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ORIGINAL ARTICLE

Switching the basal insulin to insulin glargine 300 U/ml in people with type 2 diabetes under basal insulin supported oral therapy: Observational trial on effectiveness and safety

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Abstract

Aims: This study evaluated the effectiveness and safety of switching the basal insulin (BI) in a BI-supported oral therapy (BOT) to insulin glargine 300 U/ml (Gla-300) in adults with inadequately controlled type 2 diabetes (T2D).

Materials and methods: This was a non-interventional, multicentre, prospective 12-month study, conducted in Germany, Austria and Switzerland. The study documented people with T2D with glycated haemoglobin (HbA1c) between 7.5% and 10.0%, currently treated by a non-Gla-300 BOT regimen, after the physician had decided to switch the BI to Gla-300. Primary endpoint was the proportion of patients achieving the fasting plasma glucose (FPG; ≤110 mg/dl) target.

Results: In total, 1194 participants comprised the full analysis set, of which 793 completed documentation of 12 months Gla-300 treatment (FAS-M12). The main previous BI was insulin glargine 100 U/ml (Gla-100; 47.2%). Twelve months after switching to Gla-300, 27.0% of FAS-M12 participants achieved the FPG target and 44.8% their individualized HbA1c target. The greatest FPG target achievements were seen in previous Gla-100 (29.3%), and greatest HbA1c target achievements in previous insulin detemir users (57.7%). The mean FPG decreased by −36.3 ± 51.2 mg/dl to 135.5 ± 36.9 mg/dl and mean HbA1c by −0.79 ± 1.01% to 7.45 ± 0.94%. Symptomatic and nocturnal hypoglycaemia incidence significantly decreased over 12 months of Gla-300 treatment. Body weight remained unchanged.

Conclusions: Switching the BI to Gla-300 in a BOT regimen improved metabolic control and treatment satisfaction in a substantial proportion of patients with T2D and inadequate target achievement within 12 months in clinical practice with a decreased risk of symptomatic and nocturnal hypoglycaemia and without weight gain.

KEYWORDS
basal insulin, hypoglycaemia, insulin analogues, insulin therapy, observational study, type 2 diabetes

1 | INTRODUCTION

Effective glycaemic control is essential to prevent or delay diabetes complications and to help in increasing life expectancy.[1] Treatment of type 2 diabetes (T2D) is recommended to include stepwise lifestyle changes, metformin and other oral antidiabetic drugs (OADs) depending on individualized glycaemic targets and concomitant diseases. Initiation of basal insulin (BI) supported oral therapy (BOT) is recommended in global and local guidelines, if the individual glycated haemoglobin (HbA1c) target is not achieved with double or triple OAD therapy and/or glucagon-like peptide-1 receptor agonists (GLP-1RAs) 3-6 months after last treatment intensification.[2-7] However, because of the disease progression, glycaemic control may worsen over time calling for further treatment modifications. Switching to a second-generation BI analogue such as insulin glargine 300 U/ml (Gla-300), which is considered therapeutically beneficial over insulin glargine 100 U/ml (Gla-100),[8] may provide a simple therapeutic option for metabolic improvement with a lower risk of hypoglycaemia.[9,10] Efficacy and safety of switching to Gla-300 in existing BOT regimens has been demonstrated in the phase 3a study EDITION-2,[11,12] but how these trial results translate into daily clinical practice has not been systematically and prospectively assessed. However, despite randomized controlled trials are the gold standard setting to evaluate efficacy and safety of therapies, less than one-fifth of the patients to be treated were found eligible for such trials with Gla-300.[13] Therefore, the observational trial IniTiation Of insulin glargine 300 U/ml in tyPe 2 diabetic patients after failure of pre-existing BOT treatment with any other BI (TOP-2) prospectively investigated effectiveness and safety of Gla-300 in people with T2D insufficiently controlled on a non-Gla-300 BOT regimen.

2 | METHODS

2.1 | Study design and participants

The study TOP-2 was designed as a non-interventional, multicentre, single-arm, prospective 12-month trial, conducted in Germany, Austria and Switzerland. It received approval from the local ethics committees, was conducted in accordance with the Declaration of Helsinki and is registered at the ISRCTN registry (ISRCTN56991780, www.ISRCTN.org). All participants provided written informed consent. Adults with T2D, insufficiently controlled [HbA1c 7.5%-10.0% (58-86 mmol/mol)] on a BOT regimen with non-Gla-300 BIs, were included after their physician had decided to switch to Gla-300 independent of study participation. Exclusions were patients aged <18 years, type 1 diabetes, previous insulin therapy other than BOT or with Gla-300, any contraindication for Gla-300, pregnancy, malignant disease, alcohol or drug abuse, dementia or incapable of understanding the content and goals of the study.

