

# Insulin Glargine 300 Units/mL Effectiveness in Patients with T2DM Uncontrolled by Basal Insulin in Real-Life Settings in the Czech Republic

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## Abstract

**Introduction:** To evaluate the clinical effectiveness of Gla-300 units/mL (Gla-300) in the treatment of patients with type 2 diabetes (T2DM) uncontrolled by basal insulin in real-life clinical settings in the Czech Republic (TOPAZ study).

**Methods:** TOPAZ was a prospective, multi-center, non-interventional, 6-month study. Of the 312 patients screened, 289 were evaluated at month 6. The primary objective was the change of HbA1c after 6 months. The proportion of patients with HbA1c < 7.0% DCCT (< 53 mmol/mol), and those with a decrease of at least 0.5% of HbA1c at month 6, change in FPG, body weight and insulin dose at month 3 and 6 were analysed as secondary objectives. Incidence of hypoglycemia, adverse events and patient treatment satisfaction were also assessed. **Results:** HbA1c decreased significantly after 6 months (mean change 0.9% ± 1.1% DCCT [-9.9 ± 11.6 mmol/mol], p < 0.0001). HbA1c target < 7.0% DCCT was achieved in 17.6% of patients, 66.1% of patients showed mean HbA1c decrease of 0.5% ± 0.8%. At month 6, FPG decreased (mean change from baseline -1.8 ± 3.1 mmol/L) as well as the incidence of hypoglycemia decreased by 49% (p < 0.0001) while no weight gain was observed. No significant safety signals were identified. **Conclusion:** In a real-life setting, switching to Gla-300 in T2DM patients uncontrolled with other basal insulin was associated with improved glycemic control and reduced risk of hypoglycemia without weight gain, while patients' satisfaction with treatment increased.

## Keywords

Fasting Plasma Glucose, Glycated Hemoglobin, Hypoglycemia, Insulin Glargine (Gla-300 Units/MI), Real Life Data, Type 2 Diabetes (T2DM)

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## 1. Introduction

The incidence of diabetes is growing throughout the world, and this disease is a serious problem not only for patients themselves but for whole society. The global prevalence of T2DM has nearly doubled since 1980, rising from 4.7% to 8.5% in adults. This is influenced primarily by the overall lifestyle: particularly, by the increased number of obese individuals in the population [1] [2]. It is estimated that in 2040, 642 million people will suffer from diabetes worldwide [3] [4]. Lifestyle management (including medical nutrition therapy, physical activity, weight loss, counseling for smoking cessation) together with oral antihyperglycemic drugs (OADs) are fundamental aspects of diabetes care [5] [6] [7] [8]. The early introduction of basal insulin is well established, in particular when HbA1c levels are very high ( $>97$  mmol/mol [ $>11\%$ ]), symptoms of hyperglycemia are present, or there is evidence of ongoing catabolism (e.g., weight loss) [7] [8].

International diabetes management organizations (American Diabetes Association [ADA] and European Association for the Study of Diabetes [EASD]) recommend basal insulin as the most efficient therapy in patients with insufficiently controlled diabetes by non-pharmacological treatment in combination with other antidiabetic drugs [7] [8]. Glycemic control is strictly defined by ADA and EASD as level of glycated hemoglobin HbA1c (NGSP)  $< 7.0\%$  [7] [8].

Insulin glargine 300 U/mL (Gla-300), a second-generation basal insulin analog, is approved for use in adult patients with T2DM who did not reach acceptable glycemic control with current antidiabetics and non-pharmacological treatment (diet and exercise) [9], in combination with OADs. Three phase III studies compared the efficacy and safety of Gla-300 with insulin glargine 100 U/mL (Gla-100) in different populations of patients with T2DM [10] [11] [12]. EDITION 1 included participants with T2DM not adequately controlled with basal and meal-time insulin [10], EDITION 2 included participants who had previously received basal insulin in combination with OADs [11]. In EDITION 3, participants were insulin-naive, and had received only OADs [12]. In these studies, testing insulin Gla-300 versus Gla-100, a comparable glycemic control was achieved, while the incidence of hypoglycemia was lower in patients treated with Gla-300 [10] [11] [12] [13]. Nevertheless, in RCTs, outcomes do not always mirror those seen in the real world and there is growing demand for real-world data to support decision-making [14].

Although insulin Gla-300 was approved at the end of 2015, only limited data are currently available to demonstrate its efficacy and safety in real-life clinical practice in the Czech Republic.

The purpose of the present non-interventional study was to evaluate the effectiveness and safety of switching from another basal insulin to Gla-300 in patients with insufficiently controlled T2DM in real-life setting.

