ORIGINAL RESEARCH

Real-World Effectiveness and Safety of Insulin Glargine 300 U/mL in Patients with T2D Uncontrolled on NPH or Premixed Insulins as Part of Routine Clinical Practice in Bulgaria: ToUPGRADE Study

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ABSTRACT

Introduction: The aim of this study is to demonstrate the real-life effectiveness and safety of insulin glargine 300 U/mL (Gla-300) in patients with type 2 diabetes (T2D) previously uncontrolled on NPH ± prandial insulin or premixed insulins in routine clinical practice in Bulgaria.

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Methods: This was a 24-week prospective, observational study performed in 40 inpatient and outpatient sites across the country.

Results: A total of 286 patients were included in the study. The mean age ($\pm$ SD) was 61.2 ± 10.0 years with duration of diabetes of 11.64 ± 7.5 years and body mass index (BMI) of 32.1 ± 5.7 kg/m^2. HbA1c before Gla-300 initiation was $9.8 \pm 1.0\%$, and fasting plasma glucose (FPG) was 13.1 ± 3.4 mmol/L. HbA1c and FPG change from baseline to week 24 was -1.86% ($p < 0.001$) and -4.8 mmol/L ($p < 0.001$), respectively. The proportion of patients reaching their individualized HbA1c at week 24 was 39.1% (95% CI 33.3–45.1%), while the proportion of patients reaching their individualized HbA1c target without confirmed and/or severe hypoglycaemia was 34.8% (95% CI 29.2–40.7%). At study end, 19.0% (95% CI 14.6–24.1%) achieved HbA1c $< 7\%$. Body weight decreased from 88.3 to 87.0 kg from baseline to week 24 with mean change of -1.3 kg ($p < 0.001$). The incidence and event rates of anytime confirmed (≤ 3.9 mmol/L) and/or severe hypoglycaemia were low: 7.7% and 0.42 events per patient-year, respectively. The overall Insulin Treatment Satisfaction Questionnaire (ITSQ) score increased from 53.2 to 78.2 from baseline to week 24 and the difference of 25.1 ± 21.5 points was significant ($p < 0.001$).

Conclusions: In real-life settings, Gla-300 significantly improved glycaemic control and

insulin treatment satisfaction in people with T2D who were inadequately controlled with NPH ± prandial insulin or premixed insulin analogues. Improvement of glycaemic control was associated with a very low risk of hypoglycaemia and with significant weight loss irrespective of the previous insulin regimen.

Keywords: Basal insulins; Insulin glargine 300 U/mL; Observational study; Routine clinical practice; Real-life effectiveness; ToUPGRADE; Type 2 diabetes

Key Summary Points

Insulin glargine 300 U/mL (Gla-300), a second-generation basal insulin analogue with more stable PK/PD profile and longer duration of action compared to Gla-100, has demonstrated its ability to be highly effective in controlling HbA1c while minimizing the risk of hypoglycaemia. In a wide range of patients with T2D (n = 2474) in the comprehensive EDITION clinical programme, Gla-300 demonstrated comparable glycaemic control to Gla-100, with consistently less hypoglycaemia at any time of the day and less nocturnal hypoglycaemia. However there is limited data on Gla-300 use in patients switched from previous NPH-insulin based or premixed insulins treatment in patients with T2D.

This 24-week prospective, observational study aimed to demonstrate the real-life effectiveness and safety of Gla-300 in patients with T2D previously uncontrolled on NPH ± prandial insulin or premixed insulins in routine clinical practice in Bulgaria.

In the ToUPGRADE study, treatment with Gla-300 ± prandial insulin in patients with T2D previously uncontrolled on NPH or premixed insulins was associated with marked reductions in HbA1c (− 1.86%) and FPG (− 4.8 mmol/L); however, only 19% of study patients achieved HbA1c < 7% at study end. As the individual glycaemic goals defined by treating physicians were on average higher, a larger proportion of patients reached their individualized goals at study end: 39.1% of patients reached their individualized HbA1c target and 37.7% achieved their individualized FPG target. Body weight decreased from baseline to week 24 (− 1.3 kg). The incidence and event rates of anytime confirmed (≤ 3.9 mmol/L) and/or severe hypoglycaemia were low: 7.7% and 0.42 events per patient-year, respectively. The overall ITSQ score also increased from baseline to week 24.

Despite the notable and clinically meaningful drop in mean HbA1c at the end of the observation period, the small proportion of patients reaching their glycaemic targets and the small increase in basal insulin dose (mean daily dose increment of 4.0 U/day at week 24) indicate that the majority of patients still needed to continue insulin titration beyond 24 weeks of the observational period or should have been titrated more aggressively after switching to Gla-300.

In real-life settings, Gla-300 significantly improved glycaemic control and insulin treatment satisfaction in people with T2D who were inadequately controlled with NPH ± prandial insulin or premixed insulin analogues. Improvement of glycaemic control was associated with a very low risk of hypoglycaemia and with significant weight loss irrespective of the previous insulin regimen.

DIGITAL FEATURES

This article is published with digital features, including a summary slide and video abstract to facilitate understanding of the article. To view digital features for this article go to https://doi.org/10.6084/m9.figshare.13669094.

INTRODUCTION

As a result of the progressive nature of type 2 diabetes (T2D), characterized by a steady β-cell decline over time, most patients will ultimately require insulin therapy to achieve optimal blood glucose (BG) control. However, many prospective studies have shown that achieving good glycaemic control in routine clinical practice remains a challenge. A large proportion of patients cannot reach recommended glycaemic targets even after initiating insulin treatment [1]. Fear of hypoglycaemia remains a common barrier to optimal titration, adherence and achieving glycaemic targets with insulin [2]. Recent diabetes treatment guidelines highlight the need for personalized glycated haemoglobin (HbA1c) targets to balance reductions in hyperglycaemia with the potential risks of hypoglycaemia [3].

Insulin glargine 300 U/mL (Gla-300) is a second-generation basal insulin analogue that has demonstrated its ability to be highly effective in controlling HbA1c while minimizing the risk of hypoglycaemia. Gla-300 is a new formulation of insulin glargine with more constant and prolonged release, more stable pharmacokinetic/pharmacodynamic (PK/PD) profile and longer duration of action compared to Gla-100 [4]. The efficacy and safety of Gla-300 was evaluated in the comprehensive EDITION clinical programme, which encompassed a wide range of patients with T2D (n = 2474), including insulin-naïve patients treated with oral antidiabetic drugs (OADs) (EDITION 3), patients previously treated with basal insulin in combination with OADs (EDITION 2) and patients on intensified insulin therapy consisting of a basal insulin and a short-acting mealtime insulin (EDITION 1) [5–7]. In such a large population with a broad clinical spectrum of T2D, Gla-300 demonstrated comparable glycaemic control to Gla-100, with consistently less hypoglycaemia at any time of the day and less nocturnal hypoglycaemia. When analysed by study period, more pronounced reduction of hypoglycaemia risk has been observed in the titration period and these results are consistent in all EDITION studies [8]. Thus Gla-300 allows safer titration to glycaemic targets with lower risk of hypoglycaemia in patients with T2D.

