Received: 28 June 2019 | Revised: 12 December 2019 | Accepted: 26 December 2019
DOI: 10.1111/dom.13952

ORIGINAL ARTICLE

WILEY

Effectiveness and safety of insulin glargine 300 U/mL in insulin-naïve patients with type 2 diabetes after failure of oral therapy in a real-world setting

Martin Pfohl MD[1] | François R. Jornayvaz MD[2] | Andreas Fritsche MD[3,4] | Stefan Pscherer MD[5] | Helmut Anderten MD[6] | Katrin Pegelow PhD[7] | Jochen Seufert MD[8]

[1]Department of Internal Medicine I, Evang. Bethesda-Hospital Duisburg, Duisburg, Germany

[2]Department of Endocrinology, Diabetology, Hypertension and Nutrition, University Hospital of Geneva, Geneva, Switzerland

[3]Department of Internal Medicine IV, University of Tuebingen, Tuebingen, Germany

[4]Institute for Diabetes Research and Metabolic Diseases of the Helmholtz Center Munich at the University of Tuebingen (IDM), Tuebingen, Germany

[5]Department of Internal Medicine III, Sophien- and Hufeland-Hospital, Weimar, Germany

[6]Joint Practice Anderten-Krok & Partner, Hildesheim, Germany

[7]Sanofi-Aventis Deutschland GmbH, Berlin, Germany

[8]Division of Endocrinology and Diabetology, Department of Medicine II, Medical Center – University of Freiburg, Faculty of Medicine, University of Freiburg, Germany

Correspondence
Martin Pfohl, MD, Department of Internal Medicine I, Evang. Bethesda-Hospital Duisburg, Heerstrasse 219, D-47053 Duisburg, Germany.
Email: mnpfohl@o2online.de

Funding information
Sanofi-Aventis Deutschland GmbH; German Diabetes Society; American Diabetes Association

Peer Review
The peer review history for this article is available at https://publons.com/publon/10.1111/dom.13952.

Abstract

Aim: To evaluate the effectiveness and safety of initiating basal insulin-supported oral therapy (BOT) with insulin glargine 300 U/mL (Gla-300) in patients with type 2 diabetes inadequately controlled on oral antidiabetic drugs (OADs).

Materials and Methods: This non-interventional, multi-centre, prospective 52-week study, conducted in Germany and Switzerland, documented patients with type 2 diabetes with an HbA1c of between 7.5% and 10.0%, currently treated with OADs, after the physician had decided to start a BOT regimen with Gla-300. The primary endpoint was the rate of achievement of the individualized predefined HbA1c target.

Results: Of 1748 patients included, 1153 comprised the full analysis set, of whom 721 completed documentation of 12 months of Gla-300 treatment. Twelve months after starting Gla-300, 49.9% achieved their individualized HbA1c target, and 61.1% achieved either their HbA1c target or a fasting plasma glucose (FPG) of ≤110 mg/dL. Mean HbA1c decreased by −1.22% ± 1.05% to 7.28% ± 0.92% and mean FPG by −51.5 (±48.63) mg/dl to 132.9 ± 33.0 mg/dL. Median duration of HbA1c target achievement was 341 days and probability to remain on target after 6 months was 81%. Hypoglycaemia incidence and rates remained low after 12 months of Gla-300 treatment; no severe or severe nocturnal hypoglycaemia was observed. Body weight remained unchanged.

Conclusions: Starting a BOT regimen with Gla-300 allowed about 60% of 721 German and Swiss patients with inadequately controlled type 2 diabetes to achieve glycaemic control within 12 months in daily clinical practice. Glycaemic control was achieved without weight gain or increased risk of nocturnal or severe hypoglycaemia.

KEYWORDS

glycaemic control, hypoglycaemia, insulin analogues, observational study, type 2 diabetes

1 | INTRODUCTION

Type 2 diabetes is a chronic progressive disease with increasing incidence and prevalence worldwide, resulting in a tremendous health and socioeconomic burden.[1,2] The consensus statement published by the American Diabetes Association and the European Association for the study of Diabetes in 2018 concluded that “the management of hyperglycaemia in type 2 diabetes has become extraordinarily complex with the number of glucose-lowering medications now available”, and promoted a patient-centred approach.[3] Lifestyle changes and metformin are the recommended first therapeutic steps for almost all patients with type 2 diabetes.[3] If the individual HbA1c target—usually around 53 mmol/mol (7.0%)—is not achieved with double or triple oral antidiabetic drug (OAD) therapy 3–6 months after last treatment intensification, initiation of basal insulin-supported oral therapy (BOT) is recommended. Second generation basal analogue insulins like insulin glargine 300 U/mL (Gla-300, Toujeo, Sanofi) can help to minimize the risk of experiencing hypoglycaemia when starting insulin therapy.[3] Gla-300 is a formulation of insulin glargine that delivers the same amount of insulin as insulin glargine 100 U/mL (Gla-100) in 1/3 of the volume and exhibits a longer and more evenly distributed glucose-lowering activity than Gla-100, which is considered therapeutically beneficial.[4] The efficacy and safety of initiating BOT with Gla-300 was shown in the phase 3a study EDITION 3,[5,6] but translation of the trial results into daily clinical practice has not been systematically and prospectively assessed. Therefore, Toujeo-1, an observational trial, prospectively investigated the effectiveness and safety of initiating a BOT regimen with Gla-300 in insulin-naïve patients with type 2 diabetes insufficiently controlled on OADs.

