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ORIGINAL RESEARCH

Improved Glycemic Control with Insulin Glargine 300 U/mL (Toujeo®) in Patients with Type 2 Diabetes: Real-World Effectiveness in Switzerland

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ABSTRACT

Introduction: Insulin glargine 300 U/mL (Gla-300, Toujeo®) is a long-acting, once-daily basal insulin with improved—more stable and smoother—pharmacokinetic and pharmacodynamic profiles compared to insulin glargine 100 U/mL (Gla-100) and insulin degludec (IDeg). These properties have been shown to translate into an effective HbA1c reduction with the advantage of a lower risk of hypoglycemia in randomized controlled trials of Gla-300 versus Gla-100. In this study, we assessed the effectiveness and safety of Gla-300 under real-world conditions in Switzerland.

Methods: The prospective, observational, open-label, multicenter study TOP-2 explored the effectiveness of Gla-300 in adult patients with type 2 diabetes (T2D) uncontrolled (HbA1c 7.5–10%) on their previous basal insulin in Germany, Austria, and Switzerland. The primary endpoints were the percentages of patients achieving a fasting plasma glucose (FPG) of ≤ 6.1 mmol/L after 6 and 12 months. Secondary endpoints included changes in HbA1c, FPG, body weight, and insulin dose as well as hypoglycemia incidence and safety. Here we report the results for the Swiss patient cohort after 12 months of treatment with insulin glargine 300 U/mL.

Results: The 62 patients (33 men) had a mean age of 65 years, a mean diabetes duration of 14 years, a mean body mass index (BMI) of 31 kg/m^2, and were mainly switched from Gla-100 (44%) to Gla-300. The most common concomitant oral anti-diabetes therapy was metformin (65%). The mean individual HbA1c target chosen by the investigators was 7.4%. After 12 months of therapy, Gla-300 significantly reduced mean HbA1c from 8.2% to 7.6% ($p < 0.0001$). Likewise, Gla-300 significantly reduced mean FPG from 9.1 mmol/L to 7.4 mmol/L ($p < 0.0001$). At study end, 32% of patients achieved FPG ≤ 6.1 mmol/L, 55% achieved FPG ≤ 7.2 mmol/L , and 57% achieved their individual HbA1c target. Gla-300 was uptitrated to a mean dose of 40 units per day. Symptomatic hypoglycemia incidence after 12 months was low at 9.7% and a rate of 0.23 events per patient year. Body weight remained stable and was not significantly altered during the study.

Conclusion: Upon switching basal insulin to Gla-300, overall glucose control significantly

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improved and glycemic targets were achieved with a low rate of hypoglycemia in T2D patients under real-world conditions in Switzerland.
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Keywords: Insulin glargine 300 U/mL; Real-world; Switzerland; Type 2 diabetes

INTRODUCTION

The treatment of patients with diabetes mellitus remains a major challenge for physicians and care providers. In 2017, 1 in 11 adults was estimated to suffer from diabetes, and the global prevalence is expected to rise to over 600 million patients in 2045, the majority of whom will be affected by type 2 diabetes (T2D) [1]. In recent years, a considerable number of treatment options have emerged, allowing for individualized care and improving clinical outcomes for patients with type 2 diabetes.

However, despite new antidiabetic drugs such as DPP-4 inhibitors, SGLT-2 inhibitors, or GLP-1 receptor agonists that have been shown to improve glycemic control, disease progression often ultimately necessitates the initiation of an insulin regimen. Insulin glargine 300 U/mL (Toujeo®, Sanofi–Aventis) is a basal insulin analog with improved properties, including more stable and smoother pharmacokinetic and pharmacodynamic profiles compared to insulin glargine 100 U/mL and insulin degludec 100 U/mL [2–4]. In the EDITION phase III program, these properties translated into an unaltered efficacy in terms of HbA1c reduction but with less hypoglycemia vs. Gla-100 [5]. Notably, in EDITION 2, patients with T2D on basal insulin supported oral therapy who switched to Gla-300 showed a 27% risk reduction for any hypoglycemia from baseline to month 6. Furthermore, patients with Gla-300 experienced significantly less weight gain than patients with Gla-100 [6]. These results suggested a relevant treatment benefit for patients with T2D uncontrolled on basal insulin supported oral therapy who switched to Gla-300, as hypoglycemia and weight gain are important barriers to insulin therapy initiation, adherence, and intensification.

