Effectiveness and safety of insulin glargine Gla-300 in insulin-naïve type 2 diabetes subjects in a real-life setting—the GOAL_RO trial

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Background: Basal insulin is the first choice for insulin initiation in type 2 diabetes (T2DM), with the second generation of basal insulin analogues having a lower risk of hypoglycemia compared to the first generation of basal insulins. The aim of our study was to assess on a large cohort of insulin-naïve T2DM subjects the effectiveness and safety of insulin glargine 300 U/mL (Gla-300) in a real-life setting.

Methods: This was a multicenter, prospective, non-interventional, 24 weeks, 3 visits (baseline, 3 and 6 months) trial performed in adult T2DM subjects not achieving glycemic target (HbA1c >7%) with prior oral or GLP-1 RA therapy. The study included 1,095 subjects (55.2% M/44.8% F) in 124 study sites. Mean (±SD) age was 61.1±8.5 years while mean duration of diabetes was 8.8±5.2 years. Mean BMI was 31.7±5.4 kg/m^2 with 91.2% being overweight or obese. Baseline diabetes treatment included metformin (88.4% of subjects), sulphonylureas (75.4%), DPP-4i (16.7%) and GLP-1 RAs (8%). Comparison between quantitative variables was made with the paired sample *t* test.

Results: Mean HbA1c at baseline was 9.8%±1.7% with a mean fasting plasma glucose (FBG) of 231.5±67.4 mg/dL. Mean HbA1c decreased to 7.7%±1.2% at 6 months with a mean change from baseline of –2.1% (P<0.001). Overall, 30.7% of subjects reached the HbA1c target of 7%. Final mean dose of Gla-300 was 0.4 IU/kg/day. Mean weight gain was 0.4 kg over 6 months. Adverse events (AEs) were reported by 11.1% of subjects with 2.3% reporting serious adverse events (SAEs). Overall, 4.4% of subjects reporting at least one event of symptomatic or confirmed hypoglycemia. Only 7 episodes of nocturnal and one of severe hypoglycemia were reported.

Conclusions: In conclusion, a significant 2.1% decrease of HbA1c was recorded after 6 months of treatment with Gla-300 with no unexpected safety signals, low risk of hypoglycemia and modest weight gain.

Keywords: Type 2 diabetes (T2DM); insulin treatment; insulin glargine Gla-300; real-life data

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Introduction

Despite apparently attenuating in developed countries, the type 2 diabetes (T2DM) epidemic continues to represent a major challenge worldwide, with approximately 463 million people affected in the 20–80 years old age group (1). In addition, T2DM is a major cause of morbidity and premature mortality (~11% of deaths in adults are attributable to diabetes) (1), with economic costs expected to rise to over 2 billion USD in the next decade (2). Most of these costs are related to the chronic complications of the disease that can be mostly prevented by achieving and maintaining glycemic targets, i.e., HbA1c below 7% (53 mmol/mol) for the majority of non-pregnant adults (3,4).

Current guidelines of the American Diabetes Association's (ADA) and European Association for the Study of Diabetes (EASD) tend to recommend a glucagon-like peptide 1 receptor agonist (GLP-1 RA) as the first injectable medication in T2DM subjects due to potential CV benefits, associated weight loss and low risk of hypoglycemia (3,4). However, reported adherence to GLP-1RA in real life observational studies is rather poor (5) and this leads to a ~0.5% difference in HbA1c obtained in randomized controlled trials compared to real-world data (6). Approximately 75% of the gap seems to be explained by poor medication adherence.

On the other hand, insulin has the advantage of lowering blood glucose in a dose dependent manner and when appropriately titrated, it can decrease HbA1c up to almost any target (3,4,7), limited only by the risk of hypoglycemia. In fact, due to the evolutive nature of the disease, many patients will need insulin therapy at some point during T2DM evolution in order to reach/maintain glycemic targets (8). Moreover, guidelines currently recommend early initiation of insulin in severely symptomatic patients or in the presence of high HbA1c/fasting blood glucose (FPG) (3,4,7). However, insulin treatment initiation is quite often delayed due to multiple barriers, both related to physicians and patients (9). Proper patient education and their involvement in self-monitoring of blood glucose and self-titration of insulin dose may overcome some of the barriers and improve glucose control.