2 | METHODS

2.1 | Study design and patients

Toujeo-1 was a non-interventional, multi-centre, single-arm prospective trial with 12 months of observation conducted all over Germany and Switzerland. The trial received approval from the local ethics committees, was conducted in accordance with the Declaration of Helsinki and is registered at the ISRCTN registry (ISRCTN12809144, www.ISRCTN.org). All patients provided written informed consent. Adult patients with type 2 diabetes, insufficiently controlled with OADs (HbA1c 7.5%–10.0% [58–86 mmol/mol]), were included after their treating physician had decided to initiate a BOT regimen with Gla-300, independent from study participation. Patients aged <18 years, those with type 1 diabetes, previous insulin therapy, any contraindication for Gla-300, pregnancy, malignant disease, alcohol or drug abuse, as well as dementia or incapability of understanding the content and goals of the study, were excluded.

2.2 | Documentation

The main data collection was performed at baseline, and after approximately 6 and 12 months of treatment with Gla-300 via an electronic case report form. Additional data collected monthly included self-measured fasting plasma glucose (FPG) values with the patients' own glucometer, and insulin dose information. At baseline, physicians noted the HbA1c target they individually defined for each patient in accordance with local guidelines.[7,8] HbA1c was collected every 3–6 months, and self-measured blood glucose (SMBG) profiles were noted at baseline and after 6 and 12 months, if available. At baseline and every 3 months, physicians asked their patients if any hypoglycaemia occurred during the previous 12 weeks and noted these verbally reported hypoglycaemic events. All data had to be generated during daily clinical routines, and any therapeutic decision during the 12-month observation period was strictly left to the physician's discretion. Source data verification was performed at 27 German sites (5.5% of all sites) and two Swiss sites (9.5% of all sites). All data were validated after the end of data capture by running check programs in Statistical Analysis System version 9.4 (SAS Institute, Cary, NC, USA).

2.3 | Study endpoints

The primary efficacy endpoint was the proportion of patients achieving at least once their individually predefined HbA1c target within 1–6 and 1–12 months, respectively. Secondary efficacy endpoints included target achievement rates within 1–6 and 1–12 months for FPG (≤110 mg/dL [≤6.1 mmoL/L]), HbA1c or FPG, and HbA1c and FPG, respectively, time to and duration of glycaemic responses, absolute change from baseline to 6 and 12 months, respectively, of HbA1c, FPG, four-point SMBG profiles, body weight (BW), basal insulin doses, and of patient's treatment satisfaction (Diabetes Treatment Satisfaction Questionnaire status, [DTSQs]).[9] Safety endpoints included hypoglycaemia incidence and rates per patient-year, which were calculated for symptomatic, confirmed (SMBG value of ≤70 mg/dL [≤3.9 mmol/L]) symptomatic, nocturnal (symptomatic or confirmed hypoglycaemia occurring approximately between 10:00 PM and 06:00 AM, while the patient was asleep), severe (assistance of another person required or an SMBG value of ≤56 mg/dL [≤3.0 mmol/L]), and severe nocturnal hypoglycaemia, as well as incidence of adverse events (AEs), including serious adverse events (SAEs).

2.4 | Statistical analysis

Efficacy and hypoglycaemia analyses were performed for the full analysis set (FAS), consisting of all patients who matched all of the inclusion criteria, provided written informed consent, and started Gla-300 no later than 2 weeks before study entry. Analyses of AEs and hypoglycaemic episodes were also performed for the safety analysis set (SAS), ie, those patients who provided written informed consent and used Gla-300 at least once during the study. Data are presented using descriptive statistics according to a predefined statistical analysis plan, with categorical variables expressed as frequency and continuous variables as mean plus-minus standard deviation (mean ± SD). All differences between baseline values and month 6 or month 12 values were performed for only those patients with data for both available. The number of patients with data available is given as N in brackets after each mean ± SD. Proportions were calculated for patients with available data only. All statistical tests were two-tailed with a significance level of 0.05 without adjustment for multiplicity. No adjustment for confounders was performed. Time to and duration at target and corresponding 95% CIs were analysed using Kaplan–Meier methods, and plots of the Kaplan–Meier estimates were produced. The analyses for duration at target included all patients with a documented response; those without a documented end of response were censored at the date of last measurement of FPG or HbA1c, respectively. Comparisons of baseline values with month 6 and month 12 values for FPG, HbA1c, BW, body mass index (BMI) and Gla-300 doses were performed using paired t-tests. For the analysis of hypoglycaemia incidence, 95% CIs were calculated according to the Clopper-Pearson method. Event rates per patient-year were calculated as the cumulative number of hypoglycaemic events for all patients with treatment duration and the number of events available divided by the cumulative duration of Gla-300 therapy in years. Incidence of hypoglycaemia within the last 12 weeks before starting Gla-300 was compared with the incidence of hypoglycaemia within the last 12 weeks before the end of month 6 and month 12, respectively, using McNemar's test. Comparisons of baseline values with month 12 values for DTSQs were performed using the Wilcoxon signed-rank test.

It is well known that prospective non-interventional studies are vulnerable to loss to follow-up. In our study, loss to follow-up until study end was 37.5%. Therefore, the results are presented for only those participants for whom data after 12 months of Gla-300 treatment were available. To rule out attrition bias, occurrence of any systematic differences was examined by comparing the baseline characteristics of those who dropped out and those who stayed in the study using the t-test (pooled standard error when variances were equal, and Satterthwaite approximation when variances were unequal) and chi-square test, respectively. All analyses were performed using SAS version 9.4.