2.2 | Documentation

The main data collection was done at baseline, and after 6 and 12 months of Gla-300 treatment via an electronic case report form. Additionally, self-measured fasting plasma glucose (FPG) values and insulin doses were collected monthly. At baseline, physicians documented the HbA1c target individually defined for each patient in accordance with local guidelines.[4-7] HbA1c was measured every 3-6 months, and self-measured plasma glucose (SMPG) profiles were documented at the main data collection time points, if available. At baseline and every 3 months, physicians asked their patients if any hypoglycaemia occurred during the previous 12 weeks and noted the reported events. All data had to be generated during the daily clinical routine, and any therapeutic decision during the 12-month observation period was strictly left at the physician's discretion. Source data verification was performed at 26 German, three Austrian and two Swiss sites, respectively. All results were validated after the end of data capture by running check programs in Statistical Analysis System version 9.4 (SAS Institute Inc., Cary, NC, USA).

2.3 | Study endpoints

The primary efficacy endpoint was the proportion of patients achieving at least two FPG values at target [≤110 mg/dl (≤6.1 mmol/L)] within 1-6 and 1-12 months, respectively. Secondary efficacy endpoints included target achievement rates within 1-6 and 1-12 months for individually predefined HbA1c targets, HbA1c or FPG at target, and HbA1c and FPG at target, respectively, time to and duration of glycaemic responses, absolute change from baseline to 6 and 12 months, respectively, of HbA1c, FPG, four-point SMPG profiles, body weight (BW), BI doses and patient's treatment satisfaction (Diabetes Treatment Satisfaction Questionnaire status).[14] Safety endpoints included hypoglycaemia incidence and rates per patient-year, calculated for symptomatic, confirmed [SMPG value of ≤70 mg/dl (≤3.9 mmol/L)] symptomatic, nocturnal (symptomatic or confirmed hypoglycaemia occurring approximately between 22.00 and 06.00 h, while the patient was asleep), severe [assistance of another person required or SMPG value of ≤56 mg/dl (≤3.0 mmol/L)], and severe nocturnal hypoglycaemia, as well as incidence of adverse events (AEs), related AEs, serious AEs, related serious AEs and fatal AEs.

2.4 | Statistical analysis

Efficacy and hypoglycaemia analyses were performed for the full analysis set (FAS) consisting of all participants who matched all inclusion/exclusion criteria, provided written informed consent and switched to Gla-300 less than 2 weeks before study entry. Analyses of AEs and hypoglycaemia were also performed for the safety analysis set, that is, those participants 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 ± SD. All differences between baseline and month 6 values and/or baseline and month 12 values were performed for those participants only with both data available. All statistical tests were two-tailed with a significance level of 0.05 without adjustment for multiplicity. No adjustment for confounders was done. Time to and duration at target and corresponding 95% confidence intervals (CIs) were analysed using Kaplan-Meier methods. The analyses for duration at target included all patients with documented response; those without documented end of response were censored at the date of last measurement of FPG or HbA1c, respectively. Duration at FPG target started with the first time of reaching the target value, but only, if the next documented FPG value was also at target, and ended with the first time of an FPG value above target, but only, if the next documented FPG value was also above target. Comparisons of baseline with month 6 and 12 values for FPG, HbA1c, BW, body mass index (BMI) and Gla-300 doses were performed using paired t-tests. For analysing hypoglycaemia incidence, 95% CIs were calculated using the Clopper-Pearson method. Rates per patient-year were calculated as the cumulative number of hypoglycaemic events for all participants with treatment duration and number of events available divided by the cumulative duration of Gla-300 therapy in years. Incidence of hypoglycaemia within the last 12 weeks before switching to Gla-300 was compared with the incidence of hypoglycaemia within the last 12 weeks before the end of month 6 and 12, respectively, using McNemar's test. Comparisons of baseline with month 12 values for Diabetes Treatment Satisfaction Questionnaire status were performed using Wilcoxon signed-rank test.

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 t-test (pooled standard error, when variances were equal, and Satterthwaite approximation, when variances were unequal) and chi-squared test, respectively. All analyses were performed using SAS version 9.4.