## 2. Materials and Methods

### 2.1. Study Design, Participants and Outcomes

TOPAZ was a prospective, multicenter, national, observational, single-arm, 6-month study to observe clinical effectiveness of Gla-300 in the treatment of T2DM patients insufficiently controlled by basal insulin in the Czech Republic. There were 312 patients screened and signed informed consent form between 25 May of 2016 and 27 September of 2017. This study was conducted in accordance with the principles laid down by the 18th World Medical Assembly [15], including all subsequent amendments and approved by appropriate ethical committees. The project was available to patients imminently planned for Gla-300 treatment as well as to patients where Gla-300 treatment was initiated 0 - 28 days before enrollment. Inclusion criteria were diagnosed T2DM, age  $\geq 18$  years, HbA1c  $> 7.6\%$  ( $>60$  mmol/mol) or repeated hypoglycemia during human basal insulin treatment, therapy with basal insulin with or without non-insulin antidiabetic drugs (for at least 3 months), signed informed consent form. Exclusion criteria were type 1 diabetes mellitus, patient receiving any prandial insulin, pregnancy and breastfeeding, current participation in interventional study, age  $< 18$  years and patients who could not attend all scheduled visits.

The primary endpoint was change in HbA1c between baseline and month 6. The secondary endpoints were: percentage of patients with HbA1c  $< 7.0\%$  ( $<53$  mmol/mol), percentage of patients with a decrease of HbA1c from baseline to month 6 of at least 0.5%, change in fasting plasma glucose from baseline to month 3 and month 6, change in body weight from baseline to month 3 and month 6, change in dose of Gla-300 from baseline to month 3 and month 6, hypoglycemia incidence (% of participants with at least one or more hypoglycemia events: symptomatic, symptomatic confirmed with plasma glucose  $\leq 3.9$  mmol/L, severe and nocturnal) and standardized event rate (calculated as number of events per patient—year), occurrence of adverse events (AEs) and serious adverse events (SAEs) during the duration of the study, and patient's treatment satisfaction (DTSQ) [16].

### 2.2. Data Collection

Following parameters were recorded at baseline: demography, age, gender, body height and weight, initial diagnosis, occurrence of diabetes complications, personal and medication history, changes in concomitant therapy at the time of Gla-300 initiation, previous and current antidiabetic therapy (OADs and insulins), level of HbA1c and fasting glycaemia (as close as possible at time before enrollment/at enrollment/before initiation of Gla-300 therapy), level of alanine aminotransferase (ALT), aspartate aminotransferase (AST), low-density lipoprotein (LDL) cholesterol, creatinine, values of fasting self-monitored blood glucose (SMBG) (last 3 available measurements), physician decision to initiate Gla-300,

Gla-300 therapy (total daily dose, time and date of therapy initiation), target FPG, recommendation of Gla-300 dose titration, hypoglycemia during 3 months before enrolment and diabetes treatment satisfaction questionnaire.

Following parameters were recorded at months 3 and 6: body weight, current antidiabetic therapy, current Gla-300 therapy, other concurrent therapy, HbA1c, fasting glycaemia, prebreakfast SMBG values (the last 3 available measurements), occurrence of hypoglycemia since the previous visit (self-reported), occurrence of adverse events since the previous visit, DTSQ at month 6. AEs and SAEs were collected during the whole study.

### 2.3. Statistics

Analysis of collected data was based on descriptive statistics, including absolute and relative frequencies of discrete variables. Continuous variables were described by count (without missing data), mean, and standard deviation, median, minimum, and maximum. Discrete variables were described by count (absolute frequency), and percentages (relative frequency). All statistical analyses were performed at the 2-sided 5% significance level or 2-sided 95% confidence intervals (CI). Null hypothesis, that the change in HbA1c from baseline to month 6 is equal to 0, was analysed by a non-parametric Wilcoxon signed-rank test, as data were not normally distributed (confirmed by Shapiro-Wilk test). Hypoglycemia event rate was calculated for each visit. As the data were not normally distributed (confirmed by Shapiro-Wilk test), the null hypothesis, that there is no difference in hypoglycemia rate in the period before baseline, before visit at month 3 and before month 6, was analysed by non-parametric Friedman test for dependent repeated measures. The data missing for each analysis were then accounted for. No imputation of missing data was performed. With assumed sample size of 259 patients, and expected 15% drop-out, it was planned to enroll total of 312 patients in the study, to obtain sufficient data to enable 90% power of analysis to yield a statistically significant result.

In this study, 2 analysis populations were defined: the full analysis set (FAS,  $n = 300$ ), and Safety Population ( $n = 312$ ). FAS included all eligible subjects, who had to meet all inclusion and no exclusion criteria and who should have taken at least one dose of Gla-300. If a patient was incorrectly included in the study, he/she was excluded from FAS according to ICH E9 Guideline [17]. The Safety Population consisted of patients who have signed an informed consent form and who have taken at least one dose of Gla-300. Safety population was used for evaluation of the incidence of hypoglycemia, occurrence of AEs and SAEs, and DTSQ questionnaires. No interim analyses were performed.

### 3. Results

Overall, of the 312 patients who were screened and signed informed consent form between 25 May of 2016 and 27 September of 2017 at 55 sites, 23 patients were prematurely withdrawn from the study. Therefore, 300 evaluable patients were available for analysis at baseline, 296 patients at month 3 and 289 patients at month 6.