3 | RESULTS

3.1 | Patients

Data were collected between June 2015 and December 2017. In total, 1748 patients (1680 patients in Germany and 68 patients in Switzerland) with type 2 diabetes were documented by 508 investigators (502 primary care office-based, six working in hospitals) distributed throughout Germany and Switzerland (median [IQR]: 4 [2 to 4] patients) and being a representative sample of German and Swiss physicians, who usually start and follow up basal insulin therapy in patients with type 2 diabetes (40.2% diabetologists/endocrinologists, 59.8% general practitioners/family physicians/internists). There were no significant differences in patient baseline characteristics, HbA1c target definition and insulin titration habits between diabetologists/endocrinologists and general practitioners/family physicians/internists, except for a trend towards more use of OADs with diabetologists/endocrinologists, resulting in a higher use of metformin, sulphonylurea (SU), dipeptidyl peptidase-4 (DPP-4i) and sodium-glucose co-transporter-2 inhibitors (SGLT2i; data not shown). Reasons for exclusion from SAS (N = 1503) were no Gla-300 intake (N = 239) and missing informed consent (N = 134; more than one reason could apply). Further reasons for exclusion from FAS (N = 1153) were first Gla-300 use >14 days before study entry (N = 270), baseline HbA1c >10% (N = 96), and violation of other inclusion criteria (N = 13; more than one reason could apply). Patients with Gla-300 use >14 days were excluded based on a post hoc analysis by Gla-300 use at baseline showing that patients with Gla-300 use >14 days and 14–1 days before baseline, respectively, and at baseline, received Gla-300 (median [IQR]) −47 (−78 to −27) days (N = 270) and −6 (−8 to −3) days (N = 184) before baseline, respectively, and 0 (0 to 1) days after baseline (N = 1030; missing values: N = 19). Baseline and efficacy results for those receiving Gla-300 14–1 days before and at baseline were mainly comparable, while results for those with Gla-300 use >14 days before baseline differed in several aspects from the other two, especially showing higher target achievements because of the fact that patients were not insulin-naïve at baseline and had a substantial longer duration of insulin treatment at study end (data not shown). Of 1153 FAS patients, 84 (7.3%) were excluded during the study because of a switch to another form of insulin therapy, 27 (2.3%) because of a switch to a BOT regimen with another basal insulin, and 163 (14.1%) for unknown reasons, while 879 (76.2%) continued treatment. Data after 12 months were available for 721 FAS patients (FAS-M12; 62.5%). Baseline characteristics of the FAS population (N = 1153), the FAS-M12 population (N = 721) and for those who dropped out from FAS (FAS-dropout; N = 432) are summarized in Table 1. The mean (±SD) age of FAS-M12 patients was 64.5 ± 11.3 years, with a mean diabetes duration of 8.9 ± 5.9 years. Male patients comprised 57.6% of FAS-M12, BW was 91.3 ± 18.9 kg and BMI was 31.3 ± 5.5 kg/m^2. Baseline FPG was 184.2 ± 43.1 mg/dL (10.23 ± 2.39 mmol/L) and mean HbA1c was 8.5% ± 0.8% (69 ± 9 mmol/mol) with a mean target HbA1c of 7.0% ± 0.5% (53 ± 6 mmol/mol). Information on baseline OAD use in FAS, FAS-M12 and FAS-dropout patients is provided in Table 1, and on baseline concomitant diseases and lipidaemia in FAS-M12 patients in Table S1.

The comparison of baseline characteristics between FAS-M12 and FAS-dropout populations revealed no differences in baseline characteristics; however, more FAS-M12 patients used a combination of metformin + SU (6.4% vs. 3.2%; *P* = 0.0202) and of metformin + SGLT2i (5.8% vs. 1.4%; *P* = 0.0003), respectively (Table 1).

At baseline, the most common OAD therapy was a combination of metformin + DPP-4i (30.4%), followed by metformin monotherapy (19.8%) and DPP-4i monotherapy (7.6%; Figure S1). In total, 58.7% of patients received metformin, 22.9% a fixed metformin/DPP-4i combination, and 31.9% a DPP-4i. SUs were used by 15.8% of patients (Figure S2).

3.2 | Primary efficacy endpoint

Within 6 months after initiating Gla-300 therapy, 232 FAS-M12 patients achieved their predefined individual HbA1c target (mean

TABLE 1 Baseline characteristics and main combinations of baseline OAD treatment –FAS total, FAS-M12 and FAS-dropout patients

	FAS total N = 1153	FAS-M12 N = 721	FAS-dropout N = 432	*P*-value
Baseline characteristics#				
Age [years]	64.9 ± 11.5	64.5 ± 11.3	65.5 ± 11.9	0.1381
Diabetes duration [years]	9.0 ± 6.2	8.9 ± 5.9	9.3 ± 6.7	0.4142
Gender m/f [%]*	56.6/43.4	57.6/42.4	55.0/45.0	0.3798##
BMI [kg/m^2]	31.2 ± 5.6	31.3 ± 5.5	31.2 ± 5.8	0.8189
BMI <30/≥30 kg/m^2 [%]*	46.8/53.2	44.6/55.4	50.5/49.5	0.0616##
Height [cm]	170.3 ± 9.2	170.5 ± 9.1	170.0 ± 9.3	0.4680
Weight [kg]	90.9 ± 18.7	91.3 ± 18.9	90.2 ± 18.4	0.3478
FPG [mg/dL]	185.2 ± 45.6	184.2 ± 43.1	186.9 ± 49.7	0.3573
FPG [mmol/L]	10.29 ± 2.53	10.23 ± 2.39	10.38 ± 2.76	0.3573
HbA1c [%]	8.5 ± 0.8	8.5 ± 0.8	8.5 ± 0.9	0.9551
Individual target HbA1c [%]	7.0 ± 0.6	7.0 ± 0.5	7.0 ± 0.6	0.4535
OAD treatment combinations [%]‖,##				
Metformin + DPP-4i	29.7	30.4	28.7	0.5480
Metformin monotherapy	21.2	19.8	23.6	0.1291
DPP-4i monotherapy	7.7	7.6	7.9	0.8815
Metformin + SU	5.2	6.4	3.2	0.0202
Metformin + SGLT2i	4.2	5.8	1.4	0.0003
Metformin + SU + DPP-4i	2.8	3.2	2.1	0.2682
SGLT2i monotherapy	1.6	1.7	1.6	0.9547
SGLT2i + SU	0.3	0.4	0.0	0.2965‡
Metformin + SGLT2i + DPP-4i	2.4	2.2	2.8	0.5509
SU monotherapy	2.7	2.4	3.2	0.3696
SU + DPP-4i	1.1	1.0	1.4	0.5698‡
Metformin + SU + SGLT2i	0.4	0.4	0.5	1.0000‡
Others†	20.7	18.7	23.6	n.a.