3 | RESULTS

3.1 | Patient characteristics

Data were collected between June 2015 and December 2017. In total, 1864 patients (1661 patients in Germany, 103 in Austria and 100 in Switzerland) were documented by 555 investigators [540 primary care office based, 15 working in hospitals; median (IQR): 4 (2-4) patients], comprising a representative sample of German, Austrian and Swiss physicians, who usually care for BOT-treated people with T2D (49.7% diabetologists/endocrinologists, 50.3% general practitioners/family physicians/internists). No significant differences in patient baseline characteristics, HbA1c target definition and insulin titration habits (i.e. similar switching doses for Gla-300 [0.3 units per kilogram BW per day (U/kg/day)] in both groups, similar frequency of dose changes [1.6 times during the first month and 1.0-1.7 times in month 2 to month 12 after switch] in both groups, similar final doses of Gla-300 [0.36 U/kg/day (diabetologists/endocrinologists) vs. 0.37 U/kg/day (general practitioners/family physicians/internists)] and similar final FPG levels [135.8 mg/dl (7.54 mmol/L) vs. 135.2 mg/dl (7.51 mmol/L)]; data on file) were observed between diabetologists/endocrinologists and general practitioners/family physicians/internists. However, diabetologists' patients tended to be younger, more obese, at better glycaemic control when switching their BI, with longer diabetes duration and more concomitant diseases. They also tended to receive more metformin, glinides, sodium-glucose cotransporter-2 inhibitors (SGLT2i) and sulphonylurea (SU). Use of NPH insulin (NPH) and insulin degludec (IDeg) was more common, while Gla-100 was less common as previous BI (data not shown). Reasons for exclusion from safety analysis set (n = 1603) were no documented Gla-300 applications (n = 251) and/or missing informed consent (n = 148). Further reasons for exclusion from FAS (n = 1194) were first Gla-300 use >14 days before study entry (>14d; n = 362), baseline HbA1c >10% (n = 57), and/or violation of other inclusion or exclusion criteria (n = 12). Participants with Gla-300 >14d were excluded based on a post-hoc analysis by Gla-300 use at baseline indicating that participants with Gla-300 >14d and within 14-1 days before baseline, respectively, and at baseline, received Gla-300 [median, (IQR)] −53 (−91 to −31) days (n = 362) and −5 (−8 to −2) days (n = 191) before baseline, respectively, and 0 (0-1) days after baseline (n = 1037; missing values: n = 13). Baseline results for all three groups were mainly comparable; however, those receiving Gla-300 >14d showed lower starting FPG values and higher Gla-300 doses at baseline versus the other two groups because patients were already on Gla-300 for a median of nearly 2 months at baseline (data not shown). Of 1194 FAS patients, 118 (9.9%) were excluded during the study because of the switch to another form of insulin therapy, 21 (1.8%) because of the switch to a BOT regimen with another BI and 59 (4.9%) for unknown reasons, while 996 (83.4%) continued treatment. Data after 12 months were available for 793 FAS patients (FAS-M12; 66.4%). Baseline characteristics of the FAS population (n = 1194), the FAS-M12 population (n = 793) and for those who dropped out from FAS (FAS-dropout; n = 401) are summarized in Table 1. Baseline characteristics (mean ± SD) of FAS-M12 patients were as follows: age 64.7 ± 10.4 years, diabetes duration 11.6 ± 6.9 years, FPG 171.9 ± 43.3 mg/dl (9.55 ± 2.41 mmol/L), HbA1c 8.2 ± 0.8% (66 ± 9 mmol/mol), individualized target HbA1c 7.0 ± 0.5% (53 ± 6 mmol/mol), BW 93.3 ± 19.1 kg, BMI 31.9

± 5.8 kg/m^2, and 56.7% were men. Information on baseline OAD and previous BI 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.

Baseline characteristics between FAS-M12 and FAS-dropout populations were mainly comparable; however, in FAS-M12 HbA1c was lower and more patients received IDet (Table 1). FAS-M12 patients tended to have a longer duration of diabetes, to receive less