### 3.1. Baseline Patients' Characteristics

Out of 300 patients, 56.3% (169/300) were men and 43.7% (131/300) were women. The average age of patients in TOPAZ study was  $63.4 \pm 9.0$  years. Baseline patients' characteristics are summarized in **Table 1**. Basal insulins received before

**Table 1.** Baseline patients' characteristics.

Baseline characteristics	n	%	Mean $\pm$ SD	95% CI	Median
Age (years)	300		$63.4 \pm 9.0$	62.4 - 64.4	64.0
Men	169	56.3			
Women	131	43.7			
Body weight (kg)	300		$96.1 \pm 17.6$	93.1 - 98.1	95.0
BMI ( $\text{kg}/\text{m}^2$ )	299		$32.7 \pm 5.4$	32.1 - 33.3	31.8
Systolic BP (mm Hg)	300		$137.3 \pm 15.1$	135.6 - 139.0	136.0
Diastolic BP (mm Hg)	300		$74.0 \pm 9.5$	77.9 - 80.1	80.0
HbA <sub>1c</sub> (mmol/mol)	300		$72.4 \pm 10.3$	71.2 - 73.5	69.5
HbA <sub>1c</sub> (% DCCT)	300		$8.8 \pm 0.9$	8.7 - 8.9	8.5
FPG (mmol/L)	300		$9.3 \pm 2.8$	8.9 - 9.6	8.9
Creatinine ( $\mu\text{mol}/\text{L}$ )	265		$84.6 \pm 21.6$	NA	83.0
<b>Duration of diabetes</b>					
<5 years	65	22			
5 - 10 years	79	26			
>10 years	156	52			
Initial dose of insulin glargine 300 U/mL	300		$27.1 \pm 12.2$	25.7 - 28.5	24.0
<b>OAD treatment</b>					
metformin	249	83			
sulfonylurea	129	43			
pioglitazone	13	4			
DPP-4 inhibitors	102	34			
glinides	9	3			
$\alpha$ -glucosidase inhibitors	297	99			
SGLT2 inhibitors	37	12			
GLP1 receptor agonists	21	7			

BMI: Body Mass Index, BP: Blood Pressure, HbA<sub>1c</sub>: Glycated Hemoglobin, FPG: Fasting Plasma Glucose, SD: Standard Deviation, CI: Confidence Interval, DPP-4: Dipeptidyl peptidase 4, OAD: Oral Antidiabetic Drug, SGLT2: Sodium Glucose Linked Transporter 2, GLP1: Glucagon-like Peptide 1.

initiation of Gla-300 were mainly Gla-100 (45%), NPH (27%), and insulin detemir (28%) (supplementary **Table S1**). The most frequent complications of diabetes were: neuropathy in 75 (25%) of patients, followed by nephropathy in 53 (18%), retinopathy in 49 (16%), diabetic foot syndrome in 7 (2%) and amputation of the lower limb in 1 (0.3%) of patients. Patients reported following comorbidities: hypertension in 265 (88%), dyslipidemia in 248 (83%), ischemic heart disease in 61 (20%), hypothyroidism in 36 (12%), myocardial infarction in 29 (10%), lower extremity peripheral artery disease in 24 (8%), heart failure in 16 (5%), stroke in 12 (4%), transient ischemic attack in 10 (3%) and hyperthyroidism in 1 (0.3%) patient.

### 3.2. Effectiveness of Gla-300 Treatment

Mean HbA<sub>1c</sub> was  $8.8 \pm 0.9\%$  ( $72.4 \pm 10.3$  mmol/mol) at baseline and  $7.9\% \pm 1.1\%$  ( $62.5 \pm 11.8$ ) mmol/mol after 6 months of Gla-300 treatment (**Table 2**).

**Table 2.** Summary of key efficacy parameters and the daily dose of Gla-300 U/mL in U/day and in U/kg/day. Table includes descriptive statistics for HbA<sub>1c</sub> in the whole cohort of patients at baseline and at month 6 and for Fasting Plasma Glucose at baseline and months 3 and 6. HbA<sub>1c</sub> was also analyzed for subgroups of patients reaching HbA<sub>1c</sub> below and above 53 mmol/mol (7%) and with HbA<sub>1c</sub> decrease of more and less than 0.5%.