Abbreviations: BMI, body mass index; DPP-4i, dipeptidyl peptidase-4 inhibitor; FAS-M12, full analysis set of patients with month 12 data available; FAS-dropout, FAS patients without month 12 data available; FAS total, complete full analysis set; FPG, fasting plasma glucose; n.a., not applicable; OAD, oral antidiabetic drug; SGLT2i, sodium-glucose co-transporter-2 inhibitor; SU, sulphonylurea.
Data are shown as mean ± standard deviation, unless otherwise specified
*Excluding "unknown/missing data."
‖Percentage of patients including "unknown/missing data."
#Comparison between 12-month completers and patients who dropped out from FAS with t-test pooled when variances were equal (determined by method of folded F) and according to Satterthwaite when variances were unequal.
##Chi-square test.
†Others, other combinations or unknown.
‡Fisher's exact test.

proportion [95% CI]: 33.4% [29.9%; 37.0%]). Within 12 months, 355 FAS-M12 patients (49.9% [46.1%; 53.6%]) achieved the primary efficacy endpoint. A post hoc analysis of months 7–12 showed 301 patients with HbA1c values within their target range (43.6% [39.9%; 47.4%]; Figure 1).

3.3 | Secondary efficacy endpoints

An FPG at target (≤110 mg/dL [≤6.1 mmol/L]) was achieved by 209 patients (29.5% [26.1%; 33.0%]) within 12 months. A total of 436 patients (61.1% [57.4%; 64.7%]) achieved either their individually predefined HbA1c target or the FPG target within 12 months. Both targets were achieved by 104 patients (14.7% [12.2%; 17.5%]) after 12 months (Figure 1).

Starting at a mean (±SD) baseline HbA1c level of 8.52% ± 0.80% (70 ± 8.7 mmol/mol; N = 721), mean reduction from baseline to month 6 and month 12 was −1.02% ± 1.09% (−11.1 ± 11.9 mmol/mol; N = 689) and – 1.22% ± 1.05% (−13.3 ± 11.5 mmol/mol; N = 690), respectively, to a final level of 7.28% ± 0.92% (56 ± 10.1 mmol/mol; N = 690; *P* < 0.0001 for both).

Mean (±SD) FPG was significantly reduced from 184.2 ± 43.1 mg/dL (10.2 ± mmol/L; N = 703) at baseline by −45.4 ± 49.7 mg/dL (−2.52 ± 2.76 mmol/L; N = 671) at month 6 and

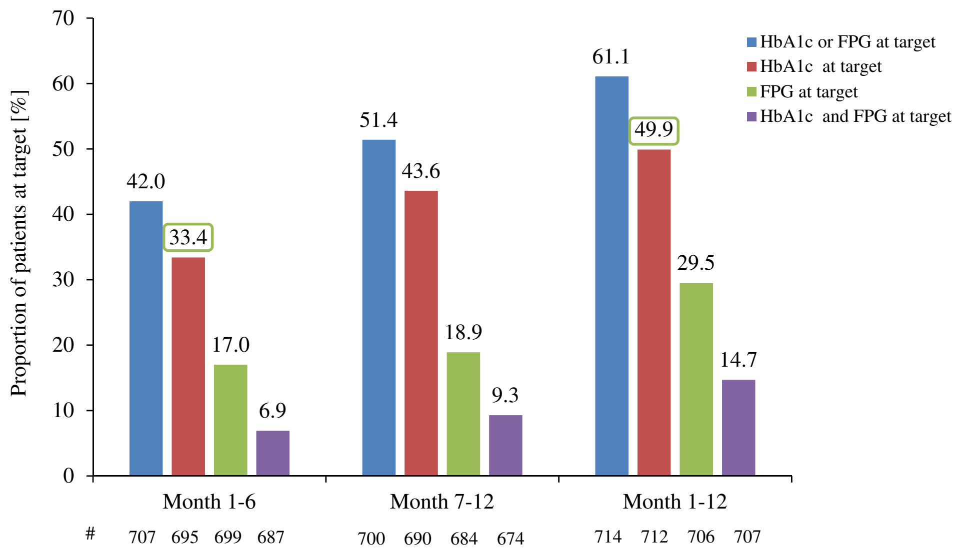

FIGURE 1 Fasting plasma glucose (FPG) (≤110 mg/dL) and HbA1c (individual) target achievement after 1–6, 7–12 and 1–12 months of Gla-300 treatment (FAS-M12; n = 721). #, number of patients with month 12 data available; primary endpoint marked with green box; Gla-300, insulin glargine 300 U/mL; post-hoc evaluation of 7–12 months: all patients with the respective variable at target during this period were included, ie, those in which target achievement occurred for the first time, was sustained from 1–6 months or occurred for a second time after occurring and ending within 1–6 months

– 51.5 ± 48.6 mg/dL (–2.86 ± 2.70 mmol/L; N = 668) at month 12, respectively, to 132.9 ± 33.0 mg/dL (7.38 ± 1.83 mmol/L; N = 676; *P* < 0.0001 for both) at month 12.