A recently published head-to-head study in insulin-naïve patients with T2D corroborated the efficacy of Gla-300 with the advantage of a lower risk of hypoglycemia versus IDeg. The HbA1c reduction was similar with both basal insulin analogs [7, 8]. However, with Gla-300, the incidence and event rate for confirmed hypoglycemia (< 3.0 mmol/L) at any time of the day were significantly reduced by 37% and 43% compared to IDeg during the titration phase [8, 9].

For the evaluation of efficacy and safety, randomized controlled trials (RCT) remain the "gold standard," and are pivotal for regulatory bodies in the drug approval process [10]. Nonetheless, the intensive monitoring and education provided during the RCTs are not always representative of daily clinical practice [11]. A gap has been identified between efficacy in RCTs and effectiveness in real-world data for GLP-1 receptor agonists and DPP-4 inhibitors. Limited resources and poor medication adherence in the real world may largely account for this finding [12]. Thus, the external validity of results obtained from RCTs needs to be confirmed in a "real-life" setting such as non-interventional trials. Non-interventional observational studies with less restrictive inclusion/exclusion criteria can include broader populations of patients and offer an important tool to better assess the real-world effectiveness of a drug [13]. Retrospective real-world evidence gathered with Gla-300 has already demonstrated a glucose control improvement along with a lower risk for hypoglycemia as compared to other basal insulins [14–16]. In this study we aimed to prospectively investigate the effectiveness and safety of Gla-300 in patients with T2D in Switzerland after 6 and 12 months in real-life conditions. The results for the German study cohort were recently presented at the 78th Scientific Sessions of the American Diabetes Association [17].

METHODS

Study Population and Methods

The prospective, observational, open-label, multicenter study TOP-2 explored the

effectiveness of Gla-300 (Toujeo®) in adult patients with T2D uncontrolled on their previous basal insulin supported oral therapy (BOT) in Germany, Austria, and Switzerland. In this study, we present the data for the Swiss patient cohort that started Gla-300 between November 2015 and December 2016 in 28 participating centers. Patients with T2D were documented if their HbA1c was $\geq$ 7.5% and $\leq$ 10.0%, age was $\geq$ 18 years, previous insulin was any other basal insulin than Gla-300, and if they were able to self-measure blood glucose levels. Patients were not to be documented if they had type 1 diabetes, any existing basal insulin regimen that included prandial insulin (e.g., basal bolus therapy), if Gla-300 was contraindicated, or if the patients were pregnant, had cancer, or a history of alcohol or drug abuse. All patients provided written informed consent, and the study was approved by independent local ethical committees. All procedures carried out were in line with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Declaration of Helsinki of 1964, as revised in 2013 [18].

A contract research organization (AKP, Freiburg, Germany) was responsible for managing the study sites in Germany, Austria, and Switzerland. Investigators were general practitioners and specialists in internal medicine, endocrinology, or diabetology. All study sites documented patient data in web-based electronic case report forms (eCRF). The observation plan included three major documentations at baseline (documentation 1), 6 months (documentation 2), and 12 months (documentation 3) after the start of Gla-300.

The observation plan did not give any recommendation on how to switch patients from their previous basal insulin to Gla-300; nor did it provide any titration algorithm. According to the Swiss summary of product characteristics, Toujeo® is indicated for the treatment of adult patients with diabetes. It is injected subcutaneously once daily at any time of the day, but preferably at the same time every day. A transition from once-daily insulin to Gla-300 can be done on a unit-to-unit basis. If the preexisting insulin is injected twice daily, a 20% dose reduction in the total daily dose of the previous insulin is recommended. Investigators were able to modify treatment according to their clinical judgment at any point during the study. Documentation ended prematurely if the treatment regimen BOT was discontinued or changed.

Outcome Measures

The primary endpoints were the percentages of patients achieving a fasting plasma glucose (FPG) of $\leq$ 6.1 mmol/L after 6 and 12 months. Secondary endpoints included changes in HbA1c, FPG, body weight, and insulin dose as well as hypoglycemia incidence and overall safety.