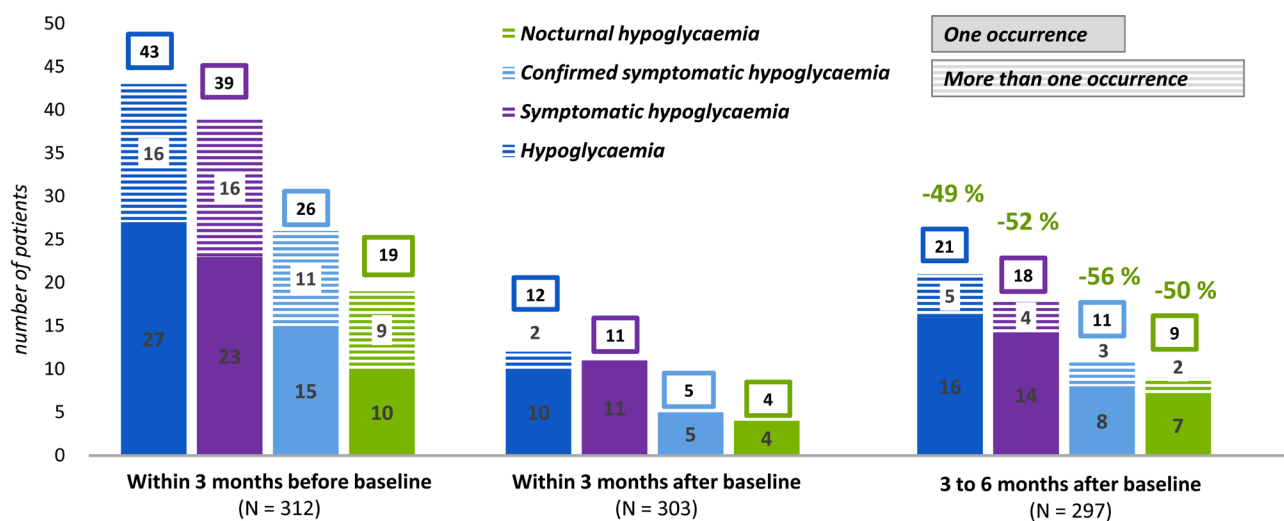
Variable	n (%)	Mean $\pm$ SD	95% CI	Min	Max	Median
HbA <sub>1c</sub> at baseline (mmol/mol)	300 (100%)	72.4 $\pm$ 10.3	71.2 - 73.5	61.0	121.0	69.5
HbA <sub>1c</sub> at baseline (% DCCT)	300 (100%)	8.8 $\pm$ 0.9	8.7 - 8.9	7.7	13.2	8.5
HbA <sub>1c</sub> at month 6 (mmol/mol)*	289 (96.3%)	62.5 $\pm$ 11.8	61.1 - 63.9	30.0	115.0	60.0
HbA <sub>1c</sub> at month 6 (% DCCT)*	289 (96.3%)	7.9 $\pm$ 1.1	7.7 - 8.0	4.9	12.7	7.6
HbA <sub>1c</sub> < 53 mmol/mol at month 6	51 (17.6%)	49.1 $\pm$ 3.7	48.1 - 50.2	30.0	52.0	50.0
HbA <sub>1c</sub> $\geq$ 53 mmol/mol at month 6	238 (82.4%)	65.4 $\pm$ 11.0	64.0 - 66.8	53.0	115.0	62.0
HbA <sub>1c</sub> < 7% at month 6	51 (17.6%)	6.7 $\pm$ 0.3	6.6 - 6.7	4.9	6.9	6.7
HbA <sub>1c</sub> $\geq$ 7% at month 6	238 (82.4%)	8.1 $\pm$ 1.0	8.0 - 8.3	7.0	12.7	7.8
HbA <sub>1c</sub> decrease of at least 0.5% at month 6	191 (66.1%)	7.5 $\pm$ 0.8	7.3 - 7.6	4.9	12.7	7.3
HbA <sub>1c</sub> decrease of less than 0.5% at month 6	98 (33.9%)	8.7 $\pm$ 1.1	8.5 - 8.9	7.4	12.1	8.5
FPG at baseline (mmol/L)	300 (100%)	9.3 $\pm$ 2.8	8.9 - 9.6	3.0	22.4	8.9
FPG at month 3 (mmol/L)	295 (98.3%)	7.8 $\pm$ 2.3	7.5 - 8.1	3.8	20.1	7.3
FPG at month 6 (mmol/L)	289 (96.3%)	7.5 $\pm$ 2.1	7.3 - 7.8	3.9	15.7	7.1
Dose of Gla-300 at baseline (U/day)	300 (100%)	27.1 $\pm$ 12.2	25.7 - 28.5	8	80	24.0
Dose of Gla-300 at month 3 (U/day)	295 (98.3%)	30.9 $\pm$ 12.9	29.4 - 32.4	8	84	28.0
Dose of Gla-300 at month 6 (U/day)	289 (96.3%)	33.7 $\pm$ 13.8	32.1 - 35.3	8	80	32.0
Dose of Gla-300 at baseline (U/kg/day)	300 (100%)	0.29 $\pm$ 0.12	0.27 - 0.30	0.07	0.82	0.27
Dose of Gla-300 at month 3 (U/kg/day)	295 (98.3%)	0.33 $\pm$ 0.13	0.31 - 0.34	0.08	0.84	0.31
Dose of Gla-300 at month 6 (U/kg/day)	289 (96.3%)	0.36 $\pm$ 0.14	0.34 - 0.37	0.08	0.91	0.34

\*Statistically significant change of HbA<sub>1c</sub> from baseline ( $p < 0.0001$ ); FPG analysis was exploratory HbA<sub>1c</sub> Glycated Hemoglobin, FPG: Fasting Plasma Glucose, SD: Standard Deviation, CI: Confidence Interval.