Median time to target achievement for the efficacy endpoint of HbA1c or FPG at target in FAS-M12 patients (N = 721) was 279 [246; 340] days. The Kaplan–Meier estimate for achieving this endpoint at month 6 was 0.35 [0.32; 0.39], and 0.58 [0.54; 0.62] at month 12 (Figure S3A). Of the 436 FAS-M12 patients achieving this endpoint within 12 months, 132 (30.3%) reported an end of target achievement during the study and 304 (69.7%) remained on target until study end. Median duration on target was 349 [287; not estimated] days (11.6 months) and the Kaplan–Meier estimate for further duration on target 180 days (6 months) after start of target achievement was 0.71 [0.65; 0.75] (Figure S3B). Median time to target achievement for the efficacy endpoint of HbA1c at target in FAS-M12 patients (N = 721) was 379 [368; 388] days. The Kaplan–Meier estimate for achieving this endpoint was 0.21 [0.18; 0.25] at month 6 and 0.44 [0.40; 0.48] at month 12, respectively (Figure S4A). Of the 354 FAS-M12 patients achieving this endpoint within 12 months, 68 (19.2%) reported an end of target achievement during the study and 286 (80.8%) remained on target until study end. Median duration on target was 341 [276; 418] days (11.4 months) and the Kaplan–Meier estimate for further duration on target 180 days (6 months) after start of target achievement was 0.81 [0.75; 0.86] (Figure S4B).

Four-point SMBG profiles were based on morning preprandial and 2-hour postprandial measurements after breakfast, lunch and dinnertime, respectively. Documentation was available for less than 30% of participants. In this subgroup, significant reductions of plasma glucose levels at all four time points were observed from baseline to month 12 (Table S2).

There was no significant change in BW and BMI during the study; BW at baseline was 91.3 ± 18.9 kg (N = 679); it increased by 0.2 ± 8.8 kg until month 6 (*P* = 0.5349; N = 589) and decreased by –0.3 ± 7.2 kg until month 12 (*P* = 0.3075; N = 607).

3.4 | Insulin dose

The mean starting dose of Gla-300 was 14.7 ± 10.0 units per day (U/d; N = 713), corresponding to 0.16 ± 0.10 units per kilogram BW per day (U/kg*d; N = 671). Until month 6, mean Gla-300 dose increased significantly by 9.5 ± 12.5 U/d (N = 691; *P* < 0.0001) and 0.10 ± 0.13 U/kg*d (N = 652; *P* < 0.0001), respectively, and until month 12 by 11.6 ± 14.3 U/d (N = 702; *P* < 0.0001) and 0.13 ± 0.14 U/kg*d (N = 661; *P* < 0.0001), respectively, resulting in a final dose of 26.2 ± 17.2 U/d (N = 709), corresponding to 0.28 ± 0.16 U/kg*d (N = 675).

3.5 | Hypoglycaemia

Incidence and event rates for symptomatic, confirmed symptomatic, nocturnal, severe and severe nocturnal hypoglycaemia over 12 months after initiation of BOT with Gla-300 are shown in Table 2. Overall, incidences and event rates were low for a type 2 diabetes population before and after starting a BOT regimen. Assessment of the hypoglycaemia incidence of the last 12 weeks before starting with Gla-300 versus the hypoglycaemia incidence of the last 12 weeks before end of month 6 and before end of month 12 after initiating Gla-300 treatment, respectively, revealed no significant changes in the incidence of confirmed, severe, nocturnal and severe nocturnal hypoglycaemia. However, a significant albeit small increase in symptomatic hypoglycaemia was observed after 12 months of treatment with basal insulin Gla-300 (0.0% vs. 0.8%; *P* = 0.0143). Neither at baseline nor after 12 months of Gla-300 treatment were severe or severe nocturnal hypoglycaemic episodes observed (Table 2).

3.6 | Patient-reported outcomes

The mean treatment satisfaction score at baseline was 23.9 ± 7.5 (N = 607), which increased significantly by 6.1 ± 8.3 (N = 523) to

TABLE 2 Hypoglycaemia incidence (within last 12 weeks) before, 6 and 12 months after starting Gla-300 and hypoglycaemia incidence and rate at month 12 after starting Gla-300 (FAS-M12)

	Incidence within last 12 weeks before start of Gla-300 (n = 721, 7 miss.)	Incidence within last 12 weeks before end of month 6 with Gla-300 (n = 721, 21 miss.)		Incidence within last 12 weeks before end of month 12 with Gla-300 (n = 721, 10–13 miss.)		Incidence within 12 months with Gla-300 (n = 721)	Rate within 12 months with Gla-300 (n = 721)
	%[§] (N)	%[§] (N)	*P*-value	%[§] (N)	*P*-value	% [95% CI][||] (N)	Events/ patient-year [95% CI][¶]
Symptomatic hypoglycaemia	0.0 (0)	0.4 (3)	0.0833	0.8 (6)	0.0143	2.5 [1.5, 3.9] (18)	0.04 [0.03, 0.06]
Confirmed* symptomatic hypoglycaemia	0.1 (1)	0.4 (3)	0.3173	0.1 (1)	1.0000	1.4 [0.7, 2.5] (10)	0.03 [0.02, 0.04]
Nocturnal[□] hypoglycaemia	0.1 (1)	0.0 (0)	0.3173	0.3 (2)	0.5637	0.6 [0.2, 1.4] (4)	0.01 [0.00, 0.02]
Severe[‡] hypoglycaemia	0.0 (0)	0.0 (0)	–	0.0 (0)	–	0.0 [0.0, 0.5] (0)	0.00 [0.00, 0.01]
Severe[‡] nocturnal[□] hypoglycaemia	0.0 (0)	0.0 (0)	–	0.0 (0)	–	0.0 [0.0, 0.5] (0)	0.00 [0.00, 0.01]

Abbreviations: FAS-M12, full analysis set of patients with month 12 data available; Gla-300, insulin glargine 300 U/mL; miss., missing; SMBG, self-measured blood glucose.
*Confirmed by SMBG ≤70 mg/dL (≤3.9 mmol/L).
□While the patient was asleep (~ 10:00 PM to 06:00 AM).
‡Assistance of another person required or SMBG ≤56 mg/dL (≤3.1 mmol/L).
§In % of all patients with data available.
||95% CI (Clopper-Pearson exact).
¶95% CI (exact Poisson).