Statistical Analyses

The study being observational, no hypotheses were pre-specified, and no sample size or power calculations were carried out. Baseline characteristics and demographics were reported as the mean $\pm$ SD or percentage, as appropriate, and were based on the full analysis set 2 (FAS2), including all patients with written informed consent who had at least one documented dose of Gla-300 at any time, initiated Gla-300 not more than 2 weeks before the first documentation, had a baseline HbA1c $\leq$ 10%, and fulfilled all inclusion/exclusion criteria. Descriptive statistics of continuous variables were compared using a two-tailed paired *t*-test.

RESULTS

Study Population Demographics and Clinical Characteristics

A total of 62 patients completed all three major documentations. Baseline demographics and clinical characteristics are specified in Table 1. Mean age was 65 $\pm$ 11 years, mean BMI was 31 $\pm$ 6 kg/m^2, and the majority of the patients had a history of long-standing T2D, i.e., a diabetes duration > 10 years. Twenty-seven patients (44%) had Gla-100, 17 patients (27%) had insulin detemir, 11 patients (18%) had insulin

Table 1 Baseline characteristics of the Swiss TOP-2 cohort

	Mean ± SD or as indicated
Age, years	65 ± 11
Male, *n* (%)	33 (53)
Diabetes duration, years	14 ± 7
Body weight, kg	87 ± 16
BMI, kg/m^2	31 ± 6
FPG, mmol/L	9.1 ± 1.9
HbA1c, %	8.2 ± 0.8
Individual HbA1c target, %	7.4 ± 0.9
Oral antidiabetic drugs, n (%)	60 (97)
Metformin	40 (65)
Metformin/DPP-4 inhibitor	10 (16)
Metformin/glitazone	4 (7)
Sulfonylurea	12 (19)
DPP-4 inhibitor	9 (15)
GLP-1 receptor agonist	7 (11)
SGLT-2 inhibitor	5 (8)
Previous basal insulin dose	
Units/day	33 ± 18
Units/kg/day	0.39 ± 0.18
Previous basal insulin, n (%)	57 (92)
Insulin glargine 100 U/mL	27 (44)
Insulin detemir	17 (27)
Insulin degludec	11 (18)
NPH	2 (3)

BMI body mass index, *DPP-4* dipeptidyl peptidase-4, *SGLT-2* sodium-glucose cotransporter-2, *GLP* glucagon-like peptide-1, *NPH* neutral protamine Hagedorn

degludec, and 2 patients (3%) had NPH insulin before transitioning basal insulin to Gla-300 (see Table 1). The previous insulin was not specified in 4 cases and premixed insulin was reported in 1 case. The investigators determined an individual HbA1c target of 7.4 ± 0.9% for this patient cohort. Non-insulin antihyperglycemic treatment remained stable throughout the study (see Fig. 1).

Real-World Effectiveness Outcomes

Switching basal insulin to Gla-300 significantly improved glycemic control and reduced mean FPG levels from 9.1 mmol/L at baseline to 7.6 mmol/L ($p < 0.0001$) at 6 months and 7.4 mmol/L ($p < 0.0001$) at 12 months (see Fig. 2). Seven (11%) and 20 (32%) patients achieved the primary endpoint of FPG ≤ 6.1 mmol/L after 6 and 12 months, respectively (see Fig. 4a). Mean HbA1c decreased from 8.2% at baseline to 7.8% ($p < 0.05$) after 6 months and 7.6% ($p < 0.0001$) after 12 months (see Fig. 3). Twenty-six (42%) and 35 (57%) patients achieved a HbA1c below their individual target after 6 and 12 months, respectively (see Fig. 4b). Gla-300 was uptitrated to 40 ± 25 U/day or 0.46 ± 0.24 U/day/kg at study end (see Table 2). Body weight was not significantly altered after one year of insulin optimization (see Fig. 5).

Hypoglycemia

During the follow-up, the hypoglycemia incidence with Gla-300 remained very low. After one year of Gla-300 intensification, 6 patients (9.7%) had at least one episode of symptomatic hypoglycemia and only 1 patient with severe hypoglycemia was reported. The annual rates for symptomatic and severe hypoglycemia were 0.23 events/patient year and 0.03 events/patient year, respectively (see Table 3).