This decrease of HbA1c (mean change  $-0.9\% \pm 1.06\%$  ( $-9.9 \pm 11.6$  mmol/mol) was statistically significant ( $p < 0.0001$ ). After 6 months of treatment with Gla-300, 17.6% (51/289) of patients uncontrolled on previous basal insulin achieved HbA1c target  $< 7.0\%$  DCCT ( $< 53$  mmol/mol) (Table 2). Mean HbA1c change from baseline to month 6 in patients with HbA1c  $< 7.0\%$  was more than double the HbA1c change in patients with HbA1c  $\geq 7.0\%$  ( $-1.77\% \pm 0.9\%$  versus  $-0.72\% \pm 1.0\%$ ). Decrease in HbA1c from baseline to month 6 of at least 0.5% was detected in 66.1% (191/289) of patients (Table 2). In this group of patients, mean HbA1c change was  $-1.47\% \pm 0.8\%$ , while in the second group of patients with HbA1c change below 0.5%, the mean HbA1c change was  $+0.2\% \pm 0.6\%$ .

FPG decreased after 3 months of Gla-300 treatment (mean change from baseline  $-1.5 \pm 3.0$  mmol/L) and persisted to month 6 (mean change from baseline  $-1.8 \pm 3.1$  mmol/L) as described in Table 2. Body weight was stable during the whole study, mean weight change from baseline to month 6 was  $0.09 \pm 4.1$  kg. During insulin titration in the study, the mean daily dose of Gla-300 increased from  $27.1 \pm 12.2$  U at baseline to  $30.9 \pm 12.9$  U at month 3 and to  $33.7 \pm 13.8$  U at month 6 (Table 2 and supplementary Figure S1). Mean change of daily dose from baseline to month 3 was  $3.7 \pm 5.8$  U and from baseline to month 6 was  $6.6 \pm 6.5$  U.

Analysis of hypoglycemia occurrence was performed in the Safety Population ( $n = 312$ ). Hypoglycemia occurrence decreased by half after Gla-300 therapy initiation as shown in Figure 1. The lowest hypoglycemia occurrence was observed in period between baseline and month 3 in all hypoglycemia categories. Although patients had reported hypoglycemia more frequently during the period between month 3 and month 6, hypoglycemia occurrence in all assessed categories did not reach the level observed at baseline. Differences among the mean ranks of hypoglycemia event rate that were 2.10 before baseline, 1.93 before visit at month 3 and 1.98 before visit at month 6 was statistically significant ( $p < 0.001$ ) as confirmed by Friedman test.