Basal insulin added to metformin, other oral drugs or a GLP-1RA is usually the first choice for insulin initiation (3,4) due to lower risk of hypoglycemia and weight gain in comparison with prandial or premix insulins. The initial recommended dose is of 10 international units QD (or 0.2 IU/kg/day) with consequent insulin dose titration for attaining the target of FBG, usually set to 70–130 mg/dL. Basal insulin analogs [glargine 100 U/mL (Gla-100), detemir] have a lower risk of hypoglycemia (mainly nocturnal) in comparison with NPH insulin while the second generation of basal insulin analogs [degludec and glargine 300 U/mL (Gla-300)] exhibit an even lower risk compared to Gla-100 (10,11).

Gla-300 is a second-generation basal insulin analog approved for clinical use since 2015 (12). It has the same molecular structure and metabolism but is 3× more concentrated in comparison with insulin Gla-100 (13). Consequently, the pharmacokinetics and pharmacodynamics of this insulin preparation are modified, with a prolonged duration of action (half-life of 19 hours and total duration beyond 24 hours), almost peak-less action profile and low intra-individual variability (14). These benefits were expected to translate in clinical benefits for diabetes subjects, both in T1DM and T2DM.

The efficacy and safety of Gla-300 was assessed in the large phase 3 EDITION clinical program of randomized controlled trials (RCTs) with Gla-100 as active comparator. The T2DM studies performed in Caucasians included the EDITION-1 (patients treated basal-bolus with NPH or Gla-100 as basal insulin), EDITION-2 (patients treated with basal insulin more than 42 IU QD and oral drugs) and EDITION-3 (patients treated only with oral drugs) (12). Primary efficacy and safety were evaluated after 6 months of treatment, with subsequent extension to 12 months. The meta-analysis of EDITION 1–3 trials indicated similar efficacy compared with insulin glargine (HbA1c decrease with 1.02% for both insulins and approximately 36% of subjects reaching <7% HbA1c target) (15). This was achieved with significant lower rates of confirmed/severe hypoglycemia for Gla-300 (RR 0.86, P=0.0116), especially due to reduced number of nocturnal hypoglycemia. Severe hypoglycemia was rarely reported, with numerically fewer episodes for Gla-300 (RR 0.85, 95% CI: 0.52 to 1.39) (15).

During the last decade, there was increasingly acceptance of the fact that results of randomized controlled trials (RCTs), usually including highly selected study populations, cannot be easily expanded to the heterogeneous population encountered in routine clinical practice. Consequently, there is an increasing demand from the main stakeholders in medicine for the use of results from real world evidence (RWE) studies in order to increase the robustness of data regarding the effectiveness and safety of different medicinal products (16).

In accordance to the higher emphasis placed recently on evidence provided by the RWE studies, the aim of our

study was to assess in real life clinical practice in Romania the effectiveness and safety of insulin Gla-300 initiated in insulin-naïve T2DM subjects.

We present the following article in accordance with the TREND reporting checklist (available at http://dx.doi.org/10.21037/atm-20-4533).

Methods

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and the ICH-GCP regulations. Approval by institutional ethics committees was obtained for each participating site. All subjects provided written informed consent prior to any study related procedure. Data monitoring was provided by the sponsor.

Design of study

This was a multicenter, prospective, observational/non-interventional, open label, 24 weeks/3 visits [baseline (V1), 3 months (V2) and 6 months (V3)] trial. It was performed in 124 active study sites (outpatient departments of diabetes) from large/medium size cities distributed across Romania, between May 2017 and June 2018. Recruitment of study subjects was made by each investigator (self-selection). Insulin Gla-300 was initiated at the decision of each investigator and no restrictions on diabetes or other treatments and no interference with dosage regimens recommended by practicing physicians were imposed. Insulin Gla-300 was self-injected QD, sub-cutaneous by each study subject at home using the Solostar® injecting pen. There were no specific interventions to increase patient adherence.

Inclusion/exclusion criteria

Subjects eligible for inclusion in the trial were adult T2DM subjects (18–75 years), not achieving glycemic target (HbA1c >7%) with prior oral or GLP-1 RA therapy, insulin-naïve, initiated with insulin Gla-300 upon the decision of the prescribing physician and have signed the informed consent prior to any study procedure.