Randomized controlled trials (RCT) remain the gold standard for the evaluation of the efficacy and safety of investigational drugs and are fundamental for the drug approval process by regulatory bodies. However, the strict inclusion and exclusion criteria and the intensive motivation, monitoring and education provided during the RCTs are not always representative of routine clinical practice. Hence the results obtained from RCTs need to be validated in a real-life setting such as non-interventional trials. Non-interventional observational studies usually have less restrictive inclusion/exclusion criteria and include broader patient populations. Thus, they offer an important tool to better assess the real-world effectiveness of a drug and to complement the data obtained in RCTs [9].

There are a number of real-world studies that have shown the real-life effectiveness and safety of Gla-300 in patients with T2D, previously treated with first-generation basal insulin analogues. While currently there is limited data on Gla-300 use in patients with T2D previously treated with human and/or premixed insulins, in many countries, including Bulgaria, human insulins and premixed insulins are commonly used in the management of T2D. Therefore, the objective of the study is to generate clinical evidence on the real-life effectiveness and safety of Gla-300 in patients with T2D uncontrolled on NPH ± prandial insulin or premixed insulin as part of routine clinical practice in Bulgaria.

METHODS

Study Design

This was a prospective, observational, multicentre study. The participating investigators were endocrinologists from inpatient and outpatient clinical centres. The study sites (final number 40) were selected to ensure appropriate coverage of regions and representativeness of the T2D insulin management in Bulgaria. All treatment decisions and procedures were fully at the physicians' discretion and followed everyday clinical practice. Gla-300 was applied according to its approved label (Summary of Product Characteristics, SmPC) and the local reimbursement conditions applicable in the country during the study conduct period. Only routine data were collected at each visit and no additional diagnostic procedures were applied as per the observational nature of the study. Collected data included demographic and clinical characteristics, diabetes history, diabetes complications and concomitant cardiovascular diseases, antihyperglycaemic treatment, glycaemic variables, hypoglycaemic and adverse events. Patients' insulin treatment satisfaction was evaluated during the routine visits. Patients were asked to complete Insulin Treatment Satisfaction Questionnaire (ITSQ) before Gla-300 initiation and after 6 months of treatment. The total score from the 22-item scale was used. Subscales related to regimen inconvenience, lifestyle, flexibility, glycaemic control, hypoglycaemic control and satisfaction with the insulin delivery method were also analysed. For each patient entering the study, investigators had to set individualized HbA1c and FPG targets based on the patient characteristics in line with American Diabetes Association (ADA)/European Association for the Study of Diabetes (EASD) guidelines. Hypoglycaemic events (confirmed, symptomatic, nocturnal and severe) were collected from patients' diaries which were used as part of routine clinical practice at the sites. Confirmed hypoglycaemia was defined as a hypoglycaemic event confirmed by a measured blood glucose level below 3.9 mmol/L. Symptomatic hypoglycaemia was defined as an event with clinical symptoms with or without documented blood glucose measurement. Severe hypoglycaemia was defined as an event requiring assistance of another person to actively administer carbohydrate, glucagon or take other corrective actions. According to the time of occurrence, the hypoglycaemia was defined as overall (24 h) and nocturnal (00:00 to 05:59 am). In addition, the composite category of confirmed and/or severe hypoglycaemia was analysed (documented by self-monitoring plasma glucose (SMPG) < 3.0 mmol/L and SMPG ≤ 3.9 mmol). All study sites documented patient data in web-based electronic case report forms (eCRF) at inclusion or baseline (visit 1), after 12 weeks (visit 2) and after 24 weeks of treatment with Gla-300 (visit 3) during the routine patient visits to the site.

Patients were eligible for inclusion in the study if they fulfilled the following criteria: adult patients with T2D ($\geq$ 18 years age), inadequately controlled on previous insulin therapy (NPH $\pm$ prandial insulin or premixed insulin) with or without OAD and switched to insulin glargine 300 U/mL regimen ($\pm$ OAD, $\pm$ prandial insulin) at the time of enrolment. As per the current local reimbursement conditions for initiation of basal insulin analogues, inadequate control was defined as HbA1c $> 9\%$ with frequent overall or nocturnal hypoglycaemia. Patients were excluded from the study if they had type 1 diabetes, if they were younger than 18 years old, if they were pregnant or breastfeeding, or if patients were treated with insulin therapy other than NPH $\pm$ prandial insulin or premixed insulins at the time of screening.

The study was conducted in accordance with the principles laid down by the 18th World Medical Assembly (Helsinki, 1964) including all subsequent amendments. It was approved by the regulatory authorities and the Central Ethics Committee of the Ministry of Health in Bulgaria. Informed consent was obtained from all individual participants included in the study.

Study Endpoints

The primary endpoint was the mean change in HbA1c after 6 months of treatment. Secondary efficacy endpoints included change in HbA1c level from baseline to week 12, changes in fasting plasma glucose (FPG), fasting SMPG, 7-point SMPG profile, body weight and daily insulin dose from baseline to week 12 and week 24 as well as the proportion of patients with at least a 0.5%-point decrease in HbA1c level, proportion of patients who have achieved HbA1c < 7%, proportion of patients achieving their individual HbA1c and FPG targets and the proportion of patients achieving their individual HbA1c target without hypoglycaemia at study end. Secondary safety endpoints included frequency of adverse events and confirmed and/or severe hypoglycaemic events. The study endpoints included also a patient-reported outcome (PRO): mean change in ITSQ score from baseline to week 24. Here we report the week 24 secondary endpoint results.

Statistical Methodology

As a result of the observational study design descriptive statistical methods have been used including case number (N) and percentage (%) for categorical variables, and summary statistics (case number, mean, standard deviation, minimum, median and maximum values) for continuous variables. The efficacy population was defined as all enrolled study patients with signed informed consent, correctly completed inclusion and exclusion criteria, and primary endpoint variables (HbA1c measurement at baseline and study end). The safety population was defined as all enrolled study patients with signed informed consent who administered Gla-300 at least once. Demographic and baseline characteristics as well as safety analyses were performed on the safety population. Primary, secondary and exploratory efficacy analyses were performed on the efficacy population. To check the distribution of analysed variables Q–Q plots were applied. The mean change in HbA1c level was analysed using a paired t test comparing the data recorded at baseline and at study end. The mean change with 95% confidence interval and the associated, two-sided p value was given. A p value below 0.05 was considered statistically significant. Primarily, all secondary efficacy endpoints were analysed descriptively; when an inferential analysis was required, independent t test was used for comparison of two groups. The 95% confidence intervals were also reported, when appropriate.

Sample size calculation was determined on the expected mean change in HbA1c over 24 weeks of treatment. Recent data from real-world database analyses in patients with T2D switching from other basal insulins to Gla-300 (DELIVER-2, DELIVER-D+) showed a mean decrease in HbA1c of around 0.5–0.6% for the same treatment period [10, 11]. Assuming that the mean decrease in the HbA1c level over 24 weeks would be 0.5%, a total number of 245 analysable patients were needed in order to obtain 1.2% precision rate (based on two-sided 95% confidence interval). Considering a maximum of 20% dropout rate, a sample size of 306 patients was planned to be enrolled.

