



# Comparative effectiveness and safety of glargine 300 U/mL versus degludec 100 U/mL in insulin-naïve patients with type 2 diabetes. A multicenter retrospective real-world study (RESTORE-2 NAIVE STUDY)

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## Abstract

**Aims** This study assessed comparative effectiveness of glargine 300 U/mL (Gla-300) versus degludec 100 U/mL (Deg-100) in insulin-naïve patients with T2D.

**Methods** This is a retrospective, multicenter, non-inferiority study based on electronic medical records. All patients initiating Gla-300 or Deg-100 were 1:1 propensity score-matched (PSM). Linear mixed models were used to assess the changes in continuous endpoints. Incidence rates (IR) of hypoglycemia were compared using Poisson's regression models.

**Results** Nineteen centers provided data on 357 patients in each PSM cohort. HbA1c after 6 months (primary endpoint) decreased by  $-1.70\%$  (95%CI  $-1.90$ ;  $-1.50$ ) in Gla-300 group and  $-1.69\%$  (95%CI  $-1.89$ ;  $-1.49$ ) in Deg-100 group, confirming non-inferiority of Gla-300 versus Deg-100. Fasting blood glucose (BG) decreased by  $\sim 60$  mg/dl in both groups; body weight remained unchanged. In both groups, the mean starting dose was 12U (0.15U/kg) and it was slightly titrated to 16U (0.20U/kg). IR (episodes per patient-months) of BG  $\leq 70$  mg/dl was 0.13 in Gla-300 group and 0.14 in Deg-100 group ( $p=0.87$ ). IR of BG  $< 54$  mg/dL was 0.02 in both groups ( $p=0.49$ ). No severe hypoglycemia occurred.

**Conclusion** Initiating Gla-300 or Deg-100 was associated with similar improvements in glycemic control, no weight gain and low hypoglycemia rates, without severe episodes during 6 months of treatment.

**Keywords** Type 2 diabetes · Basal insulin · Naïve · Glargine 300 · Degludec 100 · Effectiveness · Safety

## Abbreviations

ADA American diabetes association  
BMI Body mass index  
Deg-100 Degludec 100 U/ml  
EMR Electronic medical record

FB Fasting Blood Glucose  
Gla-300 Glargine 300 U/ml  
HbA1c Glycated hemoglobin  
IR Incidence rates  
PS Propensity score  
PSM Propensity score-matched  
RCT Randomized clinical trials  
2BI Second-generation basal insulin analogues  
SMBG Self-monitoring blood glucose tests  
T1D Type 1 diabetes  
T2D Type 2 diabetes  
US United States

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## Introduction

Improving glycemic control in type 2 diabetes (T2D) is a major goal of care, to reduce the incidence of micro- and macro-vascular complications [1, 2], but it is also a major challenge for patients, physicians and healthcare systems. In fact, inertia in intensifying diabetes therapy and especially in initiating basal insulin in patients with poor metabolic control is a well-recognized problem [3]. Many barriers exist and refer to clinicians, patients and settings; fear of hypoglycemia represents the main limitation to a prompt intensification [4, 5].

Second-generation basal insulin analogues (2BI) represent an opportunity to overcome these barriers. According to randomized controlled trials (RCTs), 2BI are non-inferior to first-generation basal insulins (1BI) with regard to the reduction of HbA<sub>1c</sub> but safer in terms of hypoglycemia and with lower variability [6].

Two 2BI are currently available: insulin glargine 300 units/mL (Gla-300), commercialized in Italy in 2017, and degludec 100 units/mL (Deg-100), available since 2014.

Both insulins display a more stable pharmacokinetic and pharmacodynamic profile and a longer duration of action compared to the first-generation basal insulin glargine 100 units/mL (Gla-100) [6–10].

In the phase-3 studies from the EDITION clinical registration program [11–14], Gla-300 proved to be non-inferior to Gla-100 in T1D and T2D patients as well as among insulin naïve patients or switchers. A significantly lower percentage of patients with T2D or T1D experienced confirmed and/or severe nocturnal hypoglycemic events while being on Gla-300 compared to Gla-100 [11–14].

The BEGIN clinical registration program [15–18] showed comparable glycemic control of Deg-100 vs. Gla-100 and a lower rate of overall hypoglycemia in T2D and nocturnal hypoglycemia in T1D.

The randomized, head-to-head, parallel group BRIGHT study [19] involving insulin-naïve patients with T2D demonstrated that Gla-300 and Deg-100 provided similar glycemic control improvements with relatively low hypoglycemia risk. Hypoglycemia rate was comparable with the two basal insulins during the full study period, but lower with Gla-300 during the dose titration period. The CONCLUDE trial, involving people with T2D switching from 1BIs to Gla-300 or the new 200 U/mL formulation of insulin degludec, documented a similar rate of overall symptomatic hypoglycemia during the 36-week maintenance period [20].

Real-world evidence (RWE) is needed to assess effectiveness and safety of 2BI when prescribed in different settings [21], as the three real-world studies currently available [22–24], all conducted in US settings, provided controversial results. Therefore, real-world data on 2BI in patients with

T2D are relatively scant, and most importantly, data from European countries are missing.

Given these premises, the RESTORE-2 study aimed at assessing the comparative effectiveness and safety of Gla-300 versus Deg-100 in a cohort of insulin-naïve patients with T2D followed under routine care in Italian diabetes outpatient clinics.

## Methods

### Study design and patients

The RESTORE-2 study was a retrospective, comparative, multicenter study. Inclusion criteria were: male or female gender, age  $\geq 18$  years, diagnosis of T2D (any disease duration), initiation of Gla-300 or Deg-100 from January 2017 to January 2020 and no previous treatment with basal insulin (naïve cohort) as recorded in the electronic medical records (EMRs). Exclusion criteria were: diagnosis of T1D, more than one type of basal insulin prescribed at index date or prescription of another basal insulin analogue in the six months after initiating insulin Gla-300 or Deg-100.

Anonymous patient data were derived from the same electronic chart system adopted at all participating centers (Smart Digital Clinic software—property of METEDA s.r.l.)