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

	FAS total N = 1194	FAS-M12 N = 793	FAS-dropout N = 401	*p* value[a]
Baseline characteristics				
Age (years)	64.5 ± 11.0	64.7 ± 10.4	64.3 ± 11.9	.5771
Diabetes duration (years)	11.4 ± 6.9	11.6 ± 6.9	10.7 ± 6.7	.0852
Gender M/F (%)[b]	57.1/42.9	56.7/43.3	57.9/42.1	.7146[c]
BMI (kg/m^2)	32.1 ± 6.0	31.9 ± 5.8	32.3 ± 6.4	.2793
BMI <30/≥30 kg/m^2 (%)[b]	39.5/53.5	42.4/57.6	42.6/57.4	.9735[c]
Height (cm)	170.8 ± 9.3	170.7 ± 9.3	171.0 ± 9.3	.6057
Weight (kg)	93.7 ± 19.4	93.3 ± 19.1	94.6 ± 20.0	.2728
FPG (mg/dl)	173.4 ± 44.6	171.9 ± 43.3	176.3 ± 47.0	.1135
FPG (mmol/L)	9.63 ± 2.48	9.55 ± 2.41	9.79 ± 2.61	.1135
HbA1c (%)	8.3 ± 0.8	8.2 ± 0.8	8.4 ± 0.8	.0013
Individual target HbA1c (%)	7.0 ± 0.5	7.0 ± 0.5	7.1 ± 0.6	.1339
OAD treatment combinations (%)[c,d]				
Metformin + DPP-4i	25.5	25.6	25.2	.8774
Metformin monotherapy	21.8	20.2	24.9	.0598
DPP-4i monotherapy	7.0	7.1	7.0	.9597
Metformin + SU	3.0	3.7	1.8	.0743[e]
Metformin + SGLT2i	3.4	3.4	3.5	.9382
Metformin + SU + DPP-4i	1.7	1.8	1.5	.8157[e]
Metformin + SU + SGLT2i	0.3	0.3	0.5	.6060[e]
Metformin + SGLT2i + DPP-4i	2.8	3.2	2.2	.4626[e]
SGLT2i monotherapy	1.6	1.1	2.5	.0883[e]
SU monotherapy	2.3	2.9	1.3	.1034[e]
SU + DPP-4i	1.3	1.5	0.8	.4096[e]
Others[f]	29.3	29.2	28.8	NA
Previous basal insulin therapy (%)[c,d]				
Gla-100	48.2	46.7	50.1	.2574
NPH insulin	20.6	20.9	19.5	.5487
Insulin detemir	11.2	13.2	7.2	.0019
Insulin degludec	7.8	7.6	8.2	.6863
Others/unknown	12.2	11.6	15.0	NA

Note: Data are shown as mean ± standard deviation, unless otherwise specified.
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; NA, not applicable; OAD, oral antidiabetic drug; SGLT2i, sodium-glucose cotransporter-2 inhibitor; SU, sulphonylurea.
[a]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.
[b]Excluding unknown/missing data.
[c]Chi-square test.
[d]Percentage of patients including 'unknown/missing data'.
[e]Fisher's exact test.
[f]Others, other combinations or unknown.

metformin monotherapy and SGLT2i monotherapy, and more metformin and SU in combination (Table 1).

FAS-M12 patients mainly previously used Gla-100 as their BI (47.2%; Table 1). Most common OAD therapies were a combination of metformin + dipeptidyl peptidase-4 inhibitor (DPP-4i; 25.6%), metformin monotherapy (20.2%) and DPP-4i monotherapy (7.1%; Table 1 and Figure S1). In total, 53.7% of patients received metformin, 27.2% an DPP-4i, 22.4% a fixed DPP-4i/metformin combination, 12.4% SU and 11.3% an SGLT2i (Figure S2). Baseline characteristics and information on baseline OAD use in subgroups by previous BI use are shown in Table S2.

3.2 | Primary efficacy endpoint

Within 6 and 12 months after switching BI treatment to Gla-300, the mean proportions (95% CI) of FAS-M12 patients who achieved at least two values of FPG ≤110 mg/dl (≤6.1 mmol/L) were 13.4% (11.0%; 16.0%) and 27.0% (23.9%; 30.3%), respectively (Figure 1). Stratification by previous BI revealed proportions of FPG target achievement within 12 months of 29.3% (Gla-100), 27.1% (NPH), 25.2% (IDet) and 18.6% (IDeg), respectively (Figure S3).

3.3 | Secondary efficacy endpoints

Within 12 months, HbA1c [mean (95% CI)] at a predefined individual target was achieved by 44.8% (41.3%; 48.3%) of patients. A proportion of 55.6% (52.1%; 59.1%) achieved either their individual HbA1c or the FPG target, and both targets were achieved by 13.2% (10.9%; 15.8%) (Figure 1). Stratification by previous BI demonstrated proportions of HbA1c target achievement within 12 months of 57.7% (IDet), 47.6% (NPH), 43.1% (IDeg) and 41.0% (Gla-100), respectively (Figure S3).

Starting at a baseline HbA1c level (mean ± SD) of 8.24 ± 0.78% (67 ± 8.5 mmol/mol; n = 792), mean reductions from baseline to month 6 and 12 were −0.57 ± 0.95% (−6.2 ± 10.4 mmol/mol; n = 742; $p < .0001$) and −0.79 ± 1.01% (−8.6 ± 11.0 mmol/mol; n = 761; $p < .0001$), respectively, to a final average level of 7.45 ± 0.94% (58 ± 10.3 mmol/mol; n = 762). FPG (mean ± SD) was significantly reduced from 171.9 ± 43.3 mg/dl (9.55 ± 2.41 mmol/L; n = 779) at baseline by −33.7 ± 49.1 mg/dl (−1.87 ± 2.73 mmol/L; n = 741; $p < .0001$) at month 6, and −36.3 ± 51.2 mg/dl (−2.02 ± 2.84 mmol/L; n = 754; $p < .0001$) at month 12, respectively, to 135.5 ± 36.9 mg/dl (7.53 ± 2.05 mmol/L; n = 765) at month 12. Stratification by previous BI revealed the greatest HbA1c reduction 12 months after switching from IDet [−1.00 ± 0.94% (−10.9 ± 10.3 mmol/mol); n = 103; $p < .0001$], and greatest FPG reduction after switching from NPH [−45.9 ± 53.3 mg/dl (−2.55 ± 2.96 mmol/L); n = 163; $p < .0001$] (Figure 2).

