira also improves glycaemic control compared with previous BB therapy while simplifying the therapeutic regimen in 73.9% of patients, stopping insulin boluses and decreasing the total insulin daily dose. Although treatment

simplification was the most common reason for switching to IDegLira in the BB group, the switch also allowed treatment simplification in 41.5% of patients in the basal-only group, mainly through the reduction of non-insulin GLMs. The fact that treatment with IDegLira often enables treatment simplification can have economic implications. A cost-utility analysis carried out by the Italian National Health Service showed that IDegLira as an alternative to the BB scheme, even at the maximum dosage envisaged, not only does not imply an increase in costs for the health service, but may even lead to cost savings, considering the always favourable cost-effectiveness ratio generated by the benefits on quality of life. Moreover, IDegLira is also economically advantageous up to a dosage of 25 units compared with the BB combination.[30] Furthermore, IDegLira has recently emerged as a valid and simple alternative to a complex BB insulin regimen for patients with T2D and poorly controlled diabetes, as documented by very high HbA1c (9%-15%).[31]

The extent of HbA1c reductions in both groups of patients was consistent with that obtained in other Italian observational studies[21,22] and similar to that reported in the European retrospective study,[25] but also with the results of the randomized controlled trials of the DUAL programme.[7–12] In DUAL-V, patients on basal-only insulin randomized to IDegLira had a greater HbA1c reduction of 0.6% than those randomized to continuing and uptitrating basal insulin.[10] It was therefore expected that, in the subgroup of patients on basal-only insulin, the switch to IDegLira would induce a clinically meaningful improvement in glycaemic control. In the DUAL-VII trial, IDegLira treatment reduced HbA1c similar to BB insulin, accompanied by weight loss and less hypoglycaemia.[11] The routine care data captured by the REX study suggested that, among patients with T2D who are uncontrolled while on a BB insulin regimen, there is room for improving HbA1c and reducing body weight with less injection burden after switching to IDegLira. Previous observational studies and the BEYOND randomized trial have confirmed the feasibility of de-intensifying a BB insulin regimen, particularly in patients with a short duration of T2D and relatively low insulin doses.[27,32] However, the long-term persistence of such an effect should be carefully scrutinized. The 2-year results of the BEYOND trial found that 43% of patients initially switched from BB to a fixed-ration basal insulin/GLP-1RA combination were reallocated to a full BB insulin regimen because of a lack of efficacy (HbA1c >7%).[33] In the REX study, the majority of evaluable patients coming from a BB regimen (90.1%) remained on once-daily IDegLira at the last observation.

The duration of the REX study allowed us to show persistence on IDegLira after initiation of therapy in the overall study population (92.8% at 12 months and 86.0% at 18 months), which is considerably higher than that reported in the literature for GLP-1RA: a study conducted in Germany found a median persistence of 11 months during 2007-2020.[34] The fixed-ratio combination in IDegLira, improving convenience for the patient, is probably to drive good persistence in both those who intensified from basal-only therapy without increasing the number of injections and in those who stepped down from BB with a considerable reduction in the injection burden. The smooth titration of the GLP-1RA component of IDegLira is another rational explanation for good tolerability and persistence in treatment. Indeed, the safety results of the REX study are in line with the known safety and tolerability profile of IDegLira, characterized by a low rate of hypoglycaemia (which was non-severe) and no new safety signals.

The strengths of the REX study are the relatively long prospective follow-up and the possibility to assess two different groups of patients. When compared with a retrospective chart review, prospective studies are more expensive and time-consuming but allow for collecting more uniform data of higher quality and completeness. In addition, only in prospective studies can non-routine outcomes and measures be reliably recorded, such as the reasons for initiating a new treatment and the rates of hypoglycaemic episodes that do not generate claims. The 18-month duration of the REX study is considerably longer than that of most phase II-III clinical trials and previous retrospective or prospective observational studies with IDegLira or other diabetes medications, thereby providing data on persistence of treatment and duration of the therapeutic effects, particularly with regards to HbA1c and body weight reduction. Finally, although the REX study was not designed to compare the two groups of patients, the opportunity to enrol patients on either a basal-only or a BB regimen enabled the analysis of two very different clinical scenarios where IDegLira can be initiated, showing its benefits in routine care.

The major limitation of the REX study is the lack of a control group, implying that some of the improvements seen in glycaemic control may be driven by the so-called 'study effect', reflecting the benefits, often transient, that patients may experience when actively enrolled in a study of disease management. Although the analyses were limited to pre-post comparisons, the persistence of HbA1c reduction and weight loss up to 18 months is reassuring that these data reflect a real therapeutic effect. This is particularly true in the BB group, as it emerges that effective therapeutic simplification is feasible for a large proportion of these patients. Another limitation intrinsic to the real-world nature of the study is that IDegLira doses underwent a very modest uptitration, despite FBG not reaching the target in most patients. On one side, this reflects the well-known gap in basal insulin titration in clinical practice[33–36]; on the other side, better titration to target FBG could have achieved greater glycaemic improvements with IDegLira.

5 | CONCLUSIONS

The final findings of the REX study show that, in a real-world setting, the switch to IDegLira treatment is a valid therapeutic option for patients with T2D who have inadequate glycaemic control on basal-only or BB insulin and/or need to simplify their insulin therapy, with specific reasons and goals according to different T2D management trajectories.

AUTHOR CONTRIBUTIONS

All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take

responsibility for the integrity of the work as a whole, and have given their approval for this version to be published. GL and LS contributed to the conception and design of the study. In addition, LS contributed to the data analysis. GPF, RB, DP, ET, AS, OL and AC participated in the acquisition of data and interpretation of results. GPF, GL and LS wrote the manuscript draft; RB, DP, ET, AS, OL and AC revised it critically for important intellectual content. All authors read and approved the final manuscript.

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CONFLICT OF INTEREST STATEMENT

GPF has received honoraria, grants or lecture fees from Abbott, AstraZeneca, Boehringer, Lilly, MSD, Novartis, Novo Nordisk, Mundipharma, Sanofi, Servier and Takeda. RB has received honoraria or grants from Sanofi, Novo Nordisk, Eli Lilly, Abbott, Astrazeneca, Vertex and Guidotti. DP has received honoraria, grants or lecture fees from Abbott, Amgen, AstraZeneca, Boehringer, Lilly, Medtronic, MSD, Novo Nordisk, Mundipharma, Roche, Sanofi, Terumo and Theras. ET and AS have no conflicts of interest to declare. OL declares consulting fees from Astra-Zeneca, Boehringer Ingelheim; lecture fees from Astra-Zeneca, Eli-Lilly, MSD, Sigma-Tau, Sanofi-Aventis and Takeda; grant support from Astra-Zeneca. AC declares that in the past 5 years he has received speaker's fees from Abbot, Astra Zeneca, Boehringer Ingelheim, Eli Lilly, MSD, Menarini Diagnostici, Novo-Nordisk, Sanofi-Aventis, Sigma-Tau and Takeda; has participated in Advisory Board Meetings of AstraZeneca, Boehringer Ingelheim, Eli Lilly, Janssen Farmaceutici, MSD, Novo Nordisk and Sanofi-Aventis; has served as consultant for AstraZeneca and Novo Nordisk; and has received Research Grants from AstraZeneca, Eli Lilly and Novo Nordisk. GL is an employee of Novo Nordisk Italy (Medical Affairs Department). LS is an employee of Medineos Observational Research (an IQVIA company, Italy), hired by Novo Nordisk.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

The datasets generated during and/or analyzed during the current study are not publicly available due to local legal restriction and regulations but are available from the corresponding author on reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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