Centers recorded data on EMRs according to their clinical practice, taking into consideration that patients with T2D who need intensification are generally seen by the diabetologist on a 3–6 months basis. The date of the first prescription of the 2BI was considered as the index date (T<sub>0</sub>, baseline). All data relative to the period before and after the index date ( $\pm 6$  months) for each patient were extracted and analyzed. Data recorded in the 6 months previous T<sub>0</sub> were used to identify the baseline characteristics of patients, whereas data collected after 6 months (T<sub>6</sub>) represented the follow-up data. When more values of the same parameters were available during the before and after T<sub>0</sub> periods, those recorded in the nearest date to T<sub>0</sub> and T<sub>6</sub> were considered. Data relative to the efficacy endpoints were considered only if values were recorded at T<sub>0</sub> $\pm 30$  days and T<sub>6</sub> $\pm 30$  days. The following characteristics were considered to describe the baseline patient profile: age, gender, diabetes duration, HbA<sub>1c</sub>, fasting blood glucose (FBG), weight/body mass index (BMI), total, basal and short-acting insulin dose, number of insulin injections, glucose-lowering drugs other than insulin, blood pressure, lipid profile, diabetes complications (low glomerular filtration rate, albuminuria, cardiovascular complications—i.e., myocardial infarction, coronary revascularization, coronary artery bypass, stroke, lower limb complications, peripheral artery disease—by ICD-9 CM codes).

Efficacy endpoints were: changes at 6 months (T6) in HbA<sub>1c</sub>, insulin doses, FBG and body weight (continuous endpoints); and frequency and proportion of patients with HbA<sub>1c</sub> <7% and HbA<sub>1c</sub> <8% at T0 and T6 (categorical endpoints). Changes in HbA<sub>1c</sub> at 6 months from the Gla-300 or Deg-100 initiation represented the primary endpoint.

Safety endpoints were: episodes of hypoglycemia  $\leq 70$  mg/dl or <54 mg/dl from self-monitoring blood glucose tests (SMBG) downloaded in EMR (cutoffs recommended by ADA guidelines 2017) during 6 months, severe hypoglycemia (defined as “need of assistance by a third party” and reported in a dedicated module of the EMR) during 6 months.

In addition, the change in HbA<sub>1c</sub> at 12 months was evaluated as a post hoc analysis in the subgroup of patients with available data.

### Statistical analysis

Sample size estimation was based on the primary endpoint, represented by the change in HbA<sub>1c</sub> levels after 6 months from the initiation of Gla-300 or Deg-100. We calculated that 296 patients per group were needed in order to achieve 80% power to detect non-inferiority using a one-sided, two-sample t-test. The margin of non-inferiority was set at 0.3%, which is generally considered a clinically meaningful difference. The true difference between the means was assumed to be 0.0. The significance level (alpha) of the test was 0.025. The standard deviation of HbA<sub>1c</sub> was assumed to be 1.3 in both groups.

Baseline patient characteristics according to the initiation of Gla-300 or Deg-100 were compared using the unpaired t-test or the Mann–Whitney U-test in case of normal and skewed continuous variables, respectively, and the Chi-square test or the Fisher exact test for categorical variables, as appropriate.

To allow for an unbiased comparison between patients initiating Gla-300 vs. Deg-100, a propensity score (PS) matching algorithm on a one-to-one basis was applied. To compute PS, we performed a logistic regression model taking into consideration age, gender, diabetes duration, baseline HbA<sub>1c</sub>, FBG, BMI, basal insulin dose, glucose-lowering drugs other than insulin as covariates. Variables included in the logistic model were those showing a statistically significant between-group difference at baseline [25]. A five-to-one greedy matching algorithm was used to identify a unique matched control in the initial Deg-100 group for each Gla-300 patient according to the individual PS. Adequacy of balance for the covariates in the matched sample was assessed via standardized mean difference between the 2 groups, considering differences less than 10% (absolute value) as indicative of a good balance.

PS matching was performed separately in the efficacy population and in the safety population.

Changes in HbA<sub>1c</sub>, FBG, body weight and insulin dose were assessed using mixed models for repeated measurements. Results are expressed as estimated mean or estimated mean difference from T0 with their 95% confidence interval (95% CI). Paired and unpaired t-test derived from linear mixed models for repeated measurements were applied for within-group and between-group comparisons, respectively.

As secondary outcomes, the proportions of patients with HbA<sub>1c</sub> <7.0% and HbA<sub>1c</sub> <8.0% at T0 and T6 were evaluated. Both within-group (McNemar test for change vs. baseline) and between-group (Chi-square test) statistical comparisons were applied.

Incidence rates (IR) of hypoglycemic events were calculated and expressed as numbers of events per patient-month with their 95% CI. Incidence of hypoglycemic events was compared between groups using Poisson’s regression model with correction for overdispersion.

The main analysis was conducted on the intention-to-treat (ITT) population, including all patients meeting eligibility criteria. The post hoc population included the subgroup of PS matched patients with a HbA<sub>1c</sub> value available at baseline and after 12 months.

For the evaluation of severe hypoglycemia, the safety population was represented by the ITT post-PS matching population (data derived from EMRs). For the evaluation of glycemic values  $\leq 70$  mg/dl and <54 mg/dl, a subsample of the safety population (PS matched patients having at least 1 SMBG value available) was considered.

## Results

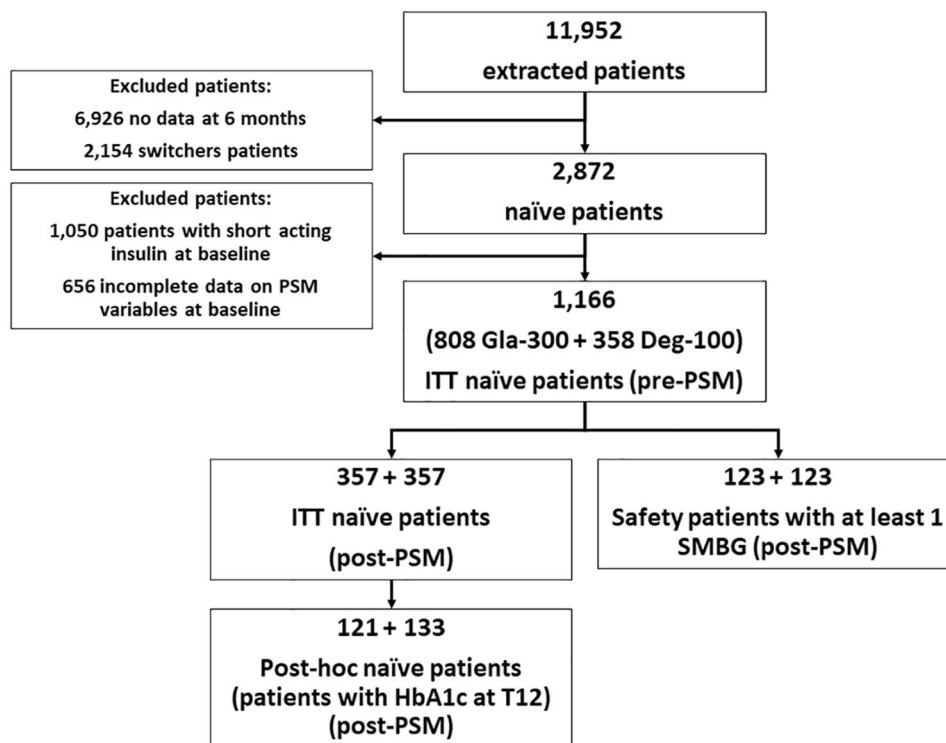
### Patient disposition and characteristics

Data were extracted from 19 centers (Fig. 1), yielding initial information from 1,166 patients (808 initiating Gla-300 and 358 initiating Deg-100), who were eligible insulin-naïve patients with first prescription of either 2BI as recorded in EMRs from January 2017 to January 2020. Centers with SMBG tests downloaded in the EMRs were 14 out of 19 (73.7%).