Subjects were excluded if having type 1 diabetes, contraindications to insulin treatment, previous insulin treatment for more than a week within one year prior to study inclusion, pregnancy or breastfeeding or intention to become pregnant during the duration the

study, concomitant participation in another clinical trial, concomitance of severe medical conditions which might interfere with their participation in the study, severe mental conditions and refusal to sign the informed consent form.

Study objectives

The primary endpoint of the study was the change in HbA1c from the inclusion in the study up to the end of the follow-up period of 6 months.
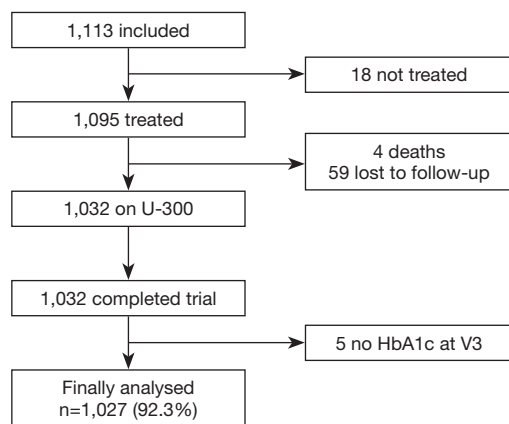
Secondary objectives included percentage of subjects reaching HbA1c ≤7.0% after 6 months, percentage of subjects reaching the individualized target of HbA1c after 6 months, change from baseline in fasting plasma glucose (FPG) after 3 and 6 months, change from baseline in the dose of insulin Gla-300 after 3 and 6 months, change in body weight from baseline to 6 months and the frequency of confirmed/symptomatic, nocturnal or severe hypoglycemic episodes. The 2013 criteria of the ADA/Endocrine Society of hypoglycemia definition were used (17).

Other study objectives included stratification based on the initial value of HbA1c (< or ≥8%) of the percentage of subjects reaching HbA1c ≤7.0% after 6 months.

Study assessments

The data collected during each visit was related to those captured and documented during current care of each subject. The following was recorded: the demographical and anthropometric data of the patient (height, weight, waist circumference), the medical history (other than diabetes), duration of diabetes, presence of diabetes and cardiovascular complications, the individual glycemic targets proposed by physicians, concomitant medication (other than antidiabetics), the dose of insulin Gla-300 at all visits, the diabetes medication prior to entering the trial. Data were obtained from the medical records of the patient from the database of the treating physician according to the current practice. Blood samples were collected for the compulsory assessment of HbA1c and (optionally) of FPG at baseline and at 6 months.

Information was collected regarding the frequency with which physicians recommend a particular insulin titration algorithm and its description [collected data included target fasting blood glucose performed by patients using SMBG, frequency of dose adjustments (per week) number of insulin units for each step of titration, person who initiates titration (physician *vs*. patient) etc.]. Influence of the titration

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┌─────────────────────┐
│   1,113 included    │
└─────────────────────┘
          │ ──────────────→ ┌──────────────────┐
          ▼                 │  18 not treated  │
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│    1,095 treated    │
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          │ ──────────────→ ┌──────────────────┐
          ▼                 │    4 deaths      │
┌─────────────────────┐     │ 59 lost to       │
│   1,032 on U-300    │     │ follow-up        │
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│ 1,032 completed     │
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          ▼                 │ 5 no HbA1c at V3 │
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│  Finally analysed   │
│  n=1,027 (92.3%)    │
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Figure 1 Patient disposition. U-300, insulin glargine U-300; V3, visit 3.

algorithm on final HbA1c was assessed.

All the information was entered into an electronic Case Report File (eCRF) by the prescribing physician.

Safety data collection

Self-reported hypoglycemic events, adverse events (AEs), serious adverse events (SAEs), acute cardiovascular events, reactions at the injection site, quality/technical issues of Gla-300 were obtained from the medical records of the patients by the treating physician. The following types of hypoglycemic events were recorded: any hypoglycemic event (symptomatic or confirmed); any confirmed symptomatic hypoglycemic event (blood glucose ≤70 mg/dL); any nocturnal hypoglycemic event (during sleep) and any severe hypoglycemic event (an event which requires the assistance of another person if the patient cannot help himself/herself).

During/after each visit, the treating physician entered the data listed above in the eCRF.