The median time (95% CI) to target achievement for the efficacy endpoint of HbA1c or FPG at target in FAS-M12 patients (n = 793)

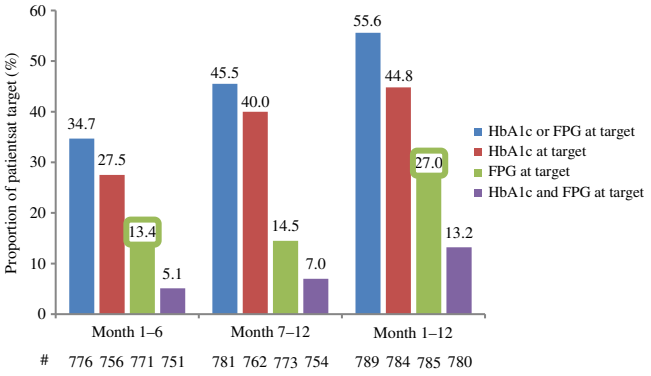

FIGURE 1 FPG [≤ 110 mg/dl (≤ 6.1 mmol/L)] and HbA1c (individual) target achievement after 1-6, 7-12 and 1-12 months of Gla-300 treatment (FAS-M12; n = 793); #, number of patients with month 12 data available; primary endpoint marked with green box; FAS-M12, full analysis set of patients with month 12 data available; FPG, fasting plasma glucose; Gla-300, insulin glargine 300 U/ml; HbA1c, glycated haemoglobin; post-hoc evaluation of 7-12 months: All patients with the respective parameter at target during this period were included, that is those in which target achievement occurred for the first time, was sustained during 1-6-month period or occurred for a second time after occurring and ending within 1-6 month period

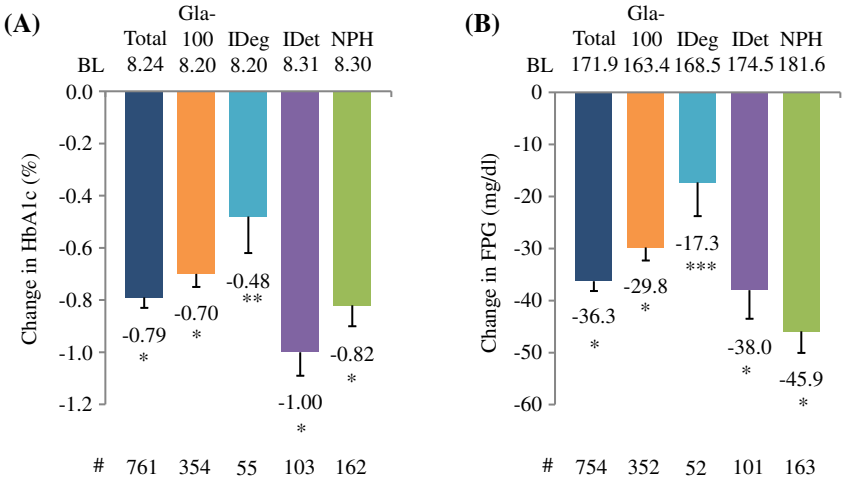

FIGURE 2 Change in (A) HbA1c and (B) FPG levels after 12 months of insulin glargine 300 U/ml treatment by previous basal insulin treatment (FAS-M12; n = 793); *$p < .0001$; **$p = .0011$; ***$p = .0103$; #, number of patients with month 12 data available; BL, baseline; FPG, fasting plasma glucose; Gla-100, insulin glargine 100 U/ml; IDeg, insulin degludec; IDet, insulin detemir; NPH, neutral protamine Hagedorn insulin