DISCUSSION

The observational TOP-2 study investigated patients with T2D who switched to Gla-300 after the failure of their previous basal insulin therapy. To our knowledge, this is the first study to explore the effectiveness and safety of Gla-300 in Switzerland. Patients were successfully switched to Gla-300 and adequately titrated afterwards. Glycemic control was significantly

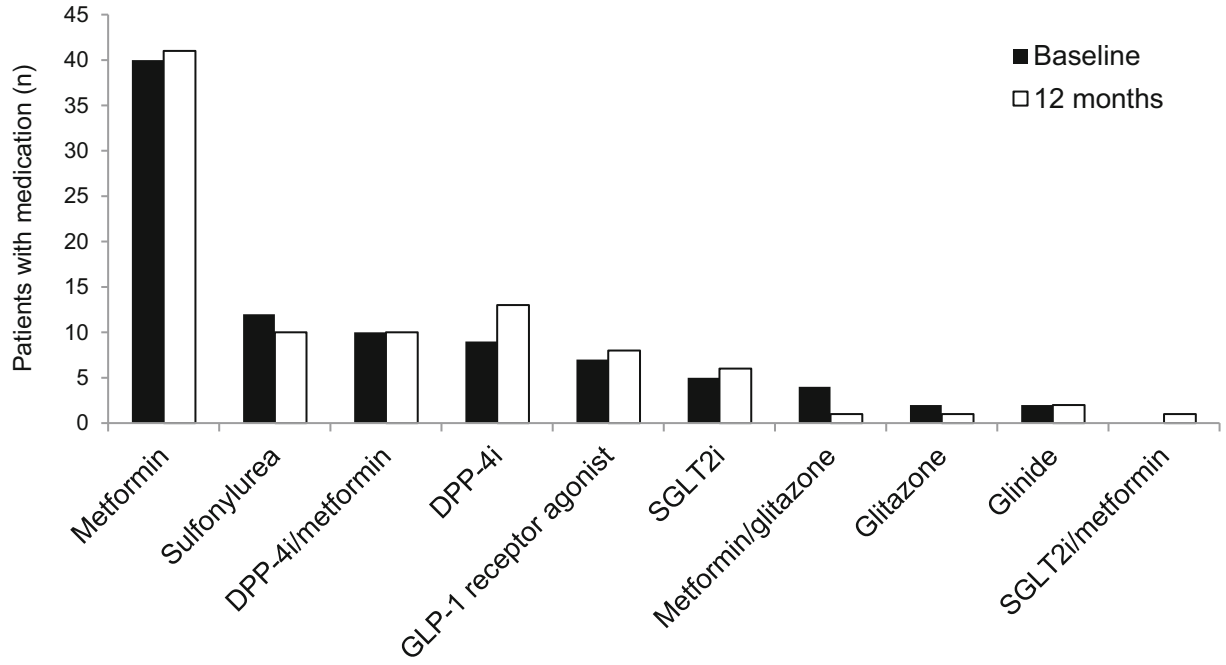

Fig. 1 Non-insulin antihyperglycemic medication at baseline and at 12 months

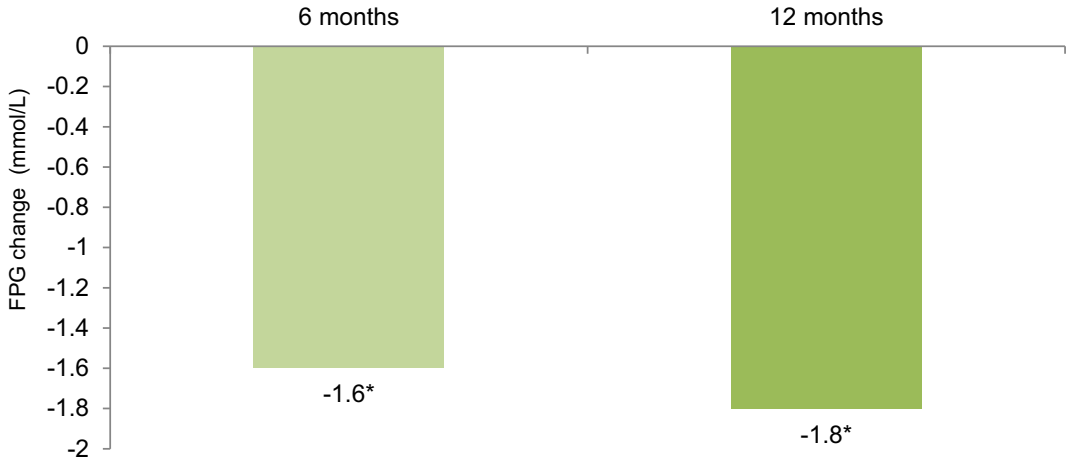

Fig. 2 Mean FPG change. *$p < 0.0001$ for mean change from baseline

improved with a very low incidence of hypoglycemia and no weight change.

Transitioning basal insulin to Gla-300 has been studied in previous trials, albeit with important differences in study design and