Statistical analyses

Sample size was calculated initially at 1,100 subjects from approximately 130 study centers with 10±5 subjects/center. Effectiveness endpoints were assessed in subjects having at least baseline and 6 months HbA1c assessment (analyzable population—per protocol population). No method for imputing missing data was used. Safety was assessed on the safety population set, defined as all subjects included in the trial that received at least one dose of Gla-300. Safety assessments included self-reported AEs and self-reported

hypoglycemic episodes.

Descriptive statistical analysis was performed. In addition, for the change in trial outcomes statistical testing included the 95% CI: and used a paired samples T test to evaluate if the change registered from baseline was statistically significant. Testing was performed at a significance level of α=0.05. The SPSS v21 software was used for statistical analysis.

Results

Patient population

A total of 1,113 T2DM subjects were included in 124 study sites. Of these, 1,095 received at least one dose of Gla-300 and represent the safety population. According to the patient disposition (*Figure 1*), the population attending V3 with an available HbA1c at this timepoint included 1,027 subjects—per protocol population that was finally analyzed.

Baseline clinical and demographic characteristics are reported in *Table 1* and are typical for a population with long standing T2DM (mean duration of 8.8 years) requiring treatment intensification with a basal insulin. The study population had a balanced gender distribution, mean BMI of 31.7 kg/m^2 and not at glycemic target with a mean HbA1c of 9.8% (83.6 mmol/mol). Majority of subjects were taking metformin (~88%) and/or a sulphonylurea (~75%). Most subjects presented cardiovascular risks factors, including hypertension (76.1%), dyslipidemia (72.0%) and obesity (70.5%). We also found that 138 subjects (13.4%) were active smokers. The frequency of chronic microvascular and macrovascular diabetes complications is reported in *Table 1*.

Efficacy

Glycemic endpoints
Treatment with Gla-300 led to a robust decrease of HbA1c in the per protocol population both at 3 months (data available for 542 subjects)—mean ± SD change of –1.9%±1.9% (95% CI: –2.1%, –1.7%, P<0.001) and 6 months (data available for all 1,027 subjects) –2.1%±2% (95% CI: –2.2%, –2.0%, P<0.001) timepoints (*Table 2*). There was no correlation between the titration algorithm used by investigators and the change in HbA1c from baseline to the end of trial.

Overall, 383 subjects (37.3%, 95% CI: 34.4%, 40.3%) reached the HbA1c target of 7% after a mean duration of insulin Gla-300 treatment of 18.2±8 weeks. The proportion was higher in subjects with a lower HbA1c at baseline (<8%)

Table 1 Baseline demographic and clinical characteristics (per protocol analysis, n=1,027)

Characteristic	Values
Age (years), mean ± SD (range)	61.1±8.5 (30 to 80)
Male/female, n (%)	460 (44.8)/567 (55.2)
Weight (kg), mean ± SD	88.0±16.9
BMI (kg/m^2), mean ± SD	31.7±5.4
BMI group, n (%)	
<25 kg/m^2	90 (8.8)
≥25 to <30 kg/m^2	330 (32.1)
≥30 kg/m^2	606 (59.1)
Diabetes duration (years), mean ± SD	8.8±5.2
HbA1c (%), mean ± SD	9.85±1.7
HbA1c group, n (%)	
<7.0%	4 (0.4)
≥7.0% to <8.0%	79 (7.7)
≥8.0%	944 (91.9)
FPG (mg/dL), mean ± SD	231.5±67.4
Diabetes complications/comorbidities, n (%)	
Neuropathy	515 (50.1)
Retinopathy	107 (10.4)
Chronic kidney disease	116 (11.3)
Myocardial infarction/stroke	40 (3.9)/58 (5.6)
Heart failure	81 (7.9)
Peripheral artery disease	101 (9.8)
Hypertension	782 (76.1)
Dyslipidemia	739 (72.0)
Diabetes treatment at baseline, n (%)	
Metformin	908 (88.4)
Sulphonylureas	774 (75.4)
GLP-1 RAs	82 (8.0)
DPP-4 inhibitors	173 (16.8)
Meglitinides	23 (2.2)
SGLT-2 inhibitors	39 (3.8)
α-glucosidase inhibitor	116 (11.3)
Thiazolidinediones	12 (1.2)

SD, standard deviation; n, number of patients; BMI, body mass index; HbA1c, glycated hemoglobin; FPG, fasting plasma glucose; GLP-1 RAs, glucagon like peptide 1 receptor agonists; DPP-4, dipeptidyl peptidase 4; SGLT-2, sodium glucose cotransporter-2.