30.2 ± 5.5 (N = 562) at month 12 (*P* < 0.0001). The score for perceived frequency of hyperglycaemia was 3.9 ± 1.5 (N = 605) at baseline, which decreased significantly by −1.7 ± 2.1 (N = 520) to 2.1 ± 1.7 (N = 561) at month 12 (*P* < 0.0001). The perceived frequency of hypoglycaemia score did not change significantly (1.1 ± 1.5 [N = 608] at baseline vs. 1.0 ± 1.4 [N = 562] at month 12; difference – 0.1 ± 1.7 [N = 524; *P* = 0.1905]).

3.7 | Safety

Overall, AEs were reported for 124 (8.3%) patients in the SAS (N = 1503). AEs considered to be possibly related to the use of Gla-300 by the investigator or the sponsor were reported for 31 patients (2.1%). SAEs were reported for 32 patients (2.1%). The most commonly reported SAEs were general disorders and administration site conditions (0.6%), and neoplasms that were benign, malignant and unspecified (including cysts and polyps) (0.5%). One patient (0.1%) reported a related SAE of inadequate control of diabetes. Fatal AEs were reported for four patients (0.3%); the Medical Dictionary for Regulatory Activities Preferred Terms reported, each for one single patient (0.1%), were sudden cardiac death, sudden death, hepatic cancer, and circulatory collapse. None of the fatal AEs were considered to be associated with Gla-300 by the reporter or the sponsor.

4 | DISCUSSION

The randomized, open-label phase 3a clinical trial EDITION 3 has shown that Gla-300 provided similar glycaemic control to Gla-100 in adult insulin-naïve patients with type 2 diabetes, but with a lower overall risk of hypoglycaemia, especially at the threshold of <3.0 mmoL/L, over 6 and 12 months.[5,6] More recently, the BRIGHT study,[10] a direct comparison of the two second generation basal analogue insulins, Gla-300 and insulin degludec, has shown similar glycaemic control in adult insulin-naïve patients with type 2 diabetes. Hypoglycaemia incidence and rates were comparable with both insulins during the full 6-month study period, but lower in favour of Gla-300 during the titration period (0–12 weeks).[10] The current prospective observational multi-centre study, Toujeo-1, conducted in Germany and Switzerland, was designed to evaluate if the beneficial effects of Gla-300 found in randomized controlled trials translate into conditions of daily routine use. Baseline values regarding BMI, age, diabetes duration, HbA1c and FPG were comparable with those documented in EDITION 3 and BRIGHT. However, the insulin-naïve patients with type 2 diabetes in our study were approximately 4 to 7 years older at basal insulin initiation (65 vs. 58[5] and 61 years[10]); they received less metformin (81% vs. 91% and 92%), substantially fewer SUs (17% vs. 59% and 66%), and substantially more DPP-4i (53% vs. 22% and 24%). This might have contributed to the low incidence of hypoglycaemia observed in our study at baseline and at study end.

The study shows that within 12 months half of the patients (50%) achieved their predefined individualized HbA1c target, and 61% either the HbA1c or the FPG target after initiating a BOT with Gla-300. The median duration of HbA1c target achievement was 341 days (11.4 months), and the probability of remaining on target 6 months after achieving control was 81%. This benefit of time at target levels is also reflected by an improved glycaemic control, as indicated by a mean decrease in HbA1c level of −1.0% and −1.22% (−11.1 and −13.3 mmol/mol), respectively, 6 and 12 months after starting Gla-300 therapy. The patients in our study more slowly improved glycaemic control after 6 months of treatment in daily clinical practice than the patients in EDITION 3[5] (−1.42% [−15.5 mmol/mol]) and BRIGHT[10] (−1.64% [−18.0 mmol/mol]) starting from similar baseline HbA1c levels (8.52% vs. 8.49% and 8.72% [70 vs. 69 and 72 mmol/mol]).[5,10] This observation may be attributable to a less stringent basal insulin titration used in daily clinical practice compared with randomized controlled clinical trials. However, the mean HbA1c level in our study continued to decrease from month 7 to month 12 to a final level of 7.28%, while it slightly increased in EDITION 3 (7.08% to 7.13%).[6] This led to comparable mean reductions in HbA1c (−1.22% vs. −1.29%) observed 12 months after starting Gla-300 treatment in our study and in EDITION 3.[6] In two recently published observational studies evaluating electronic medical records, insulin-naïve type 2 diabetes patients in the United States were reported to reduce HbA1c levels by −1.67% and −1.52%, respectively, during 3 to 6 months follow-up; however, both studies started from higher baseline HbA1c values of 9.7% and 9.6%, respectively.[11,12]

Furthermore, glycaemic improvement in clinical practice was shown in our study by a significant decrease in FPG of −45.4 mg/dL (−2.52 mmol/L) after 6 months and −51.5 mg/dL (−2.86 mmol/L) after 12 months of Gla-300 treatment. Because of the tighter titration at study start, a greater difference to baseline in FPG was observed in EDITION 3 after 6 months (−61.1 mg/dL [−3.39 mmol/L]), and less after 12 months (−57.0 mg/dL [−3.16 mmol/L]).[6]