RESULTS

A total of 286 patients were included in the study between October 2017 and November 2018 and followed up by April 2019, representing the safety population. Seven of the subjects (2.4%) did not complete the study because of drug discontinuation before study end for one patient, loss to follow-up for one patient, withdrawal of consent for three patients and death for two patients. In the three cases of patient withdrawal, the reason was not an adverse event. The two reported deaths are adverse events but they were not related to the study drug. Considering only completers, 279 subjects were included in the efficacy population.

Demographic and Clinical Characteristics of the Study Population

The mean age ($\pm$ SD) of the study cohort was 61.2 ± 10.0 years with more female patients enrolled (55.9%). The mean body mass index

Table 1 Baseline characteristics

	Overall study population ($n = 286$)[a]	NPH pre-treated patient group ($n = 205$)[a]	Premix pre-treated patient group ($n = 81$)[a]
Age, years	61.2 ± 10.0	60.5 ± 10.5	63.1 ± 8.3
Male, n (%)	126 (44.1%)	97 (47.3%)	29 (35.8%)
Weight, kg	88.0 ± 17.0	88.7 ± 17.8	86.4 ± 14.8
Height, cm	165.8 ± 8.8	166.5 ± 9.2	164.0 ± 7.4
BMI, kg/m^2	32.1 ± 5.7	32.0 ± 5.8	32.2 ± 5.7
Duration of diabetes, years	11.6 ± 7.5	10.0 ± 6.9	15.7 ± 7.3
Duration of insulin pre-treatment, years	5.8 ± 5.6	4.3 ± 4.7	9.5 ± 6.1
HbA1c, %	9.8 ± 1.0	9.6 ± 0.9	10.2 ± 1.1
FPG, mmol/L	13.1 ± 3.4	12.5 ± 3.2	14.5 ± 3.6
eGFR, mL/min/1.73 m^2	82.1 ± 68.7	85.7 ± 79.7	73.1 ± 22.5

BMI body mass index, *HbA1c* glycated haemoglobin, *FPG* fasting plasma glucose, *eGFR* estimated glomerular filtration rate

[a] Mean $\pm$ SD or as indicated

(BMI) was 32.1 ± 5.7 kg/m^2. The majority of the patients (69.9%) were obese with BMI > 30 kg/m^2 at baseline. The mean duration of diabetes was 11.6 ± 7.5 years and the mean duration of insulin pre-treatment was 5.8 ± 5.6 years. The mean baseline HbA1c was 9.8 ± 1.0%, while the mean FPG before Gla-300 initiation was 13.1 ± 3.4 mmol/L. Baseline demographic and clinical characteristics for the overall safety population and the two insulin pre-treatment groups are specified in Table 1.

Almost half of the patients (47.6%) experienced at least one confirmed and/or symptomatic hypoglycaemic event during the last 3 months prior to initiation of Gla-300. A higher proportion of patients previously treated with premixed insulins reported hypoglycaemia events (60.5%) vs those treated with NPH $\pm$ prandial insulin (42.4%). The event rate of confirmed and/or symptomatic hypoglycaemia 3 months prior to initiation of Gla-300 was 17.9 episodes per patient-year with a higher event rate in the premixed insulin pre-treated group vs NPH group: 30.2 vs 13.1 episodes per patient-year. The incidence and event rates of hypoglycaemia prior Gla-300 initiation by

categories (confirmed and/or symptomatic, severe, nocturnal) can be found in Supplementary Table 1.

Clinical data related to chronic complications of T2D showed a significantly higher proportion of microvascular complications, compared to macrovascular complications. The most frequent microvascular complication was neuropathy, reported in 83.2% of the patients, followed by retinopathy in 18.2% and nephropathy in 8.0% of the patients, while the most frequent macrovascular complication was ischaemic heart disease, reported in 30.1% of the patients. Myocardial infarction and stroke/transitory ischaemic stroke were reported in 7.3% and 6.6% of the patients, respectively. The most frequent concomitant cardiovascular disease was arterial hypertension in 78.7% and dyslipidaemia in 36.0% of the patients. Only 15.4% of the patients had no microvascular complication reported and 18.2% of patients had no macrovascular complication or concomitant cardiovascular disease reported. The prevalence of all diabetes complications and concomitant cardiovascular diseases at baseline can be found in Supplementary Table 2.

Table 2 Number of injections of prandial insulin treatment continuation/start with the introduction of Gla-300 per day at baseline by pre-treatment categories

Number of injections per day	NPH insulin, N (%)		Premixed insulin, N (%)		Total, N (%)	
1	3	3.2%	1	1.4%	4	2.4%
2	3	3.2%	7	9.5%	10	6.0%
≥ 3	87	93.5%	66	89.2%	153	91.6%
Total	93	100.0%	74	100.0%	167	100.0%

As per study inclusion criteria, all enrolled patients had previous insulin treatment before introduction of Gla-300. Among them 205 patients (71.7%) were treated with NPH ± prandial insulin and 81 patients (28.3%) with premixed insulins. In the subgroup treated with NPH insulin 93 patients (45.4%) received one injection of NPH insulin per day and 112 patients (54.6%) received two injections per day. The mean daily NPH insulin dose before Gla-300 introduction was 34.0 ± 14.8 U/day. Approximately half of the patients in the NPH-treated group were on basal-oral insulin regimen before the introduction of Gla-300 (107 patients, 52.2%), while the other half of the patients (98 patients, 47.8%) were also using prandial insulin. Among the prandial insulin users, 88 patients (89.8%) were treated with a short-acting human insulin and 10 patients (10.2%) received an insulin analogue (insulin lispro, aspart or glulisine). The majority of the prandial insulin users (86 patients, 87.8%) were treated with three or more injections per day. Only 8 patients (8.2%) and 4 patients (4.1%) were treated with one and two injections, respectively. The mean daily dose of prandial insulin before Gla-300 initiation was 35.0 ± 13.4 U/day. All patients treated with premixed insulins before Gla-300 have been administered premixed insulin analogues. Premixed insulins were mainly applied twice (in 40 patients, 49.4%) or ≥ 3 times per day (40 patients, 49.4%). Only one patient (1.2%) has applied the premixed insulin once per day. The mean daily premixed insulin dose was 63.6 ± 18.8 U/day. The mean dose of the basal component in the premixed insulin users was 42.0 ± 13.4 U/day while the mean dose of the rapid component was 21.7 ± 9.1 U/day.

More than half of the study population (176 patients, 61.5%) was treated with OADs before the introduction of Gla-300. The most frequently used OAD was metformin in 168 (95.5%) of the patients, followed by gliclazide MR (11 patients, 6.3%), gliclazide (5 patients, 2.8%) and glimepiride (5 patients, 2.8%) respectively. Overall, 23 patients (13.1%) were treated with sulfonylurea products (SUs). Details on antidiabetes treatment before Gla-300 introduction can be found in Supplementary Table 3.

Baseline Gla-300 Therapy and Concomitant Insulin and Other Antihyperglycaemic Treatment

The mean starting Gla-300 dose was 32.2 ± 13.6 U/day. For both patient groups treated prior to Gla-300 either with NPH or with premixed insulins, the initial Gla-300 dose did not differ substantially: 32.5 ± 13.8 U and 31.6 ± 13.3 U, respectively. Gla-300 was injected once-daily in all patients. The majority of the patients (77.6%) injected Gla-300 in the evening and only 22.0% injected it in the morning. The most frequent time of administration was at 22:00 hours (bedtime) in 43.5% of the patients.