[45.8% (95% CI: 35.5%, 56.4%)] compared to those with a higher HbA1c at baseline (≥8%) [29.3% (95% CI: 26.5%, 32.3%)].

Improvement of HbA1c was accompanied by a significant decrease of the fasting plasma glucose (FPG) values (*Table 2*). Thus, from a baseline of 231.5±67.4 mg/dL (95% CI: 227.1–235.9 mg/dL), data available for 885 subjects, mean change recorded after 3 months (data available for 876 subjects) was –87.5±71.4 mg/dL (95% CI: –92.2, –82.8 mg/dL, P<0.001) and plateaued at 6 months (data available for 880 subjects) with a mean change of –94.8±72.5 (95% CI: –99.6, –90.0, P<0.001). Final mean FPG was 136.8±33.7 mg/dL (95% CI: 134.6–139.0 mg/dL), above recommended targets, indicating insufficient titration of insulin.

Change in body weight
The mean ± SD change in body weight from baseline (data available for 1,026 subjects) to 3 months (data available for 1,025 subjects) was of 0.1±3.2 kg (95% CI: –0.1, 0.3) and of 0.4±4.5 kg (95% CI: 0.1–0.7, P=0.01) at 6 months (data available for all 1,027 subjects). Despite being marginally statistically significant, weight gain of 0.4 kg after 6 months of treatment with insulin Gla-300 was clinically not relevant, especially taken into account the marked improvement of glycemic control.

Change of insulin dose
Mean insulin dose recommended at Gla-300 treatment initiation was of 0.26±0.2 IU/kg (95% CI: 0.25–0.27), in accordance with American Association of Clinical Endocrinologists (AACE) guideline recommending a 0.2–0.3 IU/kg dose if HbA1c is above 8% (18). Titration of insulin after baseline led to a mean insulin dose increase of 0.1±0.2 IU/kg (95% CI: 0.09–0.11) at 3 months and of 0.2±0.3 IU/kg (95% CI: 0.18–0.22) at 6 months. Final insulin Gla-300 dose at 6 months reached 0.39±0.2 IU/kg (95% CI: 0.38–0.40). In the majority of cases (85.3%) investigators declared basal insulin titration will continue after study completion. In 64 cases (6.2%), subjects received "rescue" therapy with prandial insulin from baseline to visit V3.

Titration algorithm and correlation with final HbA1c
Titration was self-performed by the patient according to the titration algorithm agreed with the prescribing physician in 89.1% of cases at visit V2 and by 90.3% of subjects at visit V3. Overall, 28.1% of subjects used a titration algorithm with 2 IU per week while 65.5% of subjects used a titration

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Table 2 Glycemic endpoints (per protocol analysis, n=1,027)

Characteristic	Baseline	3 months	6 months
HbA1c, n	1,027	542	1,027
HbA1c (%), mean ± SD	9.8±1.7	8.0±1.2	7.7±1.2
HbA1c change, mean ± SD (95% CI)	–	−1.9±1.9 (−2.1, −1.7); P<0.001	−2.1±2.0 (−2.2, −2.0); P<0.001
FPG, n	885	876	880
FPG (mg/dL)	231.5±67.4	144.1±36.3	136.8±33.7
FPG change, mean ± SD (95% CI)	–	−87.5±71.4 (−92.2, −82.8); P<0.001	−94.8±72.5 (−99.6, −90.0); P<0.001

HbA1c, glycated hemoglobin; n, number of patients; FPG, fasting plasma glucose; SD, standard deviation; CI, confidence interval.

Table 3 Hypoglycemic events (safety population, n=1,095)

Characteristic	3 months (n=1,069*)	6 months (n=1,069*)
Symptomatic or confirmed hypoglycemia (≤70 mg/dL), n (%)	21 (2.0)	47 (4.4)
Confirmed hypoglycemia (≤70 mg/dL), n (%)	15 (1.4)	28 (2.6)
Nocturnal hypoglycemia, n (%)	0 (0.0)	7 (0.7)
Severe hypoglycemia, n (%)	0 (0.0)	1 (0.1)

*, for 26 subjects the eCRF lacked data regarding occurrence of hypoglycemic episodes. n, number of patients.

algorithm with 2–3 IU every 3–4 days.