Before PS matching, age, gender, diabetes duration, FBG, HbA<sub>1c</sub> were balanced between groups. On the other side, patients initiating Gla-300 ( $N=808$ ) differed from those initiating Deg-100 ( $N=358$ ) in terms of use of secretagogues (42.6% vs. 50.0%;  $p=0.02$ ), glitazones (5.9% vs. 11.2%;  $p=0.002$ ) and SGLT2i (27.5% vs. 19.6%;  $p=0.004$ ) (Table 1). Differences of borderline statistical significance in BMI and use of GLP1-RA were also documented.

After PS matching, 357 subjects were included in each group (post-PSM ITT). The standardized differences of the

Fig. 1 Study flowchart



PSM = propensity score matching; SMBG = self-monitoring-blood-glucose

variables before and after the PS matching are shown in Appendix 1. All selected variables had an absolute standardized mean difference  $>10\%$  before matching and  $<10\%$  after matching. The complete baseline characteristics of the ITT matched population are reported in Table 2.

### Comparative effectiveness analysis

The mean follow-up time of patients was similar in the Gla-300 and Deg-100 groups ( $6.4 \pm 1.4$  vs.  $6.6 \pm 1.4$  months,  $p=0.17$ ), as was the mean number of visits per patient during 6 months ( $3.0 \pm 1.3$  vs.  $3.0 \pm 1.2$ ,  $p=0.79$ ).

Both groups had estimated mean levels of HbA<sub>1c</sub> at baseline of about 9.2%. For Gla-300 group, a statistically significant reduction in HbA<sub>1c</sub> levels from baseline to 6 months ( $-1.70\%$ , 95% CI  $-1.90$ ;  $-1.50$ ) was documented. Similarly, for Deg-100 group, a statistically significant reduction in HbA<sub>1c</sub> levels from baseline to 6 months ( $-1.69\%$ , 95% CI  $-1.89$ ;  $-1.49$ ) was documented. No between-group difference emerged in the change from baseline in HbA<sub>1c</sub> ( $-0.01\%$ , 95% CI  $-0.29$ ;  $0.27$ ;  $p=0.49$ ) (Table 2 and Fig. 2). The non-inferiority of Gla-300 vs. Deg-100 was confirmed (margin of non-inferiority of 0.30%; actual upper 95% CI at 6 months 0.27%).

In the Gla-300 group, the proportion of patients achieving HbA<sub>1c</sub> levels  $<7.0\%$  increased from 6.2% at T0 to 29.1% at T6 ( $p<0.0001$ ), whereas in Deg-100 group, it

increased from 4.8% at T0 to 32.9% at T6 ( $p<0.0001$ ), with no between-group difference ( $p=0.31$ ) (Appendix 2). In the Gla-300 group, the proportion of patients achieving HbA<sub>1c</sub> levels  $<8.0\%$  increased from 21.6% at T0 to 69.5% at T6 ( $p<0.0001$ ), whereas in Deg-100 group it increased from 24.9% at T0 to 71.9% at T6 ( $p<0.0001$ ), with no between-group difference ( $p=0.52$ ) (Appendix 2).

Results of longitudinal models relative to secondary continuous endpoints are shown in Table 2.

At baseline, mean levels of FBG were 212.6 mg/dl in Gla-300 group and 201.6 mg/dl in Deg-100 group. In both groups, statistically significant reductions from baseline to 6 months were shown:  $-63.23$  mg/dl in Gla-300 group and  $-61.14$  mg/dl in Deg-100 group, with no between-group differences ( $p=0.74$ ) (Table 2).

Not significant changes in body weight were documented in both groups after 6 months (Table 2).

Mean basal insulin dose was titrated during 6 months and statistically significant within-group increases were observed at T6 in both groups (Table 2). In the Gla-300 group, the estimated mean starting dose (T0) was 11.79 U and increased on average by  $+4.45$  U at T6; in Deg-100 group, the estimated mean starting dose (T0) was 12.45 U and increased by  $+3.54$  U at T6. In both groups, per-kg basal insulin dose significantly increased during the follow-up; at T6, the dose was of 0.20 U/kg in both groups.