The improved glycaemic control was achieved with a final basal insulin dose of 26.2 U/d (0.28 U/kg*d), which is less than half of the Gla-300 dose used at month 12 in the EDITION 3 study (0.67 U/kg*d).[6] In BRIGHT, the mean starting dose compared with our study was slightly higher (16.9 U/d [0.19 U/kg*d] vs. 14.7 U/d [0.16 U/kg*d]), and also increased by double when compared with our results (50.5 U/d [0.54 U/kg*d] vs. 24.2 U/d [0.26 U/kg*d]).[10] This difference might, when compared with the once-weekly dose adjustment applied in EDITION 3, be attributed to the much more cautious dose titration of once every 2 weeks, even in the first weeks of titration observed in our study (data on file). We found a similar titration frequency in the real world with Gla-100.[13,14] Slow titration appears to reduce the risk of hypoglycaemia to a very low rate and to enable the full development of the blood glucose-lowering potential of glargine insulins. However, insulin titration was finished quite early in both observational studies,[13,14] resulting in some patients missing their glycaemic targets.

While EDITION 3 reported an increase in BW of +0.97 kg at month 12,[6] BW remained stable in our study.

Hypoglycaemia incidence and annualized event rates were very low for a population of patients with type 2 diabetes. The observed higher use of DPP-4i compared with EDITION 3[5] and BRIGHT[10] (53.4% vs. 21.6% and 24.4%) and less use of SUs (16.5% vs. 58.8% and 65.7%) in our study might have contributed to lower rates of hypoglycaemia, in addition to the less stringent titration of basal insulin observed in daily clinical practice, although SUs were discontinued in EDITION 3 after starting BOT, in contrast to BRIGHT and our study.[5,10] Incidence of symptomatic hypoglycaemia increased on a low level but was significant from baseline to month 12. No significant differences were observed for any other kind of hypoglycaemia. No severe hypoglycaemia was observed in our study, which supports the results of BRIGHT, where only one severe hypoglycaemia event was reported.[8]

The major limitations of the current study are, because of the non-interventional design, a lack of randomization and a lack of a comparator arm, as well as loss to follow-up, which might have introduced selection bias.[15] However, comparisons before and after starting Gla-300 were feasible, and analyses of those who dropped out from FAS against those with month 12 results available showed no clinically relevant differences between these groups. Of the total FAS set, 9.6% were excluded because of a switch of insulin treatment. This proportion of switching patients is small compared with the 48% switches from basal insulin therapy to other therapies over 4 years observed in the CREDIT study.[16] For 13.7%, no month 12 data were documented, which might be because of the German health system, where patients referred to a diabetologist by their general practitioner will usually be re-sent after 6 months, and might not be further documented by the diabetologist. Another limitation is that some of the effects observed might be attributable to the Hawthorne effect; however, the usefulness of this term for discussion of research results is questionable.[17] Also, the contribution of factors other than the addition of Gla-300 (eg, OADs) to the results obtained cannot be ruled out. However, only minor changes of OAD use were observed from baseline to study end. A further limitation is that the patients were voluntarily enrolled and prospectively followed, which might have influenced their behaviour because they knew they were being observed. Therefore, the results obtained here might not be fully representative of all people with type 2 diabetes starting with Gla-300.

In conclusion, initiating a BOT with Gla-300 in insulin-naïve people with type 2 diabetes insufficiently controlled on OADs in German and Swiss primary care settings was effective at reducing HbA1c and FPG levels, and allowed half of the patients to achieve their personalized targeted glycaemic control within 12 months, with low overall rates of hypoglycaemia, and without increased risk of nocturnal or severe hypoglycaemia or BW gain.

ACKNOWLEDGMENTS

The authors thank Rolf Binder, MD, for providing editorial support, on behalf of Creative Clinical Research, Berlin, Germany.

Parts of this study were presented as posters at the 78th Scientific Sessions of the American Diabetes Association (ADA), Orlando, USA, 22-26 June 2018, and at the annual Meeting of the German Diabetes Society (DDG), 9-12 May 2018, Berlin, Germany.

This study was funded by and editorial support was paid for by Sanofi-Aventis Deutschland GmbH, Berlin, Germany.

CONFLICT OF INTEREST

M.P. received honoraria for talks from Novartis, Novo Nordisk and Sanofi; he is a member of Scientific Advisory Boards of Boehringer Ingelheim, Eli Lilly, Novo Nordisk and Sanofi. F.R.J. received honoraria for consultancy from Sanofi, Eli Lilly, Boehringer Ingelheim and Novo Nordisk. A.F. is a member of Scientific Advisory Boards of Sanofi, Novo Nordisk, Eli Lilly and Boehringer Ingelheim. S.P. is a member of Scientific Advisory Boards of Sanofi; he received honoraria for talks from Eli Lilly, Novartis, Novo Nordisk, MSD and Sanofi. H.A. received honoraria for consultancy from Sanofi, Merck Sharp Dome (MSD), Eli Lilly, Boehringer Ingelheim and Pfizer. K.P. is an employee of Sanofi. J.S. received honoraria for talks and/or consultancy and/or research funding from Apitope, Astra Zeneca, Bayer, Berlin Chemie, Boehringer Ingelheim, Bristol Myers Squibb (BMS), GI-Dynamics, Glaxo Smith Kline (GSK), Intarcia, Ipsen, Janssen, LifeScan, Eli Lilly, MSD, MedScape, Novartis, Novo Nordisk, Omniamed, Pfizer, Roche, Sanofi, Servier, Takeda and Ypsomed.

AUTHOR CONTRIBUTIONS

Substantial contributions to the conception and design of the work were made by M.P., A.F., S.P., H.A., K.P. and J.S. Substantial contributions to the conduction of the study and acquisition of data for the work were made by M.P., F.R.J., A.F., S.P., H.A., K.P. and J.S.