A titration algorithm was recommended in 75.2% of the patients. The most frequently recommended titration step was of 2 U in 66% of patients, followed by 4 U in 13.5% of patients. Titration was also mostly recommended to be performed once per week or every

3–4 days in 50.2% and 46.5% of patients, respectively. The titration was led by the physician in 45.6% of patients while 54.4% of patients performed self-titration based on doctor's recommendation at initiation.

With the introduction of Gla-300, prandial insulin was continued or started in 167 patients

(58.4% of safety population). Prandial insulin was continued or started in approximately half of the patients in the NPH pre-treated group (45.4%) while this proportion was much higher in the premixed insulin pre-treated group (91.4%). Of note is that 8.6% of the premix pre-treated patients were switched to basal-oral
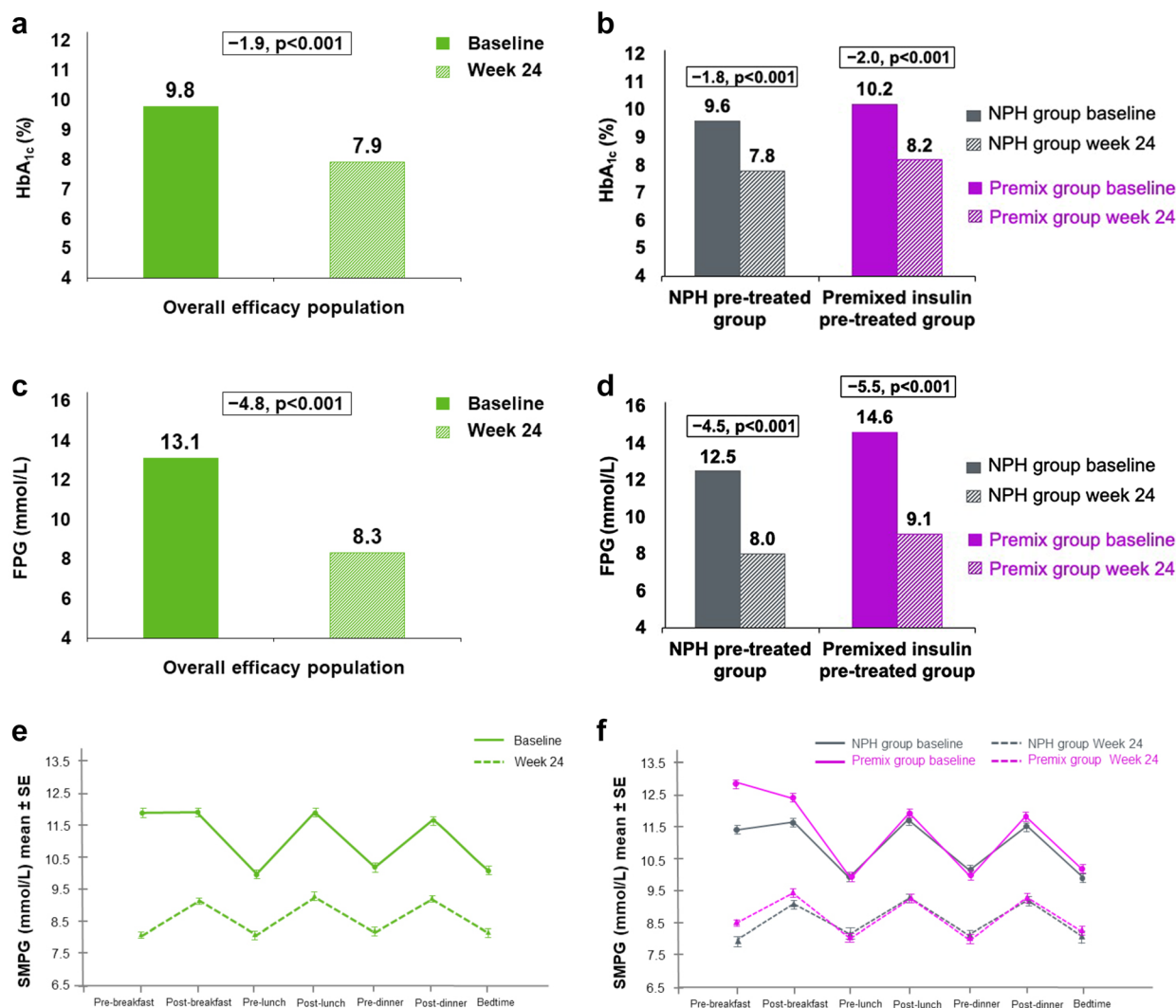
Fig. 1 Change in HbA1c, FPG and 7-point SMPG profiles from baseline to week 24 for efficacy population and per pre-treatment groups. **a** Mean change in HbA1c for the overall efficacy population from baseline to week 24. **b** Mean changes in HbA1c for the NPH and premixed insulin pre-treated groups from baseline to week 24. **c** Mean change in FPG for the efficacy population from baseline to week 24. **d** Mean changes in FPG for the NPH and premixed insulin pre-treated groups from baseline to week 24. **e** Mean changes in the 7-point SMPG profile for the efficacy population, $p < 0.001$ for all time points. **f** Mean changes in the 7-point SMPG profile for NPH pre-treated and premixed insulin pre-treated subgroups, $p \leq 0.001$ for all time points except for the mean change before lunch in the premixed insulin pre-treated patients where $p = 0.004$

insulin regimen only. The majority of the prandial users (91.6%) were treated with at least three injections per day. One or two injections of prandial insulin were applied only in 2.4% and 6.0% of patients, respectively (Table 2). The mean daily prandial insulin dose was 33.7 ± 12.2 U/day. The types of prandial insulins used as well as their mean doses are shown in Supplementary Table 4.

A total of 170 patients (59.4%) continued or started OAD treatment with the introduction of Gla-300. Metformin was applied for 161 patients. The mean total daily dose of metformin was 2049 ± 658 mg. Only 19 patients continued or started sulfonylurea treatment with the introduction of Gla-300 with gliclazide MR being most frequently applied. Six patients were treated with another OAD with the introduction of Gla-300 such as acarbose, a dipeptidyl peptidase 4 (DPP4) inhibitor and pioglitazone.

Real-World Effectiveness Outcomes

A total of 279 patients had data about laboratory assessment of HbA1c at baseline and after 6 months of treatment, representing the efficacy population. In the total efficacy population the mean HbA1c decreased from 9.8% to 7.9% (Fig. 1a). The mean change was − 1.9 ± 1.3% and it was statistically significant ($p < 0.001$). The mean FPG decreased from 13.1 to 8.3 mmol/L and the mean change was − 4.8 mmol/L, $p < 0.001$ (Fig. 1c). Significant decrease in HbA1c and FPG was also observed in both NPH and premixed insulin pre-treatment groups (refer to Fig. 1b, d, and Table 3).