There was no difference between the final achieved HbA1c at 6 months and the titration algorithm used by the subjects. Thus, final HbA1c was 7.7%±1.2% (95% CI: 7.6–7.8%) in subjects using a titration algorithm with 2 IU every 3–4 days, 7.7%±1% (95% CI: 7.6–7.8%) in subjects using a titration algorithm with 3 IU every 3–4 days and 7.9%±1.4% (95% CI: 7.6–8.1%) in subjects using a titration algorithm with 2 IU every week.

Safety

Treatment with insulin Gla-300 was well tolerated. Overall, 126 subjects (11.5%, 95% CI: 9.7–13.5%) reported a total of 264 AEs during the trial. Of these, 25 subjects (2.3%, 95% CI: 1.6–3.3%) reported a SAE. Among these, there were 4 deaths (evaluated by investigators not to be related with the trial product) and one case of intentional overdosing of insulin Gla-300 that resulted in a symptomatic hypoglycemic event. There was only one case (0.1%) of a technical complaint regarding the injecting device and only one case (0.1%) of local reaction at the injection site.

Frequency of hypoglycemic events during Gla-300 treatment was low, with a total rate of confirmed (≤70 mg/dL) hypoglycemic events of 0.18 per person per year (PPPY). There were 7 cases of nocturnal hypoglycemic events (0.7% of subjects) with a rate of 0.03 events PPPY. There was only one case of severe hypoglycemia (0.1% of subjects). A more detailed description of hypoglycemic events recorded during the trial is given in *Table 3*.

Discussion

To test the effectiveness and safety of insulin Gla-300 in real life, we performed an RWE observational/non-interventional trial in a large cohort of 1,095 insulin-naïve T2DM subjects. After 6 months of treatment, starting from a baseline HbA1c of 9.8%±1.7%, we recorded a mean decrease of HbA1c of 2.1%±2%. HbA1c reductions recorded in this study are comparable with those obtained in other RWE studies with Gla-300. For instance, in the DELIVER Naïve D study (comparing Gla-300 with insulin degludec), treatment with Gla-300 in 638 insulin-naïve T2D subjects with a mean HbA1c at baseline of 9.67% led to a mean HbA1c decrease of 1.67% after 6 months, similar with that recorded for degludec treated subjects (1.58%) (19). In the DELIVER Naïve study (comparing Gla-300 with Gla-100) (20), treatment with Gla-300 in 1,004 insulin-naïve T2DM subjects with a baseline HbA1c of 9.56% led to a mean HbA1c decrease of 1.52% after

6 months that was numerically greater compared with that recorded in 2,008 Gla-100 treated subjects (1.3% HbA1c reduction). The slightly higher decrease of HbA1c in our trial might be explained by its prospective nature (compared to retrospective Electronic Medical Records design of the DELIVER studies) as well as other differences in baseline characteristics of the trial population. Reductions are also comparable with those recorded in the EDITION-3 randomized controlled trial (21) that included insulin-naïve T2DM subjects, with a mean HbA1c reduction of 1.42%±0.05%, indicating a consistency of Gla-300 glycemic results in RWEs and RCTs.

Another retrospective observational RWE study from the USA analyzed dosing patterns and glycemic outcomes for T2D subjects initiating or switching to Gla-300 (22). In the cohort of 390 insulin-naïve patients, 298 subjects have initiated treatment with Gla-300. After 6 months of treatment, the mean least-square change in HbA1c was 1.21% from a baseline value of 8.63%. This was obtained with a mean daily dose of 0.44 IU/kg and with a significantly lower risk of hypoglycemia compared to the Gla-100 group (22). The lower drop of HbA1c in this trial might be explained by the lower baseline HbA1c value. An RWE trial with similar design performed in Canada (The REALITY Study) included an insulin-naïve T2DM cohort of 188 subjects treated with Gla-300 and 188 treated with Gla-100 (23). From a baseline HbA1c of 9.76%±1.75%, the mean HbA1c change at 6 months was of –1.78%±1.85%, a result almost identical with that recorded in our study. This was obtained with a mean insulin dose of 0.35±0.22 IU/kg, compared to 0.39±0.2 IU/kg in our trial.