**Table 1** Baseline patients' characteristics—pre- and post-PSM ITT population

Variable	Pre-PSM			Post-PSM		
	Gla-300	Deg-100	<i>p</i> -value	Gla-300	Deg-100	<i>p</i> -value
N. Group	808	358		357	357	
Age (years)	68.7±12.0	69.8±10.9	0.26	68.7±11.7	69.8±10.9	0.32
Males (%)	59.9	59.8	0.97	60.8	59.7	0.76
Diabetes duration (years)	13.8±11.4	13.5±7.4	0.42	13.6±10.6	13.5±7.4	0.32
Weight (kg)	80.8±17.9	82.2±17.9	0.21	82.5±18.3	82.1±17.9	0.85
BMI (Kg/m <sup>2</sup> )	29.3±5.8	29.9±5.6	0.07	29.9±6.1	29.9±5.6	0.75
HbA <sub>1c</sub> (%)	9.3±1.8	9.2±1.6	0.26	9.3±1.9	9.2±1.6	0.87
HbA <sub>1c</sub> (mmol/l)	78.6±20.5	76.8±17.8	0.34	77.7±21.0	76.9±17.8	0.99
Fasting blood glucose (mg/dl)	210.1±70.0	202.0±63.0	0.13	212.3±74.9	201.9±63.1	0.16
Systolic blood pressure (mmHg)	135.2±19.1	135.2±16.5	0.76	135.6±19.0	135.1±16.5	0.81
Diastolic blood pressure (mmHg)	78.5±10.3	78.9±9.9	0.83	78.4±9.2	78.9±9.9	0.94
Total cholesterol (mg/dl)	178.8±44.7	178.0±41.7	0.96	178.7±43.0	178.1±41.7	0.86
LDL-cholesterol (mg/dl)	95.6±35.5	96.1±35.3	0.79	95.5±36.9	96.2±35.4	0.74
HDL-cholesterol (mg/dl)	46.7±13.5	46.0±12.0	0.85	46.6±12.9	46.0±12.1	0.84
Triglycerides (mg/dl)	189.8±182.0	187.7±150.6	0.83	186.9±172.8	187.9±150.8	0.86
eGFR <60 ml/min*1.73m <sup>2</sup>	34.4	32.8	0.73	34.1	32.8	0.81
Microalbuminuria (%)	32.8	31.0	0.68	31.5	31.0	0.93
Diabetes complications (%)	7.2	6.4	0.64	6.4	6.4	1.00
<i>Glucose-lowering therapy</i>						
Daily basal insulin dose (U)	11.6±4.8	12.4±6.3	0.21	11.8±5.5	12.5±6.3	0.24
<i>No. of glucose-lowering drugs other than insulin</i>						
<2	18.9	19.0	0.98	20.2	19.0	0.71
≥2	81.1	81.0		79.8	81.0	
Metformin (%)	80.0	79.9	0.98	77.0	79.8	0.36
Secretagogues (%)	42.6	50.0	<b>0.02</b>	45.1	49.9	0.20
Glitazones (%)	5.9	11.2	<b>0.002</b>	9.0	10.9	0.38
Acarbose (%)	4.3	4.7	0.75	3.1	4.8	0.25
DPPIV inhibitors (%)	49.9	49.2	0.82	50.4	49.0	0.71
GLP1-RAs (%)	18.6	23.5	0.054	22.1	23.5	0.66
SGLT2 inhibitors (%)	27.5	19.6	<b>0.004</b>	18.8	19.6	0.78

Data are means and standard deviations or frequencies and proportions. Variables included in the PSM: BMI and use of GLP1-RAs, SGLT2 inhibitors, glitazones and secretagogues.

*p*-values derived from unpaired t-test or the Mann–Whitney U-test in case of continuous variables and the Chi-square test or Fisher exact test for categorical variables, as appropriate. Statistically significant *p*-values (*p*<0.05) are in bold.

No between-group differences were found in insulin dose changes over time.

At the post hoc analysis, in the subgroup of patients with a HbA<sub>1c</sub> value at 12 months (121 in Gla-300 group and 133 in Deg-100 group), a marked reduction in HbA<sub>1c</sub> mean levels was maintained in both groups; the reduction was −1.71% in Gla-300 versus −1.44% in Deg-100 group, although the between-group difference did not reach the statistical significance (*p*=0.052) (Appendix 5).

### Comparative safety analysis

The safety population (i.e., ITT patients with at least 1 SMBG downloaded in the EMRs) was PS matched for the following unbalanced variables at T0: diabetes duration, HbA<sub>1c</sub>, number of glucose-lowering drugs other than insulin (<2 or ≥2), use of metformin and secretagogues. Each PS matched group included 123 subjects (Appendix 3 and 4). No difference in the incidence of episodes of BG≤70 mg/dl or <54 mg/dl was present before insulin initiation in the two groups (Appendix 6).

**Table 2** Changes in estimated mean levels of continuous endpoints during the follow-up by treatment and within-group and between-group comparisons (T3 vs. T0 and T6 vs. T0) (post-PSM ITT population)

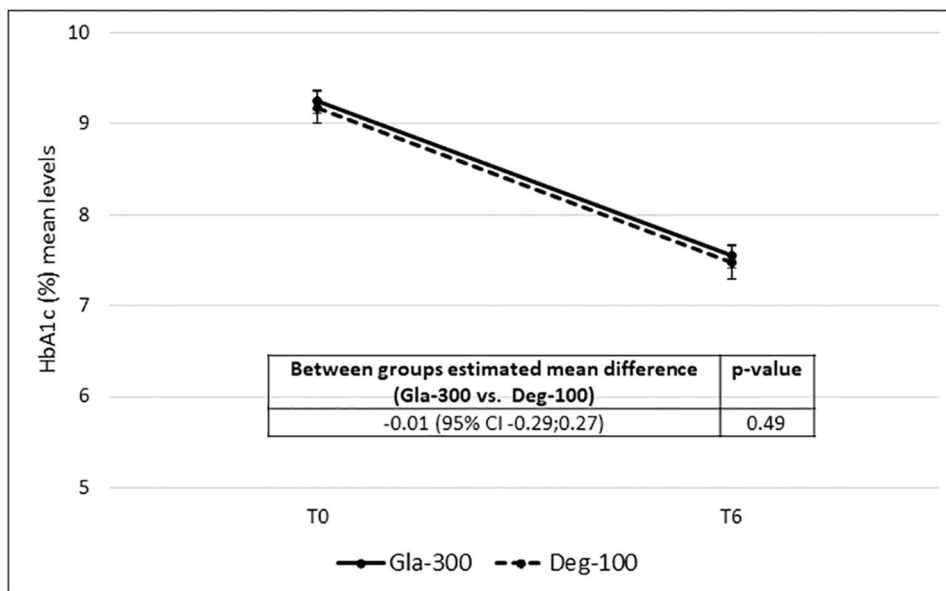
Change in	Visit	Gla-300			Deg-100			Gla-300 vs. Deg-100	
		Estimated mean and 95% CI	Estimated mean difference from T0 and 95% CI	Within-group p-value*	Estimated mean and 95% CI	Estimated mean difference from T0 and 95% CI	Within-group p-value*	Between-groups difference (estimated mean and 95% CI)	Between-group p-value**
HbA1c (%)	T0	9.25 (9.07;9.43)	–	–	9.18 (9.00;9.36)	–	–	–	–
	T6	7.55 (7.42;7.68)	–1.70 (–1.90;–1.50)	<b>&lt;0.0001</b>	7.48 (7.35;7.61)	–1.69 (–1.89;–1.49)	<b>&lt;0.0001</b>	–0.01 (–0.29;0.27)	0.49
FBG (mg/dl)	T0	212.60 (204.86;220.34)	–	–	201.61 (193.73;209.49)	–	–	–	–
	T6	149.36 (144.07;154.65)	–63.23 (–71.95;–54.51)	<b>&lt;0.0001</b>	140.47 (135.00;145.94)	–61.14 (–70.06;–52.22)	<b>&lt;0.0001</b>	–2.09 (–14.56;10.38)	0.74
Body weight (Kg)	T0	82.55 (80.68;84.42)	–	–	82.12 (80.25;83.99)	–	–	–	–
	T6	82.28 (80.44;84.12)	–0.26 (–0.72;0.20)	0.27	82.09 (80.25;83.93)	–0.03 (–0.49;0.43)	0.91	–0.23 (–0.88;0.42)	0.48
Daily basal insulin dose (U)	T0	11.79 (11.18;12.40)	–	–	12.45 (11.84;13.06)	–	–	–	–
	T6	16.25 (15.28;17.22)	4.45 (3.63;5.27)	<b>&lt;0.0001</b>	15.99 (15.03;16.95)	3.54 (2.73;4.35)	<b>&lt;0.0001</b>	0.92 (–0.23;2.07)	0.12
Daily basal insulin dose (U/Kg)	T0	0.15 (0.14;0.16)	–	–	0.16 (0.15;0.17)	–	–	–	–
	T6	0.20 (0.19;0.21)	0.05 (0.04;0.06)	<b>&lt;0.0001</b>	0.20 (0.19;0.21)	0.04 (0.03;0.05)	<b>&lt;0.0001</b>	0.01 (–0.01;0.03)	0.06