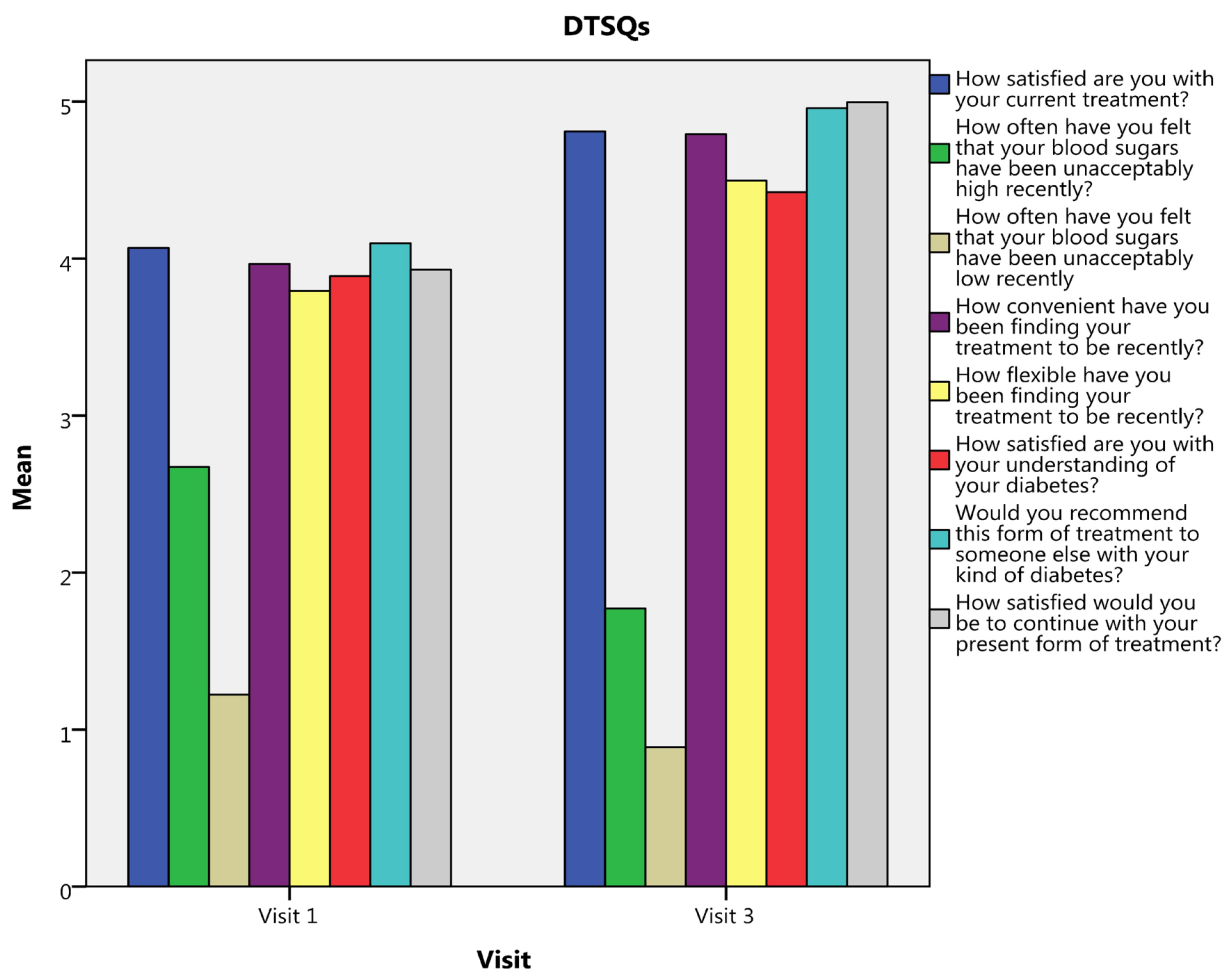


**Figure 1.** Hypoglycemia occurrence. Four hypoglycemia categories were evaluated separately. Each column represents the total number of hypoglycemia and ratio of cases of just one occurrence (full part of columns) and the number of cases with more than one hypoglycaemia event (hatched part of column). Moreover, in month 6, percentage change from baseline is presented directly in the figures.

Patients' satisfaction increased after Gla-300 treatment initiation, as assessed by Total Treatment Satisfaction Scale in DTSQ. Patients rated their satisfaction by  $23.7 \pm 7.5$  points (mean) in Total Status Scale at baseline, by  $28.5 \pm 5.4$  points (mean) at month 6, and the mean change (all means) between month 6 and baseline was  $11.1 \pm 5.3$  points ( $p < 0.0001$ ). **Figure 2** shows responses to individual DTSQ questions at baseline and after 6 months of Gla-300 treatment.

### 3.3. Safety of Gla-300 Treatment

Overall, 8 AEs (acute gastroenteritis, venous ulcer, worsening of T2DM control, cold, carpal tunnel surgery, microbial eczema, insufficient effect of Gla-300, minor brain ischemia) and 6 SAEs (basalioma, stroke, hernia in scar, embolism and thrombosis of lower limb artery, atrial fibrillation, subacute MI) were reported during the study in 13 patients. One patient experienced 2 SAEs, therefore no AE/SAE was observed in 95.7% (287/300) of study participants. Out of all 14 AEs observed, 6 (42.9%) were of mild intensity, 6 (42.9%) were moderate and 2 (14.3%) were severe. Investigators suspected Gla-300 to be related with 2 AEs (worsening of diabetes control and insufficient effect of Gla-300). These 2 AEs and 1 SAE (stroke) resulted in premature treatment discontinuation.



**Figure 2.** Patients' satisfaction with treatment (means for DTSQs questions) at baseline and at month 6.



## 4. Discussion

Real-world studies provide information that is complementary to randomized clinical trials (RCTs) and may be more generalizable and pertinent to clinicians and healthcare-delivery systems [18]. The present study was designed to comprehensively describe the use of Gla-300 in the management of T2DM in real-life conditions in Czech Republic. The primary objective of the study was to evaluate the effectiveness and safety of switching to Gla-300 from any other basal insulin over a 6 months observational period in T2DM patients.

In this study, Gla-300 (Toujeo<sup>®</sup>) treatment in real-life settings was associated with outcomes comparable with those reported from phase III clinical trials program EDITION [10] [11] [12]. Decrease of HbA1c after 6-month treatment was statistically significant. After 6 months of treatment with Gla-300, 17.6% of patients uncontrolled on previous basal insulin achieved HbA1c target < 7.0% DCCT (<53 mmol/mol). Furthermore, two thirds of patients benefited from substantial mean HbA1c decrease. This was a subgroup of patients in whom HbA1c level decreased more than 0.5% during 6-month treatment. In patients who reached the ADA and EASD (7) recommended level of HbA1c < 7.0% at month 6, we observed more than double the HbA1c change in comparison to those with HbA1c ≥ 7.0%. Other clinical parameters showed favorable profile during 6-month Gla-300 treatment.