The mean fasting SMPG also decreased from baseline to week 24 for the efficacy population and the two pre-treatment groups. The mean fasting SMPG in the efficacy population was reduced from 11.8 to 8.1 mmol/L and the mean change was − 3.8 ± 3.1 mmol/L ($p < 0.001$). Actually, the 7-point SMPG profiles decreased significantly at week 24 at all time points in the

Table 3 Change in HbA1c and FPG from baseline to week 24 for efficacy population and per pre-treatment groups

	Overall efficacy population	NPH pre-treated group	Premixed insulin pre-treated group
HbA1c			
N^*	279	201	78
Baseline value, %	9.8	9.6	10.2
Week 24 value, %	7.9	7.8	8.2
Mean change ± SD	− 1.9 ± 1.3	− 1.8 ± 1.2	− 2.0 ± 1.6
95% CI (lower; upper)	95% CI − 2.0 to − 1.7	95% CI − 2.0 to − 1.6	95% CI − 2.0 to − 1.6
p value	$p < 0.001$	$p < 0.001$	$p < 0.001$
FPG			
N^*	273	197	76
Baseline value, mmol/L	13.1	12.5	14.6
Week 24 value, mmol/L	8.3	8.0	9.1
Mean change ± SD	− 4.8 ± 4.1	− 4.5 ± 3.8%	− 5.5 ± 4.7%
95% CI (lower; upper)	95% CI − 5.3 to − 4.3	95% CI − 5.1 to − 4.0	95% CI − 6.6 to − 4.4
p value	$p < 0.001$	$p < 0.001$	$p < 0.001$

N^* number of patients with measurement at the respective time points to allow evaluation of change

efficacy population (Fig. 1e). Similar results were observed in the separate analyses for subgroups of NPH and premixed insulin pre-treated patients (Fig. 1f). More details are shown in Supplementary Table 5.

In the overall efficacy population 88.9% of patients (total $n = 279$) achieved at least a 0.5%-point decrease in HbA1c level at week 24 (95% CI 84.6–92.3%). In the NPH pre-treated group ($n = 201$) this proportion was 88.6% (95% CI 83.3–92.6%), while in the premixed insulin pre-treated group ($n = 78$) the proportion was 89.7% (95% CI 80.8–95.5%). The proportion of patients who achieved at least a 1.0%-point decrease in HbA1c level at week 24 in the overall efficacy population was 79.6% (95% CI 74.4–84.1%). In the NPH insulin pre-treated group this proportion was 79.1% (95% CI 72.8–84.5%) and in the premixed insulin pre-treated group the proportion was 80.8% (95% CI 70.3–88.8%). The proportion of patients who achieved HbA1c < 7% at week 24 from the overall efficacy population was 19.0% (95% CI 14.6–24.1%). This proportion was similar in the NPH pre-treated group: 20.0% (95% CI 14.6–26.1%); while the proportion of patients reaching HbA1c < 7% at study end was numerically lower in the premixed insulin pre-treated group: 16.7% (95% CI 9.2–26.8%).

The mean individual HbA1c target specified by the investigators at baseline was $7.5 \pm 0.7\%$ with no substantial difference for groups previously treated with NPH or premixed insulins (7.5% vs 7.6%). The mean individual FPG target was 7.2 ± 0.8 mmol/L. In the overall efficacy population, 39.1% (95% CI 33.3–45.1%) of patients reached their individualized HbA1c target and 37.7% (95% CI 32.0–43.8%) of the patients achieved their FPG target at week 24. Both results were numerically higher in the group previously treated with NPH compared to those treated with premixed insulins; however, no statistical difference was observed. In the NPH pre-treated group 40.8% (95% CI 33.9–47.9%) of patients reached their individualized HbA1c target and 39.6% (95% CI 32.7–46.8%) of the patients achieved FPG target at week 24. In the premixed insulin pre-treated group 34.6% (95% CI 24.2–46.2%) of patients reached their individualized HbA1c target and

32.9% (95% CI 22.5–44.6%) of the patients achieved FPG target at week 24. The majority of the patients had individualized HbA1c target $\leq 7\%$ (37.4%) or between 7% and 7.5% (28.0%), while only 5.2% of the patients had to achieve HbA1c > 8.5%. The proportions of patients reaching their individualized HbA1c target by target categories at week 24 are shown in Supplementary Table 6.

In the overall efficacy population, 34.8% (95% CI 29.2–40.7%) of the patients reached the individualized HbA1c target without confirmed and/or severe hypoglycaemia and 35.8% (95% CI 30.1–41.8%) reached the individualized FPG target without confirmed and/or severe hypoglycaemia at week 24. Again, the results were numerically higher in the group previously treated with NPH compared to those treated with premixed insulins. In the NPH pre-treated group 36.8% (95% CI 30.1–43.9%) of the patients reached their individualized HbA1c target without confirmed and/or severe hypoglycaemia, while only 29.5% (95% CI 19.7–40.9%) of the patients in the premixed insulin pre-treated group reached this composite goal. Similarly, numerically more patients reached the individualized FPG target without hypoglycaemia in the NPH pre-treated compared to the premixed insulin pre-treated group: 37.4% (95% CI 30.6–44.5) vs 31.6% (95% CI 21.4–43.3%), respectively.

Change in Insulin Dose and Body Weight

Mean body weight decreased from 88.3 to 87.0 kg from baseline to week 24 and this decrease of -1.3 ± 4.6 kg was significant (95% CI -1.9 to -0.8), $p < 0.001$. The weight decrease was higher in the premixed insulin pre-treated patients compared to those in the NPH pre-treated group at week 24 (-2.2 ± 6.1 kg vs -1.0 ± 3.8 kg) and the difference was statistically significant ($p = 0.045$).

In the efficacy population mean daily Gla-300 dose increased significantly from 32.2 to 36.2 U (0.37–0.42 U/kg) from baseline to week 24. The mean change in Gla-300 daily dose was 4.0 ± 7.0 U (0.05 ± 0.09 U/kg), $p < 0.001$. In the patients previously treated

Table 4 Hypoglycaemia incidence and event rates per categories for the overall safety population and per pre-treatment groups

Hypoglycaemia categories	Overall safety population (n = 286)		NPH pre-treated group (n = 205)		Premixed insulin pre-treated group (n = 81)	
	Incidence, n (%)	Event rate, patient-year	Incidence, n (%)	Event rate, patient-year	Incidence, n (%)	Event rate, patient-year
Confirmed (≤ 3.9 mmol/L) and/or severe hypoglycaemia	22 (7.7%)	0.42	13 (6.3%)	0.39	9 (11.1%)	0.52
Confirmed (< 3.0 mmol/L) and/or severe hypoglycaemia	9 (3.2%)	0.07	4 (2.0%)	0.04	5 (6.2%)	0.16
Symptomatic hypoglycaemia	22 (7.7%)	0.41	13 (6.3%)	0.39	9 (11.1%)	0.47
Nocturnal hypoglycaemia	3 (1.1%)	0.04	3 (1.5%)	0.06	0	0
Severe hypoglycaemia	1 (0.4%)	0.01	1 (0.5%)	0.01	0	0

with NPH insulin, the Gla-300 dose increase was numerically smaller compared to those previously treated with premixed insulin. In the NPH pre-treated group the mean change at study end was 3.5 ± 6.9 U (0.04 ± 0.09 U/kg), while in the premixed insulin pre-treated group it was 5.2 ± 7.2 U (0.07 ± 0.1 U/kg). Detailed results for mean change in Gla-300 dose are shown in Supplementary Table 7a.