Statistically significant p-values (p<0.05) are in bold

\*Paired t-test derived from linear mixed models for repeated measurement

\*\*Unpaired t-test derived from linear mixed models for repeated measurements

**Fig. 2** Changes in HbA1c estimated mean levels during the follow-up by cohort (post-PSM ITT population)



PSM = propensity score matching; ITT = intention-to-treat

Overall, 18,353 SMBG tests were available in Gla-300 group, and 19,621 SMBG tests were available for Deg-100 group. The incidence of BG events  $\leq 70$  mg/dl and  $< 54$  mg/dl during 6-month follow-up was very low and similar in

Gla-300 group and in Deg-100 group. No between-group differences emerged (Table 3).

No severe hypoglycemic episodes (evaluated in the safety population) were reported on EMRs in both groups.



**Table 3** Incidence rate of hypoglycemic events (BG  $\leq$ 70 mg/dl and  $<$ 54 mg/dl) during the 6-month follow-up by treatment and between-group difference (Safety population subsample: post PSM ITT patients having at least 1 SMBG value available)

Outcome	Group	Subjects	N SMBG	Events	Person-months	IR (95%CI)	IRR (95%CI)	Between-group <i>p</i> -value
BG $\leq$ 70 mg/dl	Gla-300	123	18,353	81	615	0.13 (0.07;0.26)	0.92 (0.36;2.38)	0.87
BG $\leq$ 70 mg/dl	Deg-100	123	19,621	90	631.7	0.14 (0.07;0.27)		.
BG $<$ 54 mg/dl	Gla-300	123	18,353	15	615	0.02 (0.01;0.05)	1.54 (0.45;5.30)	0.49
BG $<$ 54 mg/dl	Deg-100	123	19,621	10	631.7	0.02 (0.01;0.04)		.

## Conclusions

In this real-world study, comparative effectiveness analyses showed that initiating Gla-300 or Deg-100 in uncontrolled insulin-naïve patients with T2D was followed by statistically significant and clinically relevant HbA<sub>1c</sub> reductions ( $-1.70\%$ ) after 6 months, without significant differences between groups. In addition, after 6 months, in both groups the proportion of patients with HbA<sub>1c</sub>  $<7.0\%$  increased from a small minority to almost one-third, while about 70% achieved levels  $<8\%$ . Given the very high HbA<sub>1c</sub> and FBG levels at initiation of 2BI, this result can be considered clinically meaningful.

In the subgroup of patients with HbA<sub>1c</sub> values available at 12 months, HbA<sub>1c</sub> reduction was sustained in the two groups and numerically greater with Gla-300.

After 6 months, FBG was reduced by about 60 mg/dl in both groups and only minor changes in body weight were recorded. Insulin dose up titration was modest ( $+4$  U/day) but statistically significant; during the first 6 months of treatment, 0.2 U/kg of basal insulin was used in both groups.

Concerning safety, we found a similar profile of the two 2BIs. Indeed, incidence of hypoglycemic episodes  $\leq$ 70 mg/dl and  $<$ 54 mg/dl during 6 months was very low and similar in the two groups, and no severe hypoglycemic episodes were recorded on EMRs.

This study adds important insights into the understanding of clinical profile of T2D patients initiating Gla-300 or Deg-100 in the real world. Before PSM, socio-demographic and clinical characteristics of patients initiating Gla-300 or Deg-100 were similar. Only small between-group differences emerged in the concomitant use of some classes of diabetes therapies (secretagogues, glitazones and SGLT2i); these differences are likely to reflect the evolving scenario of T2D pharmacotherapy when the two 2BI were made available in Italy.

Our results underline the effectiveness and safety of both 2BI. Furthermore, the very high baseline HbA<sub>1c</sub> ( $>9.0\%$ ) and FBG ( $>200$  mg/dl) levels at the time of insulin initiation highlight once more the well-known problem of clinical inertia [3], suggesting a late treatment intensification. After 6 months, despite relevant improvements, many patients

were still above the recommended HbA<sub>1c</sub> and FBG targets in both groups. Low doses of basal insulin were adopted at 6-month follow-up of this real-world context (0.2 U/Kg) as compared to RCTs (0.3–0.8 U/Kg) [11–19], also considering that 0.2 U/kg should be the starting dose according to the Gla-300 label. However, a titration beyond 6 months from starting insulin therapy cannot be excluded in a real-life setting.

Results of our study were comparable to those of RCTs including insulin-naïve T2D cohorts treated with Gla-300 or Deg-100. The EDITION 3 study [13] showed that in the Gla-300 group, HbA<sub>1c</sub> at T0 was of 8.51%, and at T6, it was reduced by 1.42%; the proportion of patients reaching HbA<sub>1c</sub>  $<7.0$  at T6 was 43.1%. In the BEGIN Once-long [18], in the arm treated with Deg-100, HbA<sub>1c</sub> decreased from 8.2% at T0 by 1.06% after 6 months. In the first head-to-head RCT (BRIGHT) [19], HbA<sub>1c</sub> improved similarly in the two groups from 8.6 to 8.7% to 7.0% after 6 months. In the same study, comparable rates of hypoglycemia in the Gla-300 vs. Deg-100 group were documented (9.3 and 10.8 events per patient-year for hypoglycemia  $\leq$ 70 mg/dl and 0.6 versus 0.9 events per patient-year for hypoglycemia  $<$ 54 mg/dl). A weight gain of about 2 Kg was documented in both groups.