setting. EDITION-2 was a phase 3a randomized controlled trial and DELIVER-2 was a retrospective cohort study that used propensity score matching [6, 14]. In our current non-interventional study, we were able to confirm the effectiveness of Gla-300 in a prospective real-world setting, as we observed glycemic improvements similar to those obtained previously. After 6 and 12 months of therapy with Gla-300, we observed significant mean HbA1c reductions of − 0.40% and − 0.65%, respectively, which were in line with those observed in EDITION-2 and DELIVER-2 with Gla-300. The mean individual HbA1c target chosen by the investigators was 7.4%, which is slightly

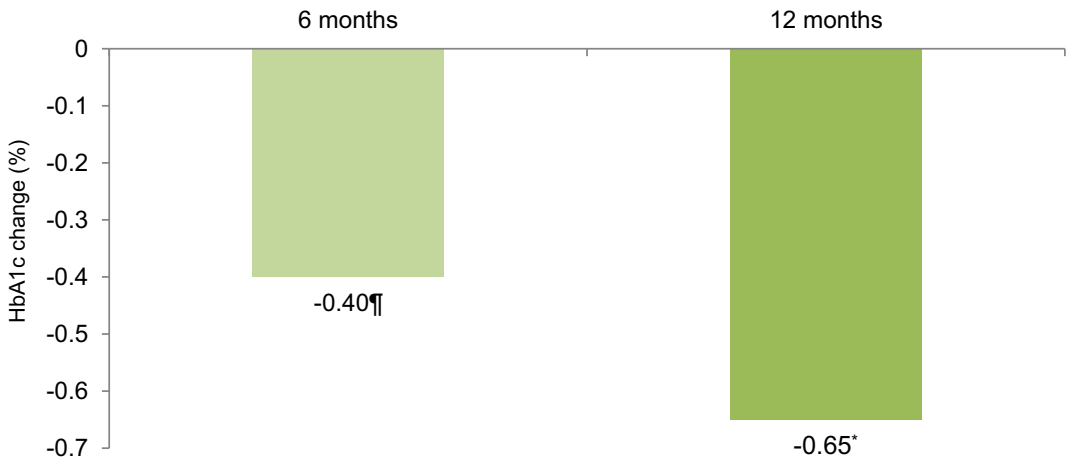

Fig. 3 Mean HbA1c change. *$p < 0.0001$ for mean change from baseline. ¶$p < 0.05$ for mean change from baseline