TABLE 2 Hypoglycaemia incidence (within last 12 weeks) before, 6 and 12 months after switching to 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 = 793, 5-8 miss.)	Incidence within last 12 weeks before end of m6 with Gla-300 (N = 793, 27-29 miss.)		Incidence within last 12 weeksbefore end of m12 with Gla-300 (N = 793, 6 miss.)		Incidence within 12 months with Gla-300 (N = 793)	Rate within 12 months with Gla-300 (N = 793)
	%[a] (N)	%[a] (N)	*p* value	%[a] (N)	*p* value	% [95% CI][b] (N)	Events/patient year [95% CI][c]
Symptomatic hypoglycaemia	3.5 (28)	1.9 (15)	.0374	2.0 (16)	.0280	4.2 [2.9, 5.8] (33)	0.11 [0.09, 0.13]
Confirmed[d] symptomatic hypoglycaemia	2.0 (16)	1.4 (11)	.3173	1.6 (13)	.5127	3.3 [2.2, 4.8] (26)	0.11 [0.09, 0.13]
Nocturnal[e] hypoglycaemia	2.9 (23)	0.6 (5)	.0007	0.6 (5)	.0002	1.3 [0.6, 2.3] (10)	0.03 [0.02, 0.04]
Severe[f] hypoglycaemia	0.4 (3)	0.0 (0)	.0833	0.3 (2)	.5637	0.3 [0.0, 0.9] (2)	0.00 [0.00, 0.01]
Severe[f] nocturnal[e] hypoglycaemia	0.1 (1)	0.0 (0)	.3173	0.1 (1)	.3173	0.1 [0.0, 0.7] (1)	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; m, month; miss., missin; SMBG, self-measured blood glucose.

[a]% of all patients with data available.

[b]95% CI (Clopper-Pearson exact).

[c]95% CI (exact Poisson).

[d]Confirmed by SMBG ≤70 mg/dl (≤3.9 mmol/L).

[e]While the patient was asleep (approximately 22.00-06.00 h).

[f]Assistance of another person required or SMBG ≤56 mg/dl (≤ 3.1 mmol/L).

was 368 (342; 379) days (12.3 months). The Kaplan-Meier estimate for achieving this endpoint at months 6 and 12 was 0.32 (0.29; 0.36) and 0.49 (0.45; 0.53), respectively (Figure S4A). Of the 438 FAS-M12 patients achieving this endpoint within 12 months, 30.1% reported an end of target achievement during the study, and 69.9% remained on target until study end. The median duration on target was 392 (325; 418) days (13.1 months) and the Kaplan-Meier estimate for further duration on target 180 days (6 months) after start of target achievement was 0.71 (0.66; 0.76) (Figure S4B).

The Kaplan-Meier estimate for achieving the efficacy endpoint of FPG target at month 6 and 12 was 0.21 (0.18; 0.24) and 0.27 (0.24; 0.30), respectively (Figure S5A); that is, <50% of FAS-M12 patients achieved this endpoint. Therefore, no estimation of median time to target achievement was possible. Of the 212 FAS-M12 patients achieving this endpoint within 12 months, 49.5% reported an end of target achievement during the study, and 50.5% remained on target until study end. The median duration on target was 232 (170; 325) days (7.7 months) and the Kaplan-Meier estimate for further duration on target 180 days (6 months) after start of target achievement was 0.56 (0.49; 0.63) (Figure S5B).

Four-point SMPG profiles consisted of morning preprandial and 2 h postprandial measurements after breakfast, lunch and dinner, respectively. Documentations were available for <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 S3).

There was no significant change in BW and BMI during the study. BW (mean ± SD) at baseline was 93.3 ± 19.1 kg (n = 755); until month 6 and 12 it decreased by −0.1 ± 6.3 kg (p = .6292; n = 650) and −0.3 ± 7.3 kg (p = .2420; n = 679), respectively.

3.4 | Insulin dose

The starting dose (mean ± SD) of Gla-300 at switch was 27.2 ± 15.0 U/day [n = 774; 0.30 ± 0.15 U/kg/day (n = 737)]. Until month 6 and 12, the Gla-300 dose increased significantly by 5.3 ± 11.2 U/day [n = 744; p < .0001; 0.06 ± 0.11 U/kg/day (n = 712; p < .0001)] and 6.0 ± 13.5 U/day [n = 762; p < .0001; 0.07 ± 0.14 U/kg/day (n = 725; p < .0001)], respectively, resulting in a final dose of 33.4 ± 19.9 U/day [n = 781; 0.36 ± 0.20 U/kg/day (n = 755)]. The final doses of previous BI, and Gla-300 start and final doses, stratified by previous BI, are provided in Tables S4 and S5.

3.5 | Hypoglycaemia

The incidence and event rates for symptomatic, confirmed symptomatic, nocturnal, severe and severe nocturnal hypoglycaemia over 12 months after switching the BI in BOT regimens to Gla-300 are shown in Table 2. Overall, incidences and event rates were low for a T2D population treated with BOT. Assessment of the hypoglycaemia incidence of the last 12 weeks before switching to Gla-300 versus hypoglycaemia incidence of the last 12 weeks before end of month

6 and 12 after starting Gla-300 treatment, respectively, revealed no significant changes in the incidence of confirmed, severe and nocturnal severe hypoglycaemia. In contrast, the incidence of symptomatic and nocturnal hypoglycaemia, respectively, decreased significantly after 6 (3.5% vs. 1.9%; $p = .0374$ and 2.9% vs. 0.6%; $p = .0007$) and 12 months (3.5% vs. 2.0%; $p = .0280$ and 2.9% vs. 0.6%; $p = .0002$), respectively (Table 2).