Study objectives and population similar to those in the TOPAZ study were previously evaluated in clinical trial EDITION 2, which compared the efficacy and safety of Gla-300 with Gla-100 in people with T2DM, using basal insulin (≥42 units/day) plus oral antihyperglycemic drugs [11]. In the EDITION 2 study, the authors reported HbA1c decrease in patients treated by Gla-300. Except for the concept of clinical trial versus real-world non-interventional study, EDITION 2 differs from TOPAZ study in baseline HbA1c level (means) 8.24% (66.6 mmol/mol) versus 8.8% (72.4 mmol/mol), and in the population of patients with and without oral antihyperglycemics. In the meta-analysis of three Gla-300 clinical trials EDITION 1 - 3, published by Ritzel [19], HbA1c change (mean) from baseline to month 6 in insulin Gla-300 group was similar to the TOPAZ result. Conversely, the proportion of participants who reached target HbA1c < 7.0% (<53 mmol/mol) was much higher in EDITION 2 (30.6%) and in meta-analysis (36.2%) performed by Ritzel [19] than in the TOPAZ study (17.6%). Lower target HbA1c attainment in the TOPAZ study may be caused by higher baseline HbA1c level, as TOPAZ inclusion criteria demanded HbA1c > 7.6% (60 mmol/mol) or repeated hypoglycemia during human basal insulin treatment. Also, dose optimization may not be the same in real-life than in treat-to-target studies, but other factors could be also relevant. The other clinical parameters were similar in EDITION 2 [11], meta-analysis [19] and TOPAZ study after 6-month of Gla-300 treatment: improvement of fasting plasma glucose and no weight gain.

Moreover, meta-analysis of three EDITION clinical trials after 12 months of Gla-300 treatment has recently been published by Ritzel [20], where mean HbA1c change from baseline to month 12 was -0.91% (-9.95 mmol/mol). Although the

dose of Gla-300 after 12 months of treatment slightly increased, clinical benefits, including lowering risk of hypoglycemia and favorable safety profile of Gla-300 treatment were sustained in a broad population of people with T2DM over 12 months [20].

Recently, Zhou *et al.* (2018) published results of a retrospective cohort study comparing the real-world clinical and healthcare-resource utilization (HCRU) data in patients with type 2 diabetes using basal insulin (BI) who switched to Gla-300 or another BI [14]. They reported significant decrease of HbA1c during 6 months of insulin treatment, and the decrease was similar in both matched cohorts (Gla-300 and BI). Significantly fewer patients using Gla-300 experienced hypoglycemia compared to those using other BIs. Patients switching to Gla-300 had a significantly lower incidence of HCRU related to hypoglycemia. All-cause and diabetes-related hospitalization and emergency department HCRU were also favorable for Gla-300. These results are consistent with those observed in the TOPAZ study, except for HCRU, which was not evaluated in TOPAZ [14]. The observation of the lowest hypoglycemia occurrence with Gla-300 versus another basal insulin in period between baseline and month 3, therefore after the insulin switch, is in accord with BRIGHT study, by Rosenstock recently published first head-to-head randomized controlled trial, comparing Gla-300 and insulin degludec, which showed lower hypoglycemia incidence in favor of Gla-300 during the titration period [21].

According to Gla-300 (Toujeo<sup>®</sup>) Summary of Product Characteristics, as for all insulins, hypoglycemia is a common side effect [9]. Results from clinical trials demonstrated that the incidence of confirmed hypoglycemia was lower in patients treated with Gla-300, compared to Gla-100, in patients with type 2 diabetes treated in combination with either a non-insulin anti-hyperglycemic medicinal product (18% risk reduction) or mealtime insulin (21% risk reduction) [11]. The occurrence of hypoglycemia in the TOPAZ study decreased during Gla-300 treatment in comparison to the baseline level, and lower hypoglycemia occurrence persisted during the whole observed period to the end of the study.

The incidence of AEs/SAEs during Gla-300 treatment in the TOPAZ study was low: 8 AEs (2.6% of patients) and 6 SAEs (2.0% of patients) were reported during the study, 3 patients (1.0%) discontinued Gla-300 treatment prematurely because of AE/SAE, and 2 AEs (0.6%) were related to Gla-300 treatment according to physician judgement. In meta-analysis of all Gla-300 clinical trials [19], the following AEs/SAEs frequencies were reported: 57.3% AEs and 5.2% SAEs in total and 1.4% patients were withdrawn from the study due to AEs/SAEs. In the EDITION 2 study [11], 1.7% AEs were related to the study treatment. In the TOPAZ study, participating physicians were obliged to record all the adverse events on every visit, as described in the protocol. However, diabetes care in the Czech Republic is performed almost exclusively by specialists in diabetology and not by general practitioners, who are usually much better informed about all patients' comorbidities, and who coordinate healthcare provided to a patient by other specialists. In a meta-analysis published by Ritzel [19], the most common AEs

were: nervous system disorders, gastrointestinal disorders, musculoskeletal and connective tissue disorders, general disorders and administration site conditions. These AEs were different from those we observed in our study. Only two AEs related to Gla-300 treatment in the TOPAZ study were associated with diabetes (worsening of diabetes control and insufficient treatment efficiency). Overall, no new, or major safety signals were observed during treatment in TOPAZ study. High patient satisfaction assessed by DTSQ was reported in the TOPAZ study and in both Gla-300 and Gla-100 patient groups of the EDITION 2 study [11].