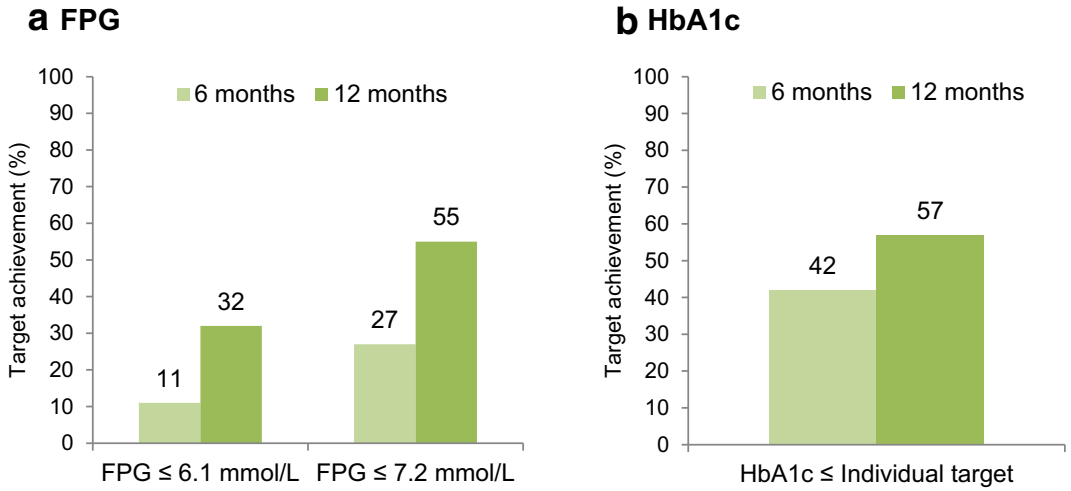

Fig. 4a–b Glycemic target achievement at 6 and 12 months. **a** Fasting plasma glucose targets. **b** HbA1c target

higher than the usual targeted of 7% but appears appropriate for the studied cohort, taking into account age and diabetes duration [19]. The majority of the patients (57%) achieved their individual HbA1c target by switching their basal insulin to Gla-300. A recently published cohort study in Switzerland (SwissDiab) provided data on the adherence to Swiss national targets for good disease management in diabetes. The authors demonstrated that the target goals were achieved by the majority of patients with type 2 diabetes, and that 77% and 44% achieved HbA1c levels of $< 8\%$ and $< 7\%$, respectively [20]. As the HbA1c target was individualized in TOP-2, rates of achievement cannot be compared directly. However, as both the target and the success rate were between the values published for the SwissDiab cohort, we would assume similarly effective glucose control with Gla-300 in TOP-2. Mean FPG levels were lowered to 7.6 mmol/L after 6 months and 7.4 mmol/L after 12 months, allowing 55% of patients to achieve FPG levels of ≤ 7.2 mmol/L, a threshold recommended by international guidelines [19].

Adequate dose titration is essential after the initiation of an insulin regimen, but is often delayed in clinical practice. This phenomenon

Table 2 Gla-300 titration

	Baseline	6 months	12 months
Gla-300 dose (units)	28.5 ± 17.0	37.6 ± 23.0	39.5 ± 25.2
p value for change from baseline		$p < 0.0001$	$p < 0.0001$
Gla-300 dose (units/kg)	0.33 ± 0.17	0.43 ± 0.22	0.46 ± 0.24
p value for change from baseline		$p < 0.0001$	$p < 0.0001$

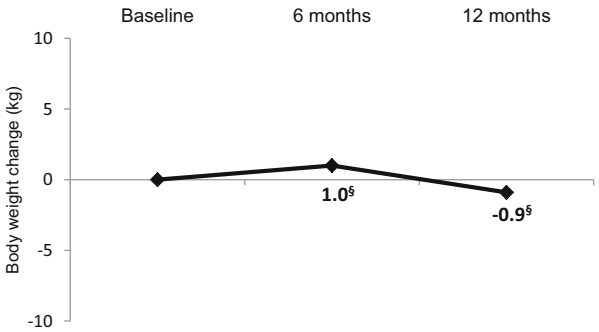

Fig. 5 Mean body weight change. §Not statistically significant for mean change from baseline

is often referred to as clinical inertia and increases with age, diabetes duration, and comorbidities [21, 22]. Multiple barriers have been identified at physician and patient levels that lead to deferred intensification. Fear of weight gain and concerns about hypoglycemia are important obstacles to address in this respect [23, 24]. First-generation basal insulin analogs such as Gla-100 were shown to provide significant advantages over NPH insulin regarding the risk for hypoglycemic events and administration [25], and recently approved second-generation basal insulins such as Gla-300 afford even greater improvements [26].

The increased glycemic control was achieved by titrating Gla-300 from a mean of 29 units per day to 38 units per day at 6 months and 40 units per day after 12 months. It is important to highlight that with the observational design in TOP-2, the titration algorithms used were completely at the investigators' discretion, and started with doses as low as 10 units per day. This contrasts with EDITION-2, where only patients with basal insulin doses of at least 42 units per day were included, and a protocol-driven titration plan was applied [6]. So, for the first time, TOP-2 prospectively followed-up on patients with low doses of Gla-300 and demonstrated its effectiveness.