3.6 | Patient-reported outcomes

The treatment satisfaction score (mean ± SD) at baseline was 24.9 ± 7.5 (n = 622), which increased significantly by 5.0 ± 7.8 (n = 525) to 29.9 ± 5.2 (n = 591) at month 12 ($p < .0001$). The scores for perceived frequency of hypoglycaemia and hyperglycaemia at baseline were 1.3 ± 1.4 (n = 619) and 3.5 ± 1.5 (n = 622), respectively; both decreased significantly by −0.1 ± 1.7 (n = 524) to 1.1 ± 1.5 (n = 591; $p = .0087$) and by −1.2 ± 1.9 (n = 525) to 2.3 ± 1.7 (n = 591; $p < .0001$) at month 12, respectively.

3.7 | Safety

Table S6 shows the incidence of AEs, and serious and fatal AEs, reported for patients in the safety analysis set (n = 1603) over 12 months.

4 | DISCUSSION

The present prospective observational multicentre study, TOP-2, was conducted in Germany, Austria and Switzerland. It shows that within 12 months one-quarter of the patients achieved the FPG target and 56% achieved either their predefined individualized HbA1c or the FPG target after switching the BI in a non-Gla-300 BOT to Gla-300, with the highest FPG target achievement after switching from Gla-100 and lowest after switching from IDeg. The median duration at FPG target after achievement was nearly 8 months, and the probability to remain on target 6 months after achieving control was 56%. This benefit of time at target levels is also reflected by an improved glycaemic control: despite higher baseline levels in our study, FPG was significantly reduced showing comparable levels versus the Gla-300 arm in EDITION-2 at month 12.[12]

TOP-2 was designed to evaluate if the beneficial effects of switching the non-Gla-300 BI in BOT regimens to Gla-300 found in EDITION-2 translate into conditions of real-world use. The randomized, open-label phase 3a clinical trial EDITION-2 showed similar glycaemic control with Gla-100 and Gla-300, respectively, in adult people with T2D, but at a lower risk of overall hypoglycaemia from baseline to month 6[11] and of nocturnal hypoglycaemia to month 6 and 12[11,12] with Gla-300. In TOP-2, baseline values regarding diabetes duration and HbA1c were comparable with those documented in EDITION-2.[11] However, our study participants were approximately 7 years older, with lower BMI, higher FPG levels and more male participants. The final dose of previous BI was substantially lower than in EDITION-2.[11] Furthermore, previous BI included Gla-100, NPH, IDet and IDeg; the latter two were not included in EDITION-2.[11] Participants in TOP-2 versus EDITION-2[11] received less metformin, but more SU, DPP-4i and SGLT2i. In the pragmatic trials, REGAIN[15] and TRANSITION-2,[16] evaluating BOT-treated patients with T2D switching to Gla-300 versus other BI (Gla-100, NPH, IDet, IDeg), within the Gla-300 study arm, age,[15,16] proportion of male participants,[15] diabetes duration,[15] FPG,[15,16] metformin and SGLT2i[16] use at baseline were comparable with TOP-2. However, TOP-2 participants showed lower HbA1c,[15,16] less use of SU,[15,16] GLP-1RA[15,16] and used more DPP-4i.[15,16] In Take Control,[17] evaluating self- versus physician-managed titration of Gla-300 in insulin-naïve and BOT pre-treated patients with T2D, age, BMI, diabetes duration and baseline HbA1c (BOT pre-treated patients) were comparable with TOP-2, whereas baseline SU, GLP-1RA and metformin use was higher.