It is widely accepted that observational studies may play an important role in providing real-life outcomes, particularly in large cohorts with complex chronic diseases such as diabetes mellitus. Besides the strength of the dataset, the prospective collection of presented data on effectiveness and safety of Gla-300 there are some limitations to the current analysis deserving consideration. In the observational uncontrolled study design, we can't distinguish between the specific effects of the treatment and non-specific effects associated with the enrollment into the study. We thus do not suggest any causality between the observed effects and the switch to glargine 300 U/mL. Our findings should be exclusively understood as the association between the study outcomes and initial insulin switch. Another study limitation may be represented by probable underreporting AEs including hypoglycemia by physicians specialized in diabetes care, and patients not discussing their health conditions other than associated with diabetes with investigators. In the Czech Republic, health conditions reported as AEs in the Gla-300 clinical trials [19] and general disorders are typically discussed with general practitioners or physicians with other specialties.

The strength of the TOPAZ study was that most of the endpoints were objective clinical laboratory values (HbA1c, FPG), or parameters (weight, dose). Furthermore, the number of enrolled patients was sufficient to enable 90% power of analysis to yield a statistically significant result.

## 5. Conclusion

In conclusion, in 300 Czech patients with T2DM uncontrolled by another basal insulin, switching to the second-generation basal insulin analogue glargine 300 U/mL was associated with statistically and clinically significant HbA1c reduction, less hypoglycemia, no weight change and increased patients' satisfaction. Our results suggest that beneficial effects of Gla-300 shown in randomized controlled trials may be observed also in real-life settings.

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tional Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

### Conflicts of Interest

M.P. has served as consultant for Abbott, AstraZeneca, Boehringer Ingelheim, Dexcom, Eli Lilly, Medtronic, Novo Nordisk, Roche, Sanofi, and Takeda and is on Speakers Bureaus for Abbott, Boehringer Ingelheim, Dexcom, Eli Lilly, Medtronic, Novartis, Novo Nordisk, Roche, Sanofi and Teva. P.J. is employee and stockholder of Sanofi. J.M. is an employee of NEOX Clinical Research—clinical research organization that provided the following services funded by the sponsor: data management, statistical analyses and medical writing.

### Compliance with Ethics Guidelines

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

### Author's Contribution

M.P. undertook main study supervision, participated in study design, discussed the data and their interpretation, participated in writing, editing and critical review of the manuscript; and gave final approval of the manuscript. M.F. participated in study design, conducted the clinical trial and collected data, reviewed, edited and revised manuscript drafts; and gave final approval of the manuscript. P.J. participated in study design, participated on data acquisition, reviewed, edited and revised manuscript drafts; and gave final approval of the manuscript. J.M. participated on data acquisition, discussed the data and their interpretation, reviewed, edited and revised manuscript drafts; and gave final approval of the manuscript.

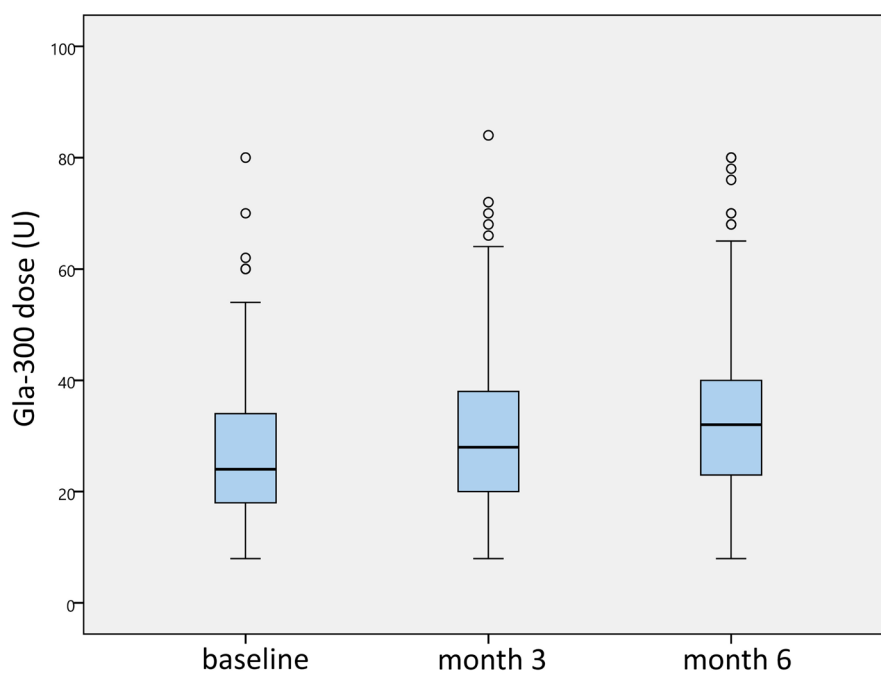
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## Appendix



**Figure S1.** Mean change of daily dose from baseline to month 6.

**Table S1.** Basal insulin treatment before initiation of Gla-300.

Types of insulins	Patients (n)	Patients (%)	Mean dose (U)	Median dose (U)	Administration/day
NPH human insulin	80	26.7%	20	20	1
Insulin glargine 100 U/ml	135	45.0%	29	26	1
Insulin detemir	84	28.0%	24	22	1
Insulin degludec	0	0.0%			
Other insulin analogue - Abasaglar	1	0.3%	16	16	1
Total	300	100.0%	26	22	1