Among the prandial users in the efficacy population, mean daily prandial insulin dose increased from 33.5 U to 34.2 U from baseline to week 24. While the increase in mean prandial insulin dose at week 24 in the overall efficacy population was modest (0.7 ± 7.7 U) and not significant ($p = 0.249$), the increase observed in the patients previously treated with premixed insulins was higher (2.1 ± 8.8 U) and significant ($p = 0.05$). Of note is that mean prandial insulin dose in the NPH pre-treated patients decreased at week 24 with $- 0.4 \pm 6.5$ U; however, this decrease was not significant. The mean total (basal plus prandial) daily insulin dose in the prandial users also increased from baseline to week 24 (from 64.7 to 69.2 U). The difference of 4.5 ± 10.6 U was significant, $p < 0.001$. Higher total insulin dose increase was observed in patients previously treated with premixed insulins (7.3 ± 11.5 U) compared to those previously treated with NPH insulin (2.4 ± 9.4 U), $p = 0.004$. Detailed results for the mean change in prandial and total daily insulin doses are shown in Supplementary Table 7b.

Correlation Between Gla-300 Titration Scheme and Achieved HbA1c at Week 24

There was a weak but statistically significant correlation between HbA1c value at week 24 and titration of Gla-300 performed ($r = 0.160$, $p = 0.005$). There were statistically significant differences in the HbA1c achieved at week 24 between the physician-led titration and the patient self-titration. The HbA1c at week 24 was higher if the patient performed titration vs physician-led titration (8.1% vs 7.7%, respectively, $p = 0.029$). There was also statistically significant greater change in HbA1c from baseline to week 24 if the physician led titration vs patient self-titration ($- 2.1 \pm 1.4\%$ vs $- 1.6 \pm 1.4\%$; $p = 0.009$).

Hypoglycaemia

Throughout the study 22 (7.7%) patients had experienced at least one hypoglycaemic episode. Nocturnal episodes were reported in three patients with $n = 6$ events. The total number of hypoglycaemic events reported was 60. Among them 57 events (95%) were symptomatic while 3 events (5%) were asymptomatic. Only one
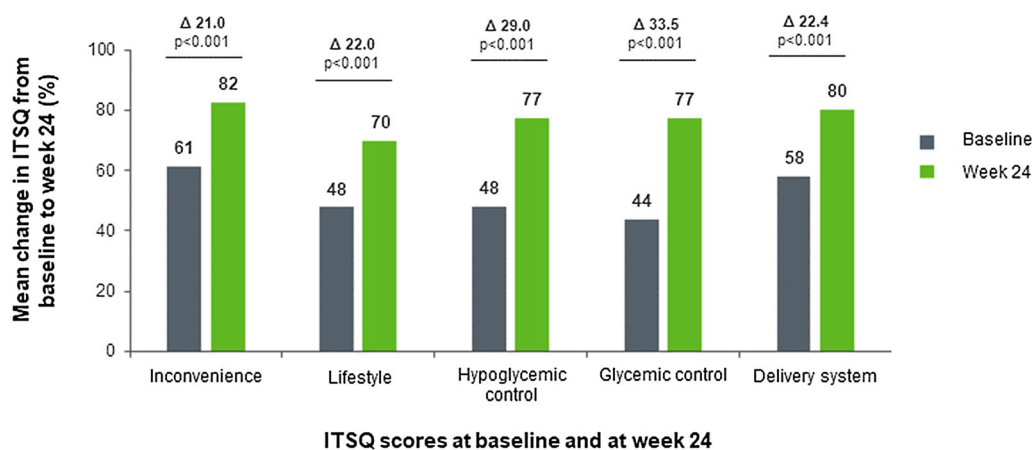
Fig. 2 Mean change in patients' insulin treatment satisfaction from baseline to week 24

event required assistance. There was no event leading to unconsciousness/coma, or seizure, emergency department visit, or fulfilling the definition of a serious AE. The hypoglycaemia incidence and event rates per categories (confirmed and/or severe, symptomatic, nocturnal, and severe) for the overall safety population and per treatment groups are shown in Table 4.

Adverse Events

During the entire 6-month observational period, 11 patients (3.8%) from the safety population had reported a total of 11 adverse events. Ischaemic stroke occurred in two patients, with the remaining 9 events occurring once (Supplementary Table 8). Eight of the events recovered or resolved, one event was stabilized, and two events were fatal. Both deaths were unrelated to the study drug (one due to pneumonia and one due to acute heart failure). In five patients adverse events required or prolonged hospitalization. For all events the causality assessment was unrelated to the study drug. Four events were mild, three moderate and three severe. Intensity was missing for one event. Seven events (in 2.4% of patients) were serious and four (in 1.4% of patients) were not serious adverse events. Three patients withdrew from the study and none of these cases was reported as linked to an adverse event.

Patient-Reported Outcomes

In the efficacy population 275 patients filled in the ITSQ questionnaire. The questionnaire comprised of 22 questions and for each of them there was a statistically significant improvement 24 weeks after Gla-300 treatment initiation. Mean total score increased from 53.2 to 78.2 from baseline to week 24 and the difference of 25.1 ± 21.5 points (95% CI 22.5–27.6) was significant ($p < 0.001$). There was no substantial difference in the improvement of insulin treatment satisfaction at study end for the groups previously treated with NPH or premixed insulins (mean difference was 24.8 vs 25.6 points, respectively). The score for each of the five ITSQ domains (inconvenience, lifestyle, hypoglycaemic control, glycaemic control and delivery system) was significantly improved 24 weeks after Gla-300 initiation (Fig. 2). Best improvement was observed in the domains hypoglycaemic and glycaemic control. More details for the improvement in ITSQ scores in the NPH- and premixed insulins pre-treated groups are shown in Supplementary Table 9.

DISCUSSION

The ToUPGRADE study evaluated the real-life effectiveness and safety of Gla-300 in patients with T2D uncontrolled on NPH or premixed

insulins as part of routine clinical practice in Bulgaria. While Gla-300 has been extensively evaluated in a comprehensive EDITION clinical programme as well as number of real-world studies, there is limited data on Gla-300 use in patients switched from previous NPH-insulin based or premixed insulins treatment in patients with T2D. As a result of reimbursement criteria, in Bulgaria as some other countries in the Balkan region insulin treatment can only be initiated with human insulins (NPH or human premixed insulins). As per current reimbursement criteria in Bulgaria at the time of the study, switch to basal insulin analogues may be considered only after at least 6 months of treatment with NPH ± prandial insulin or pre-mixed insulin analogues and only if patients are uncontrolled. For both insulin regimens inadequate control as per local reimbursement criteria was defined as HbA1c > 9% with frequent overall or nocturnal hypoglycaemia. For patients on NPH ± prandial insulin another criterion is FPG > 10 mmol/L, while for patients on basal-oral therapy (NPH + OAD) BMI > 30 kg/m^2 can be also taken into consideration. These conditions impact the characteristics of patients enrolled and observations made during this observational study. Nowadays the aforementioned HbA1c criterion has been changed to > 7.5%.