Results of our study are also comparable with those obtained in the US real-world setting among insulin-naïve patients with T2D [23]. RESTORE-2 study shows very similar results to DELIVER D naïve study [23], where HbA<sub>1c</sub> reduction was comparable in the Gla-300 and Deg-100 cohorts ( $-1.67\%$  vs.  $-1.58\%$ ;  $p = 0.51$ ), as was HbA<sub>1c</sub> target attainment (HbA<sub>1c</sub>  $<7\%$ : 23.8% and 27.4%;  $p = 0.20$ ; HbA<sub>1c</sub>  $<8\%$ : 55.0% and 57.1%;  $p = 0.63$ ). Furthermore, similarly low rates of hypoglycemia were reported in the two groups. In the LIGHTING study [24], data were collected from the Optum Humedica US electronic health records database. In the naïve matched cohort, a HbA<sub>1c</sub> reduction of 1.5% was detected in patients treated with Gla-300 and Deg-100. Furthermore, severe hypoglycemic event rates with Gla-300 (estimated through a predictive modeling approach) were not different from those with Deg-100, whereas predicted rates of non-severe hypoglycemia were significantly lower with Gla-300 versus all comparators (first- and second-generation

basal insulins). In the CONFIRM study [22], significantly greater HbA<sub>1c</sub> reduction, larger reductions in hypoglycemia rates and lower risk of treatment discontinuation were demonstrated with Deg-100 versus Gla-300. However, these results should be interpreted with caution for at least two reasons: i) Both HbA<sub>1c</sub> and hypoglycemia were analyzed in subgroups of the PS matched cohort without any further check on between-group imbalance and ii) pattern of baseline medications and an initial daily insulin dose of 40 U are poorly consistent with the expected profile of insulin-naïve patients [23]. Furthermore, there was no match with regard to hypoglycemia rates prior to insulin initiation and there was an imbalance that could per se drive the differences of the changes in hypoglycemia rates with Deg-100 versus Glar-300 [26].

A study on T1D (RESTORE-1) based on the same methodology described here has recently been published [27]. In agreement with RESTORE-1 findings, the take-home message from our new RESTORE-2 is the confirmation of a similar effectiveness and safety of the two 2BI. Yet, the need to overcome clinical inertia is still not met. Late insulin initiation and slow titration are likely due at least in part to the fear of hypoglycemia and weight gain. From a methodological standpoint, both studies confirm the importance of the secondary use of preexisting data for clinical research purposes. In this respect, the Italian network of diabetes centers adopting the same EMRs system represents a unique opportunity to conduct large, real-world effectiveness studies.

Among notable strengths of this study, we underline that this is the first RWE comparative study conducted outside the USA on the effectiveness and safety of 2BIs in T2D. Thanks to the large sample of patients with T2D routinely cared for by centers located in different areas of Italy, and

the efficient use of EMR for research purposes, our data have good generalizability to the population of individuals with T2D followed under diabetologist care in Italy. The comparison of hypoglycemic episodes was based on documented events, with the caveat that only a subset of patients had their SMBG downloaded on EMRs. Indeed, the main limitation of this retrospective analysis was the lack of information on SMBG tests for a relevant proportion of patients, although the performed analysis is robust due to the large number of SMBG tests analyzed, the post-matching balance between the two groups, and the lack of difference in baseline risk of hypoglycemia. The download of SMBG values from glucose meters on EMRs was not a common practice in participating centers, suggesting the need to implement the systematic revision of SMBG data through EMRs.

Furthermore, between-group comparison was at least partially limited by the modest dose titration, preventing a head-to-head comparison between the two insulins when optimally used. Nevertheless, data reflect real-life practice and the barriers to optimize insulin doses, especially when patients or diabetologists are concerned by the risk of hypoglycemia. This is a key point deserving consideration in view of the importance of bringing more patients to their HbA<sub>1c</sub> target.

In conclusion, in this comparative real-world study with PS matched cohorts of adult patients with T2D, initiating Gla-300 or Deg-100 was associated with similar improvements in glycemic control both in medium and long term, without weight gain and with low rate of hypoglycemia, with no severe episodes observed during an average of 6-month follow-up. The RESTORE-2 study confirms the effectiveness and safety of Gla-300, with comparable results with respect to Deg-100.



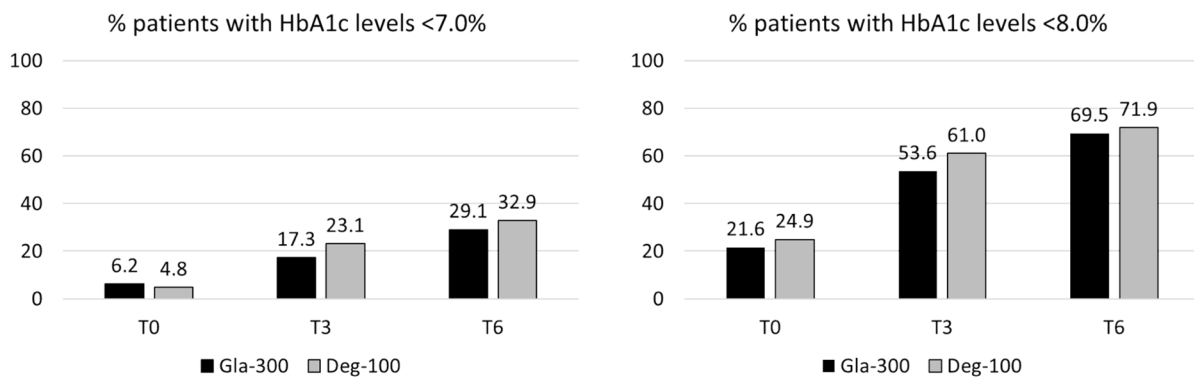
### Appendix 1: Variables used in PS matching—pre- and post-PSM baseline patients' characteristics (ITT population)