Table 3 Hypoglycemia endpoints

	Baseline[a]	6 months	12 months
Symptomatic hypoglycemia			
Incidence, *n* (%)	3 (4.8)	4 (6.5)	6 (9.7)
Events, *n*	15	6	15
Rate, events/patient year (95% CI)			0.23 (0.13, 0.38)
Severe hypoglycemia			
Incidence, *n* (%)	1 (1.6)	0 (0)	1 (1.6)
Events, *n*	3	0	2
Rate, events/patient year (95% CI)			0.03 (0.00, 0.11)

[a] Baseline hypoglycemia data refer to the 12-week period before baseline, i.e., before the start of Gla-300

In TOP-2, we were able to demonstrate that the switch to Gla-300 in the real world was associated with a low incidence of hypoglycemia. During the first 6 and 12 months of therapy with Gla-300 in Switzerland, only 4 (6.5%) and 6 (9.7%) patients, respectively, experienced any hypoglycemia, resulting in an annualized rate of 0.23 events/patient year. The observed rate in our study is very low compared with the estimated global annual rate of 19.3 hypoglycemic events/patient year for patients with T2D and also with the hypoglycemia results for Gla-300 in EDITION-2 [6, 27]. This is in line with previous real-world studies on Gla-

100, which also showed a lower incidence of hypoglycemia compared to RCTs with Gla-100 [28]. It can be hypothesized that this is due to more cautious and individualized insulin titration in clinical practice than in an ambitious research environment. The low risk of hypoglycemia with Gla-300 and the significant improvements in glycemic control are of particular importance, as they indicate that a reasonable balance between safety and effectiveness can be achieved with Gla-300 in real life.

EDITION 2 provided evidence that body weight can be stabilized more effectively with Gla-300 than with Gla-100. After switching basal insulin to Gla-300, there was a significant weight benefit vs. Gla-100 which was maintained until 12 months of therapy [29]. Our study confirmed these results, as body weight remained stable throughout the trial without exhibiting any significant changes.

A limitation of the current study was the small number of patients ($n = 62$) that were followed up until 12 months. Also, at study start, only a few physicians had much practical experience with Gla-300, which had been approved in Switzerland only shortly before trial initiation. It can be assumed that the population selected comprised a particularly challenging cohort of patients, since their pre-existing basal insulin regimens had failed. The lack of a direct comparator is another limitation, as no information on the outcomes with alternative therapies is available. The question of whether the obvious benefits seen in our trial are solely a result of the properties of Gla-300 or if the root cause is improved adherence to insulin therapy/fostered insulin titration cannot be fully answered. However, the EDITION program demonstrated consistent and sustained glucose control with Gla-300 and a significantly lower risk of hypoglycemia as compared to Gla-100. In EDITION 2, these superior safety results were most prominent in the titration phase from baseline to week 8, with a relative risk reduction for any hypoglycemia at any time of the day of 23% [6]. The strengths of TOP-2 are its prospective multicenter design with observational monitoring and follow-up that can be considered representative of primary care in Switzerland.

CONCLUSION

In patients with type 2 diabetes, switching basal insulin to Gla-300 improves glycemic control, with a low incidence of hypoglycemia and no weight gain. These results confirm the effectiveness and safety of Gla-300 in a real-world setting and show that Gla-300 is a suitable therapy option in Switzerland for patients with diabetes.

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Disclosures. Peter Wiesli participated at advisory boards of Sanofi–Aventis (Suisse) SA. Marcus Schories participated at advisory boards of Sanofi–Aventis (Suisse) SA.

Compliance with Ethics Guidelines. All patients provided written informed consent and the study was approved by independent local ethical committees. All procedures carried out were in line with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Declaration of Helsinki of 1964, as revised in 2013.

Data Availability. Qualified researchers may request access to patient-level data and related study documents, including the clinical study report, study protocol with any amendments, blank case report form, statistical analysis plan, and dataset specifications. Patient-level data will be anonymized and study documents will be redacted to protect the privacy of trial participants.

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