The baseline characteristics of T2D participants enrolled in the ToUPGRADE study were similar to those uncontrolled on previous insulin regimens and commencing Gla-300 in other studies. In the EDITION 2 study (basal-oral population) like the current study, there were more women (54%) enrolled. Interestingly the patients were younger (57.9 ± 9.1 years) but more obese (BMI of 34.8 ± 6.6 kg/m^2) with somewhat longer duration of diabetes (12.7 ± 7.1 years) [6]. The EDITION 1 study (basal-bolus population) included patients with T2D (slightly more men, 54%), at similar age (60.1 ± 8.5 years), more obese (BMI 36.6 ± 6.8 kg/m^2) and with longer duration of T2D (15.6 ± 7.2 years) [7]. Yet in both RCTs, the mean baseline HbA1c was lower in comparison with ToUPGRADE with mean values of 8.3 ± 0.9% and 8.2 ± 0.8% in EDITION 2 and 1, respectively, thus indicating that in real-

world clinical practice in Bulgaria switching of insulin therapy or intensifying insulin regimen is apparently undertaken with considerable delay in individuals with T2D presenting with a much higher HbA1c of 9.8% ± 1.0%. Recent data from real-world database analyses in patients with T2D switching from first-generation basal insulin analogues to Gla-300 (DELIVER-2 and DELIVER-D+ studies) observed similar patient characteristics as in our study at the time of switch of basal insulin therapy with an average age of 59 to 60 years, a balanced gender proportion (50.6% male and 50.9% female, respectively) and average BMI of 34.6–34.8 kg/m^2 [10, 11]. Despite that the mean baseline HbA1c in DELIVER-2 and DELIVER-D+ (8.9 and 9.1%) was higher than in EDITION 1 and 2 studies, this parameter was still lower compared to our study. In recently published observational study from Hungary [12] where patients with T2D were switched from human basal-bolus insulin regimen to Gla-300 plus insulin glulisine, the patient population was similar to that in our study with age at enrolment 60.9 ± 10.4 years, 47.1% male sex and BMI of 32.8 ± 5.8 kg/m^2. However, the mean baseline HbA1c was still lower (8.9 ± 1.5%) compared to our study. When considering diabetes complications, the incidence of microvascular complications in our study was higher compared to other real-life studies. For example, in the DELIVER-D+ study nephropathy, retinopathy and neuropathy were reported in approximately 9%, 11% and 30% of the patients, respectively, while in the ToUPGRADE cohort nephropathy was reported in 8%, retinopathy in 18% and neuropathy in 83% of patients. Diabetic neuropathy is the most common diabetic microvascular complication with prevalence in the literature ranging largely between 10% and 90% depending on the diagnostic methods. The higher incidence of diabetic neuropathy in our study could be related to the fact that diagnosis relies not only on quantitative testing but also on clinical signs. In many cases without a neurologist's evaluation, clinical signs in the lower limbs such as pain, numbness and tingling could be misinterpreted as diabetic neuropathy while actually they may be related to other diseases like lumbar disc

disease, spondyloarthritis, etc. Of note is that the incidence of microvascular complications in our study was higher in the premixed insulin pre-treated group where the patients had longer duration of diabetes and worse baseline glycaemic control compared to the patients previously treated with NPH ± prandial insulin. These findings further suggest that in Bulgaria insulin switching or intensification in patients with T2D treated with NPH ± prandial insulins and especially with premixed insulins is done too late and at a high level of uncontrolled diabetes which may lead to a faster development of diabetes-related complications.

Overall, the use of OADs in the study cohort was low. At baseline only 61% of the patients were treated with OADs. The most frequently used OAD was metformin in 59%, followed by SUs in 8% of the patients. Other medications such as thiazolidinediones (TZD), DPP4 inhibitors and glucagon-like peptide 1 receptor agonists (GLP-1 RAs) were used just in 3% of the patients as only metformin was allowed to be prescribed in combination with insulin as per local reimbursement conditions at the time of the study.

The primary objective of our study was to assess the change in HbA1c over 6 months of treatment with Gla-300. A significant improvement of − 1.9% was observed; however, this was still at an inadequate level of 7.9% at week 24. This reduction in HbA1c was greater compared to the real-world studies DELIVER 2 and DELIVER D+, where the mean change from baseline was − 0.5% and − 0.6%, respectively [10, 11]. The observed reduction was even greater compared to the phase 3 studies from the Gla-300 clinical programme EDITION 2 and EDITION 1, where the mean change was − 0.6% and − 0.8%, respectively [6, 7]. Yet the baseline HbA1c was considerably worse in our study cohort compared to the aforementioned studies, which would explain the greater glycaemic response. Mean FPG also decreased significantly over the 6 months of treatment with Gla-300 (− 4.8 mmol/L) also at an inadequate level of 8.3 mmol/L. These results complement the RCT and retrospective real-world data where Gla-300 has mainly been initiated after first-generation basal insulin analogues. Our study provides

further evidence that patients with T2D not well controlled on NPH and premixed insulin regimens may benefit from switching to Gla-300.

Despite the notable and clinically meaningful drop in mean HbA1c at study end, only 19% of the enrolled patients achieved HbA1c ≤ 7%. This finding indicates that the majority of study patients still needed to continue insulin titration beyond the 24-week observational period or should have been titrated more aggressively after switching to Gla-300. It has been proven in treat-to-target RCTs that about 30–40% of study participants achieved HbA1c target < 7.0% at 6 months with Gla-300 ± prandial insulin [5–7]. In addition, in these RCTs, final daily Gla-300 dose ranged between 59 and 103 U/day at month 6. In our study the improved glycaemic control was associated with a mean Gla-300 daily dose increment of only 4.0 U/day (from 32 to 36 U/day). Adjusted to body weight Gla-300 mean daily dose in ToUPGRADE increased from 0.37 to 0.42 U/kg/day at week 24. This increase of 0.05 U/kg/day was substantially lower than in RCTs. In the EDITION 1 study, Gla-300 dose increased by 0.30 U/kg/day (from 0.67 to 0.97 U/kg/day) in a similar patient population on basal-bolus regimen and lower baseline HbA1c [7]. Furthermore, the mean Gla-300 daily dose of 0.42 U/kg/day at week 24 was considerably lower compared to the ADA/EASD recommendations according to which basal insulin should be titrated up to the patient FPG target or until daily dose of 0.7–1.0 U/kg is reached without hypoglycaemia [3]. The current findings from real-world practice in Bulgaria confirm other real-world study outcomes that clinical inertia and suboptimal basal insulin titration may be key factors explaining why the majority of patients with T2D remain uncontrolled [13, 14]. Another interesting finding is that prandial insulin was widely used at Gla-300 initiation with 92% of the prandial users treated with three or more injections per day. This treatment pattern differs from the approach in EDITION 1 where mealtime insulin doses were adjusted at the discretion of the investigator only after basal insulin had been optimized [7]. Latest ADA/EASD consensus also highlights that a standard approach for

optimising basal insulin regimens is to titrate the dose on the basis of a target FPG and to consider adding one injection of short- or rapid-acting insulin formulation at the largest meal of the day (basal plus regimen). If later glycaemic target is still not met, additional prandial injections can be added during the rest of the meals [3].