Variable	Category	PRE-PSM				POST-PSM			
		Gla-300	Deg-100	<i>p</i> -value	Standardized difference	Gla-300	Deg-100	<i>p</i> -value	Standardized difference
N group		808	358	.	.	357	357	.	.
BMI (Kg/m <sup>2</sup> )		29.31 (5.79)	29.89 (5.64)	0.07	10.0026	29.91 (6.05)	29.86 (5.62)	0.75	−0.83529
GLP1-RAs (%)	No	658 (81.44)	274 (76.54)	0.054	−12.0474	278 (77.87)	273 (76.47)	0.66	−3.33727
	Yes	150 (18.56)	84 (23.46)	.	.	79 (22.13)	84 (23.53)	.	.
SGLT2 inhibitors (%)	No	586 (72.52)	288 (80.45)	0.004	18.7626	290 (81.23)	287 (80.39)	0.78	−2.13416
	Yes	222 (27.48)	70 (19.55)	.	.	67 (18.77)	70 (19.61)	.	.
Glitazones (%)	No	760 (94.06)	318 (88.83)	0.002	−18.7885	325 (91.04)	318 (89.08)	0.38	−6.55581
	Yes	48 (5.94)	40 (11.17)	.	.	32 (8.96)	39 (10.92)	.	.
Secretagogues (%)	No	464 (57.43)	179 (50.00)	0.02	−14.9341	196 (54.90)	179 (50.14)	0.20	−9.5468
	Yes	344 (42.57)	179 (50.00)	.	.	161 (45.10)	178 (49.86)	.	.

Data are means and standard deviations or frequencies and proportions.

*p*-values derived from unpaired *t*-test or the Mann–Whitney *U*-test in case of continuous variables and the chi-square test or Fisher exact test for categorical variables, as appropriate. Statistically significant *p*-values (*p*<0.05) are in bold. A standardized mean difference less than 10 (absolute values) indicates a good balance between groups.

### Appendix 2: proportions of patients achieving HbA1c levels <7.0% and <8.0% at each visit by treatment group (Post- PSM ITT population)



Between-group <i>p</i> -value*	T0	T3	T6
	0.41	0.09	0.31

Between-group <i>p</i> -value*	T0	T3	T6
	0.29	0.09	0.52

Within-group <i>p</i> -value**	-	T3 vs. T0	T6 vs. T0
Gla-300	-	<0.0001	<0.0001
Deg-100	-	<0.0001	<0.0001

\*chi-square test \*\*McNemar test

Statistically significant *p*-values (*p*<0.05) are in bold.

### Appendix 3: Safety population—baseline patients' characteristics—pre- and post-PSM

Variable	PRE-PSM			POST-PSM		
	Gla-300	Deg-100	<i>p</i> -value	Gla-300	Deg-100	<i>p</i> -value
N group	241	129		123	123	
Age (years)	70.2 (11.0)	69.6 (10.5)	0.48	70.0 (11.0)	69.7 (10.4)	0.71
Males (%)	144 (59.8)	78 (60.5)	0.89	78 (63.4)	76 (61.8)	0.79
Diabetes duration (years)	14.21 (10.7)	13.12 (7.8)	0.39	13.0 (8.5)	13.2 (7.9)	0.70
BMI (Kg/m <sup>2</sup> )	29.3 (6.0)	29.1 (5.0)	0.82	29.5 (6.2)	29.2 (5.0)	1.00
HbA1c (%)	8.6 (1.4)	8.7 (1.5)	0.92	8.7 (1.5)	8.7 (1.4)	0.93
HbA1c (mmol/l)	70.5 (15.4)	71.6 (15.9)	0.94	71.4 (16.1)	70.9 (14.9)	0.87
Fasting blood glucose (mg/dl)	182.1 (55.4)	191.3 (58.1)	0.21	190.5 (60.9)	188.2 (57.5)	0.80
Systolic blood pressure (mmHg)	135.2 (19.7)	133.6 (15.9)	0.43	133.3 (18.0)	133.7 (15.9)	0.71
Diastolic blood pressure (mmHg)	75.9 (10.0)	77.6 (10.4)	0.46	74.7 (10.2)	77.6 (10.2)	0.07
Total cholesterol (mg/dl)	171.7 (40.7)	181.1 (43.6)	0.10	175.1 (44.6)	179.8 (42.8)	0.32
LDL-cholesterol (mg/dl)	91.7 (33.5)	101.6 (39.5)	0.06	94.8 (36.6)	100.9 (39.0)	0.34
HDL-cholesterol (mg/dl)	47.4 (13.5)	45.4 (11.0)	0.36	46.7 (12.6)	45.4 (10.4)	0.59
Triglycerides (mg/dl)	157.2 (86.7)	174.7 (156.3)	0.77	154.8 (87.5)	171.0 (158.4)	0.84
eGFR <60 ml/min*1.73m <sup>2</sup>	45 (41.3)	13 (41.9)	0.95	18 (35.3)	10 (37.0)	0.89
Microalbuminuria (%)	34 (31.78)	18 (29.51)	0.76	18 (35.29)	17 (29.31)	0.50
Diabetes complications (%)	17 (7.1)	7 (5.4)	0.54	6 (4.9)	7 (5.7)	0.78
<i>Glucose-lowering therapy</i>						
Daily basal insulin dose (U)	12.2 (5.9)	12.6 (7.2)	0.69	12.6 (6.3)	12.4 (6.9)	0.23
<i>No. of glucose-lowering drugs other than insulin</i>						
<2	32 (13.3)	24 (18.6)	0.17	18 (14.6)	20 (16.3)	0.72
≥2	209 (86.7)	105 (81.4)		105 (85.4)	103 (83.7)	
Metformin (%)	202 (83.8)	100 (77.5)	0.13	102 (82.9)	97 (78.9)	0.42
Secretagogues (%)	92 (38.2)	60 (46.5)	0.12	56 (45.5)	57 (46.3)	0.90
Glitazones (%)	20 (8.3)	12 (9.3)	0.74	9 (7.3)	12 (9.8)	0.49
Acarbose (%)	18 (7.5)	8 (6.2)	0.65	5 (4.1)	8 (6.5)	0.39
DPPIV inhibitors (%)	129 (53.5)	63 (48.8)	0.39	66 (53.7)	62 (50.4)	0.61
GLP1-RAs (%)	60 (24.9)	37 (28.7)	0.43	25 (20.3)	36 (29.3)	0.10
SGLT2 inhibitors (%)	80 (33.2)	21 (16.3)	<b>0.0005</b>	31 (25.2)	21 (17.1)	0.12
Mean no. of available SMBG tests per patient in the study period (%)	178.8 (446.5)	158.4 (163.8)	0.47	149.2 (108.2)	159.5 (167.4)	0.92

Data are means and standard deviations or frequencies and proportions.

Variables included in the PSM: No. of glucose-lowering drugs other than insulin, diabetes duration, use of metformin and secretagogues, HbA1c.