Similar improvements in HbA1c were reported by RWE trials in which T2DM subjects treated with other basal insulins were switched to Gla-300 (24,25).

Regarding the percentage of subjects reaching the target of HbA1c of 7%, a total of 30.7% of patients in our trial reached this HbA1c target. In comparison, in the DELIVER Naïve D study, 23.8% of subjects attained the target HbA1c of 7% (19) while in the DELIVER Naïve study the percentage was of 25% (20). In the Canadian REALITY study, 27% of subjects reached the 7% HbA1c target (23), again very close to the percentage recorded in the current GOAL_RO trial. In our trial, the percentage of subjects reaching target was higher (45.5%) in subjects with a lower HbA1c at baseline, highlighting the importance of an early treatment initiation after failure of non-insulin diabetes treatments.

In our trial, treatment with Gla-300 proved to be safe, with only 4.4% of subjects reporting an episode of symptomatic or confirmed hypoglycemia and only 1 patient (0.1%) with an episode of severe hypoglycemia. The rate of confirmed hypoglycemic events was 0.18 events per person per year (PPPY). For comparison, in the DELIVER Naïve study, the incidence of all hypoglycemic events in the Gla-300 treated subjects was 9.7% (20), with a rate of 0.35 events PPPY. In the DELIVER Naïve D study, the total incidence of hypoglycemic events was 10.3% for Gla-300 subjects, with an event rate of 0.45 PPPY. Finally, in the REALITY study, the proportion of subjects reporting at least an episode of hypoglycemia was 8.7%. The frequency of hypoglycemic events in our trial was again much lower compared to that recorded in the EDITION-3 trials (21). Differences might be explained by the differences in patient populations, insulin titration algorithms and definition/ collection of hypoglycemic events. We hypothesize that insufficient titration of Gla-300 in our trial, indicative of clinical titration inertia, (insulin dose increased by only 0.2±0.3 IU/kg over 6 months despite final FPG value at 136 mg/dL being above the 80–100 mg/dL target included in the protocol) might have also contributed to the lower frequency of hypoglycemia in our cohort compared to similar RWE trials and, especially to RCTs.

Our study has several limitations. First, this is a non-randomized, real life, observational, trial with all the inherent drawbacks compared to RCTs. Inclusion of subjects was at the latitude of investigators so that a selection bias cannot be ruled out. For instance, the medications used at baseline (with 16.8% of subjects on DPP4i and 8% on GLP-1 RAs) does not reflect the current pattern from the general T2DM population in Romania. SMBG was not reinforced by the use of a specific journal/log and this might explain also the low frequency of hypoglycemic episodes recorded in our trial. Finally, different outcome values were not available for all subjects both at the 3 months (V2) and 6 months (V3) evaluations. This is why the findings of our study cannot be generalized to the whole insulin-naïve T2DM population in Romania.

Our study has also some strengths, including the large number of subjects (to our best knowledge this is the largest observational study analyzing the practice of Gla-300 insulin initiation in a real-life practice setting in Romania) and its prospective design.

Conclusions

In this prospective, observational/non-interventional trial

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performed in an insulin-naïve T2DM population we found a significant decrease of HbA1c and FBG after 6 months of treatment with insulin Gla-300. Titration inertia was evidenced, with a mean insulin dose increase of only 15 IU despite a mean FPG above target. There were no unexpected safety signals, with an overall low number of hypoglycemic events and modest/no clinically relevant weight gain.

The results of this prospective real-world evidence trial confirm the effectiveness and safety results obtained with Gla-300 in T2DM subjects in other populations and complement those of Gla-300 from the randomized controlled trials.

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Footnote

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Ethical Statement: The authors are accountable for 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. The study was conducted in accordance with the Declaration of Helsinki from 1964, revised in 2013 (available at http://www.wma.net/en/30publications/10policies/b3/%20index.html) and its later amendments and the ICH-GCP regulations. Approval by institutional ethics committees was obtained for each participating site. All patients provided written informed consent prior to any study related procedure. Data monitoring was provided by the sponsor.

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