Analysis or interpretation of data for the work were undertaken by M.P., A.F., K.P. and J.S. The work was drafted by M.P., J.S. and K.P. and was revised critically for important intellectual content by F.R.J., A.F., S.P. and H.A. M.P., F.R.J., A.F., S.P., H.A., K.P. and J.S gave final approval for the version to be published and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

FUNDING INFORMATION

This study was funded by Sanofi-Aventis Deutschland GmbH, Berlin, Germany.

ORCID

Jochen Seufert https://orcid.org/0000-0001-5654-7310

REFERENCES

1. Ulrich S, Holle R, Wacker M, et al. Cost burden of type 2 diabetes in Germany: results from the population-based KORA studies. *BMJ Open*. 2016;6:e012527.
2. Cannon A, Handelsman Y, Heile M, Shannon M. Burden of illness in type 2 diabetes mellitus. *J Manag Care Spec Pharm*. 2018;24:S5-S13.
3. Davies MJ, D'Alession DA, Fradkin J, et al. Management of hyperglycaemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the study of Diabetes (EASD). *Diabetologia*. 2018;61:2461-2498.
4. Sutton G, Minguet J, Ferrero C, Bramlage P. U300, a novel long-acting insulin formulation. *Expert Opin Biol Ther*. 2014;14:1849-1860.
5. Bolli GB, Riddle MC, Bergenstal RM, et al. on behalf of the EDITION 3 study investigators. New insulin glargine 300 U/mL compared with glargine 100 U/mL in insulin-naïve people with type 2 diabetes on oral glucose-lowering drugs: a randomized controlled trial (EDITION 3). *Diabetes Obes Metab*. 2015;17:386-394.
6. Bolli GB, Riddle MC, Bergenstal RM, et al. EDITION 3 study investigators. Glycaemic control and hypoglycaemia with insulin glargine 300U/mL versus insulin glargine 100U/mL in insulin-naïve people with type 2 diabetes: 12-month results from the EDITION 3 trial. *Diabetes Metab*. 2017;43:351-358.
7. Bundesärztekammer (BÄK), Kassenärztliche Bundesvereinigung (KBV), Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF). Nationale VersorgungsLeitlinie Therapie des Typ-2-Diabetes – Langfassung, 1. Auflage. Version 3. 2013, zuletzt geändert: April 2014. http://www.versorgungsleitlinien.de/themen/diabetes2/dm2_therapie; [cited: November 14, 2019]; https://doi.org/10.6101/AZQ/000203. Accessed November 14, 2019.
8. Lehmann R, Bianda T, Brändle M, et al. Empfehlungen der SGED/SSED: Massnahmen zur Blutzuckerkontrolle bei Patienten mit Diabetes mellitus Typ 2. Empfehlungen der SGED, 24. August 2016, rev. 30. März 2017. https://www.sgedssed.ch/fileadmin/user_upload/6_Diabetologie/61_Empfehlungen_Facharzt/1703_SGED_Empfehlung_BZ-Kontrolle_T2DM_Finale_Version_13_oTabellen.pdf. Accessed November 14, 2019.
9. Bradley C. The Diabetes Treatment Satisfaction Questionnaire: DTSQ. *Handbook of Psychology and Diabetes: A Guide to Psychological Measurement in Diabetes Research and Practice*. Amsterdam, the Netherlands: Harwood Academic Publishers; 1994.
10. Rosenstock J, Cheng A, Ritzel R, et al. More similarities than differences testing insulin glargine 300 units/mL versus insulin degludec 100 units/mL in insulin-naive type 2 diabetes: the randomized head-to-head BRIGHT trial. *Diabetes Care*. 2018;41:2147-2154.
11. Sullivan SD, Nicholls CJ, Gupta RA, et al. Comparable glycaemic control and hypoglycaemia in adults with type 2 diabetes after initiating insulin glargine 300 units/mL or insulin degludec: DELIVER Naïve D real-world study. *Diabetes Obes Metab*. 2019;21:2123-2132.
12. Bailey TS, Zhou FL, Gupta RA, et al. Glycaemic goal attainment and hypoglycaemia outcomes in type 2 diabetes patients initiating insulin glargine 300 units/mL or 100 units/mL: Real-world results from the DELIVER Naïve cohort study. *Diabetes Obes Metab*. 2019;21:1596-1605.
13. Seufert J, Fritsche A, Pscherer S, et al. Titration and optimization trial for the initiation of insulin glargine 100 U/mL in patients with inadequately controlled type 2 diabetes on oral antidiabetic drugs. *Diabetes Obes Metab*. 2019;21:439-443.
14. Pscherer S, Anderten H, Pfohl M, et al. Titration of insulin glargine 100 U/mL when added to oral antidiabetic drugs in patients with type 2 diabetes: results of the TOP-1 real-world study [published online ahead of print July 24, 2019]. *Acta Diabetol*. https://doi.org/10.1007/s00592-019-01383-w.
15. Howe CJ, Cole SR, Lau B, Napravnik S, Eron JJ Jr. Selection bias due to loss to follow up in cohort studies. *Epidemiology*. 2016;27:91-97.
16. Home PD, Dain MP, Freemantle N, et al. Four-year evolution of insulin regimens, glycaemic control, hypoglycaemia and body weight after starting insulin therapy in type 2 diabetes across three continents. *Diab Res Clin Pract*. 2015;108:350-359.
17. Chiesa M, Hobbs S. Making sense of social research: how useful is the Hawthorne Effect? *Eur J Soc Psychol*. 2008;38:67-74.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

How to cite this article: Pfohl M, Jornayvaz FR, Fritsche A, et al. Effectiveness and safety of insulin glargine 300 U/mL in insulin-naïve patients with type 2 diabetes after failure of oral therapy in a real-world setting. *Diabetes Obes Metab*. 2020;22:759–766. https://doi.org/10.1111/dom.13952