*p*-values derived from unpaired t-test or the Mann-Whitney U-test in case of continuous variables and the chi-square test or two-sided Fisher exact test for categorical variables, as appropriate. Statistically significant *p*-values (*p*<0.05) are in bold.

## Appendix 4: Safety population: variables used in PS matching—pre- and post-PSM baseline patient characteristics

Variable	Category	PRE-PSM				POST-PSM			
		Gla-300	Deg-100	<i>p</i> -value	Standardized difference	Gla-300	Deg-100	<i>p</i> -value	Standardized difference
<i>N</i> group		241	129	.	.	123	123	.	.
No. of glucose-lowering drugs other than insulin (%)	<2	32 (13.28)	24 (18.60)	0.1731	14.5899	18 (14.63)	20 (16.26)	0.7242	4.5004
	>=2	209 (86.72)	105 (81.40)	.	.	105 (85.37)	103 (83.74)	.	.
Diabetes duration in classes (%)	<=5 years	37 (15.35)	17 (13.18)	0.1355	-6.2205	18 (14.63)	17 (13.82)	0.8504	-2.3275
	6-10 years	44 (18.26)	29 (22.48)	.	.	34 (27.64)	27 (21.95)	.	.
	11-20 years	111 (46.06)	53 (41.09)	.	.	46 (37.40)	52 (42.28)	.	.
	>20 years	46 (19.09)	23 (17.83)	.	.	22 (17.89)	23 (18.70)	.	.
	NA	3 (1.24)	7 (5.43)	.	.	3 (2.44)	4 (3.25)	.	.
Metformin (%)	No	39 (16.18)	29 (22.48)	0.1361	15.9995	21 (17.07)	26 (21.14)	0.4174	10.3539
	Yes	202 (83.82)	100 (77.52)	.	.	102 (82.93)	97 (78.86)	.	.
Secretagogues (%)	No	149 (61.83)	69 (53.49)	0.1203	-16.9341	67 (54.47)	66 (53.66)	0.8982	-1.6315
	Yes	92 (38.17)	60 (46.51)	.	.	56 (45.53)	57 (46.34)	.	.
HbA1c in classes	3.0-6.9%	23 (9.54)	5 (3.88)	0.0095	-22.7998	4 (3.25)	5 (4.07)	0.9891	4.3315
	7.0-8.0%	63 (26.14)	50 (38.76)	.	.	48 (39.02)	47 (38.21)	.	.
	8.1-9.0%	90 (37.34)	34 (26.36)	.	.	34 (27.64)	34 (27.64)	.	.
	>9.0%	65 (26.97)	40 (31.01)	.	.	37 (30.08)	37 (30.08)	.	.

Data are means and standard deviations or frequencies and proportions.

*p*-values derived from unpaired *t*-test or the Mann–Whitney *U*-test in case of continuous variables and the chi-square test or Fisher exact test for categorical variables, as appropriate. Statistically significant *p*-values ( $p < 0.05$ ) are in bold. A standardized mean difference less than 10 (absolute values) indicates a good balance between groups.

## Appendix 5: Changes in estimated mean levels of HbA1c in the subgroup of ITT PS-matched naive population with HbA1c values at T12 (N=121 in Gla-300 group and N=133 in Deg-100 group)

Visit	Gla-300			Deg-100			
	Estimated mean and 95% CI	Estimated mean difference from T0 and 95% CI	Within group <i>p</i> -value*	Estimated mean and 95% CI	Estimated mean difference from T0 and 95% CI	Within group <i>p</i> -value*	Between-group <i>p</i> -value**
T0	9.25 (9.07;9.43)	–	–	9.18 (9.00; 9.36)	–	–	
T12	7.55 (7.37;7.73)	– 1.71 (– 1.94; – 1.48)	<b>&lt;0.0001</b>	7.74 (7.56;7.92)	– 1.44 (– 1.67; – 1.21)	<b>&lt;0.0001</b>	0.052

\* Estimates and Paired t-test derived from linear mixed models for repeated measurements.

\*\*One side Paired t-test derived from linear mixed models for repeated measurements.

Statistically significant *p*-values (*p*<0.05) are in bold.

## Appendix 6: Incidence rate of hypoglycemic events ≤70 mg/dl and <54 mg/dl by treatment at T0 (Safety Naïve population: PS matched patients having at least 1 SMBG value available)

Endpoint	Group	Subjects	No. SMBG tests	Events	Person-months	IR (95% CIs)	IRR (95% CIs)	Between-group <i>p</i> -value
BG ≤70 mg/dl	Gla-300	123	4,781	14	274.7	0.05 (0.02;0.14)	0.55 (0.16;1.88)	0.34
	Deg-100	123	6,367	24	259	0.09 (0.04;0.20)	–	–
BG <54 mg/dl	Gla-300	123	4,781	4	274.7	0.01 (0.00;0.06)	0.42 (0.07;2.36)	0.32
	Deg-100	123	6,367	9	259	0.03 (0.01;0.09)	–	–

*p*-values derived from Poisson regression models with correction for overdispersion. IR=incidence rate (number of events per person-months); IRR=incidence rate ratio; 95%CI=95% Confidence Intervals

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**Author Contributions** GPF, RB, ML, AN and DC made substantial contributions to the conception and design of the work. GPF and RB contributed to the data collection. MCR and AN conducted the statistical analyses and drafted the article. All authors revised the article critically for important intellectual content. All authors approved the final version to be published. All authors agreed all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article.

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**Data availability** The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request. Qualified researchers may request access to patient-level data and related documents [including, e.g., the clinical study report, study protocol with any amendments, blank case report form, statistical analysis plan and dataset specifications]. Patient-level data will be anonymized, and study documents will be redacted to protect the privacy of trial participants.

### Declarations

**Conflict of interest** GPF has received consultancy of lecture fees from Abbott, AstraZeneca, Boehringer, Lilly, MSC, NovoNordisk, Mundipharma, Sanofi, Servier and Takeda. RB has received consultancy of

lecture fees from Abbott, AstraZeneca, Lilly, NovoNordisk, Mundipharma and Sanofi. ML is an employee of Sanofi and may hold shares and/or stock options in the company. MCR and AN have received funding for research from Sanofi, NovoNordisk, Alfasigma, Artsana, AstraZeneca, Johnson&Johnson, Medtronic, Shionogi, SOBI, Meteda and Theras. DC has received consultation fees and speaker honoraria from Eli Lilly, Novo Nordisk, Roche Diagnostics, Sanofi and Takeda.

**Human and animal rights** All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. The study protocol was approved by all local ethics committees of the participating centers.

**Informed consent** Informed consent was obtained from all patients for being included in the study.

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