Titration of Gla-300 dose was recommended by the treating physicians in 75% of patients. Of note is that better glycaemic control was reached if the physician led the titration vs patient self-titration. This observation contradicts the current RCT findings where patient-led Gla-300 titration has resulted in greater HbA1c reductions vs physician-led titration [15]. This comes to show that in routine clinical practice in Bulgaria there is limited experience in patient self-titration partly due to test strip reimbursement restrictions. However, the main reason for this is the insufficient healthcare professional resources (diabetes nurses, educators, etc.) to educate the patients regarding effective titration. The current data emphasize that in real-world practice, titration of basal insulin needs to be well defined by simple algorithms and clear explanation of individual glycaemic goals. A targeted time frame and educational support need to be provided to the patients to empower them to take a more active role in their treatment and thus to improve their glycaemic control.

There were no substantial differences in the overall effectiveness of Gla-300 for the two insulin pre-treatment groups. However, there was a tendency for the proportion of patients reaching HbA1c $\leq 7\%$ and their individual HbA1c and FPG targets with or without hypoglycaemia at week 24 to be higher in the NPH pre-treated group compared to those in the premixed insulin pre-treated group. This could be explained by the fact that the patients previously treated with premixed insulins were generally more difficult to treat compared to those treated with NPH $\pm$ prandial insulins. They had longer duration of diabetes (15.7 vs 10.0 years), longer duration of insulin treatment (9.5 vs 4.3 years), worse baseline glycaemic control (HbA1c of 10.2 vs 9.6%) and higher frequency of hypoglycaemia prior to

Gla-300 introduction (30.2 vs 13.1 events per patient-year).

In general, the overall study population was at high risk of hypoglycaemia, as documented by previous episodes. Approximately half of the patients (47.6%) experienced at least one confirmed and/or symptomatic hypoglycaemic event during 3 months prior to initiation of Gla-300. Hypoglycaemia data prior to Gla-300 initiation was collected retrospectively, which could introduce bias. However, it may also indicate poor patient insulin treatment management. Switching to Gla-300 in NPH and premixed insulin pre-treated patients led to clinically meaningful improvement of HbA1c at a low risk of hypoglycaemia. The incidences of any time and nocturnal hypoglycaemia in our study (7.7% and 1.1%, respectively) were lower than those reported in EDITION studies. In EDITION 1 any time and nocturnal hypoglycaemia were observed in 82% and 45% of patients, while in EDITION 2 these incidences were 70% and 28%, respectively [6, 7]. Another reason for these different incidences observed could be the substantially lower Gla-300 dose in real-world practice in Bulgaria and the lower number of patients who achieved HbA1c target < 7.0% (19%) vs 40% who achieved HbA1c < 7.0% in EDITION 1 [7]. Underreporting of hypoglycaemia in real-world vs randomized studies may have also accounted for the differences observed. When comparing the two groups of patients on type of insulin treatment prior Gla-300 initiation, both incidence and event rate of any hypoglycaemia (confirmed and/or symptomatic, nocturnal and severe) at baseline were higher in the premixed insulin pre-treated group compared to patients previously treated with NPH. Interestingly, the confirmed and/or severe hypoglycaemia incidence and event rate were numerically higher in the premixed insulin pre-treated group at study end as well (11% vs 6% and 0.52 vs 0.39 events per patient-year, respectively); however, there was no statistically significant difference. This hypoglycaemia frequency among prior users of premixed insulins may contribute to the more advanced disease with longer duration of diabetes, longer duration of insulin therapy and higher exposure to hypoglycaemia during the

premix treatment. Another factor could be the higher total insulin dose increase at study end in the premix insulins vs NPH pre-treated group: 7.3 vs 2.4 U at week 24.

Overall, the reported adverse events in the study were consistent with Gla-300's established safety profile. Gla-300 was well tolerated with few patients having adverse events or discontinuing therapy. No injection site reactions were reported which differs from observation in EDITION 1 where 2.2% of patients on Gla-300 experienced this adverse event [7]. This may be explained by underreporting in patients in a real-life setting who have been switched from another insulin regimen.

In the current study the switch to Gla-300 from NPH ± prandial insulin or premixed insulin analogues led to a modest but statistically significant mean body weight reduction of − 1.3 kg from baseline to week 24. This observation differs from the RCT study results where patients switched to Gla-300 from previous insulin therapy may gain body weight. For example, in EDITION 1 the mean weight gain over 6 months of treatment was 0.9 kg, while in EDITION 2 no change in mean weight was observed [6, 7]. However, in these randomized studies basal insulin dose was titrated much more effectively and the mean Gla-300 dose increase was substantially higher (0.30 and 0.28 U/kg/day in EDITION 1 and 2, respectively) vs the mean Gla-300 dose increase in our study (0.05 U/kg/day). In addition, our study population included patients at high risk of hypoglycaemia on their previous insulin therapy. Usually the risk of hypoglycaemia leads to protective overeating and weight gain. In this study the improvement of glycaemic control has been reached with relatively low risk of hypoglycaemia, thus escaping the protective overeating. Switching from insulin regimens with high hypoglycaemia risk such as human basal-bolus insulin regimen or premixed insulins to insulin glargine-based regimen has been already associated with modest body weight reduction in other real-world studies. The reported mean body weight decrease in the Hungarian observational study in patients with T2D switched from human to Gla-300 based basal-bolus insulin regimen (− 0.94 kg) was similar to the mean body weight decrease in our study (− 1.3 kg) [12]. Switching from premixed insulins to insulin glargine-based regimen in patients with T2D has been also associated with a significant reduction in body weight (− 1.2 kg) in the real-life practice [16]. As OAD treatment continued in 97% of patients after switching to Gla-300. We consider that the observed body weight reduction in the ToUP-GRADE study cannot be contributed to concomitant OADs (metformin was discontinued in seven patients and SUs were discontinued in four patients only).

The present study results should be interpreted within the context of certain limitations. They include the observational nature of the study and lack of a comparator arm, which have the potential to introduce bias and confounding into the analysis. Potential underreporting of asymptomatic hypoglycaemia cannot be excluded as a result of the observational design and unawareness of hypoglycaemia in patients with long duration of diabetes. In addition, the study population included patients with poor metabolic control and high risk of hypoglycaemia on their previous insulin regimen, which could limit extrapolating the results to other populations. On the other hand, the strengths of the ToUPGRADE study include the large real-world patient population, prospective follow-up and multicentre study design. This prospective collection of hypoglycaemic and adverse events ensures increased reliability of data when compared to retrospective real-world data analyses.

CONCLUSION

This prospective, observational study showed that Gla-300 significantly improved glycaemic control and insulin treatment satisfaction in people with type 2 diabetes who were inadequately controlled with NPH ± prandial insulin or premixed insulin analogues. Improvement of glycaemic control was associated with a very low risk of hypoglycaemia and with significant weight loss over 6 months irrespective of the previous insulin regimen. Gla-300 was well tolerated with few patients having adverse events

or discontinuing therapy. Overall, these findings are consistent with Gla-300's established efficacy and safety profile and provide new insights into Gla-300's effectiveness in patients previously treated with insulins that were not investigated before, i.e. NPH or premix insulins.

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