Glycaemic improvement in daily practice was also shown in TOP-2 by a clinically meaningful and continuous decrease in HbA1c, which after 6 months was comparable with that observed in EDITION-2,[11] starting from similar baseline levels. In TOP-2, HbA1c decreased slightly further, by an average of 0.2% until 12 months, suggesting an effective and stable glycaemic control in daily clinical practice over time. HbA1c reduction in TRANSITION-2[16] and Take Control[17] (BOT pre-treated patients) after 6 months was comparable with our results. Furthermore, similar proportions of patients achieved target HbA1c in TOP-2 and Take Control[17] after 6 months. In REGAIN,[15] FPG and HbA1c levels within the Gla-300 study arm showed smaller reductions from baseline until 6 and 12 months, respectively, compared with TOP-2; similarly, the HbA1c reductions observed in many other real-world analyses[10,18-22] were smaller than in TOP-2. Of note, in these studies,[10,18,19,21,22] 50%-80% of the participants used prandial insulin in addition to BI and they had longer diabetes duration. In two retrospective medical record analyses,[9,23] HbA1c reduction was greater than in our study; however, in these studies, 29% of patients also received prandial insulin after the switch to Gla-300. When stratified by previous BI use, in TOP-2, the highest proportions in FPG and HbA1c target achievement were observed in previous users of Gla-100 and NPH (FPG), and IDet and NPH (HbA1c), respectively, and least with previous IDeg. In addition, the most pronounced reductions in HbA1c and FPG levels were seen for IDet and NPH. This is in line with observations from DELIVER-2[10] and DELIVER-D+.[18] The observed trend in the results for NPH and IDet might partially be explained by the fact that baseline FPG and HbA1c levels were higher than those observed for Gla-100 and IDeg. However, previous Gla-100 users showed higher HbA1c and FPG reduction than previous IDeg users, despite lower baseline FPG [163.4 mg/dl (9.08 mmol/L) vs. 168.5 mg/dl (9.36 mmol/L)] and similar HbA1c (8.2% for both) levels with Gla-100. We did not observe any other differences between the subgroups, which might further explain these results.

Improvements in glycaemic control were achieved with final Gla-300 doses, which were less than half of those used at baseline and

month 12, respectively, in EDITION-2.[12] While starting doses in Take Control[17] were only slightly higher than in TOP-2, the dose increase was also double as high compared to TOP-2. These differences might, compared with the once-weekly dose adjustment applied in EDITION-2[11] and Take Control,[17] be because of the much more cautious dose titration of once every 2-4 weeks observed in TOP-2, even in the first weeks of titration (data on file). We found similar titration frequencies in real-world BI initiation with Gla-300[24] and Gla-100.[25,26] Slow titration appears to reduce the risk of hypoglycaemia to very low rates and to enable better development of the blood glucose lowering potential of glargine insulins. This is supported by the findings of King, who previously found a BI dose of about 0.2 U/kg/day to cover BI requirements in many patients with T2D.[27] However, with only one-quarter of patients achieving FPG target, titration might have been stopped too early in TOP-2.

Hypoglycaemia incidence and annualized event rates were very low for people with T2D treated with BI, and considerably lower than those observed in other studies.[11,12,15,16] Compared with the 12 weeks before switching the BI to Gla-300, the incidence of symptomatic overall and nocturnal hypoglycaemia significantly decreased with Gla-300 after 6 and 12 months. This is in line with findings from REGAIN,[15] where significantly less nocturnal symptomatic documented and overall (severe and/or symptomatic documented) hypoglycaemia were found versus other BIs, and from EDITION-2[11,12] and observational studies.[9,10,18,21,23,28]

The observed improvements in glycaemic control and hypoglycaemia were accompanied by a significant improvement in treatment satisfaction score and significant reductions in perceived frequency of hyperglycaemia and hypoglycaemia. Our results support improvements in patient-reported outcomes found in OPTIN-D,[19] captured by the short form of the Problem Areas In Diabetes Scale (PAID-SF) and the worry subscale of the Hypoglycaemia Fear Survey (HFS-W).

Major limitations of the present study were because of the non-interventional design, lack of randomization and lack of a comparator arm, as well as loss to follow-up, which might have introduced selection bias.[29] However, pre-post comparisons before and after switching to Gla-300 were feasible, and analyses of FAS-dropout patients with FAS-M12 patients have shown no clinically relevant differences between these groups. Another limitation is that part of the effects observed might be attributable to the Hawthorne effect, that is, the patients were voluntarily enrolled and prospectively followed, which might have influenced their behaviour because they knew they were being observed; however, the usefulness of this term for discussion of research results is questionable.[30] In addition, the contribution of factors other than switch to Gla-300 (e.g. OADs) to the results obtained cannot be ruled out. However, only minor changes of OAD use were observed from baseline to study end. Therefore, the results obtained here might not be fully representative for all people with T2D switching their BI in BOT regimens to Gla-300.

In conclusion, switching from another BI to Gla-300 in people with T2D insufficiently controlled on non-Gla-300 BOT regimens in German, Austrian and Swiss primary care settings was effective at reducing FPG and HbA1c levels. It allowed one-quarter of the patients to achieve the FPG target and more than half of them to achieve their personalized targeted glycaemic control within 12 months, with low overall rates of hypoglycaemia and lower incidence of symptomatic and nocturnal hypoglycaemia with Gla-300 compared with pre-switch incidences, and without weight gain.

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CONFLICTS OF INTEREST

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AUTHOR CONTRIBUTIONS

Substantial contributions to the conception and design of the work were made by Jochen Seufert, Andreas Fritsche, Stefan Pscherer, Helmut Anderten, Katrin Pegelow and Martin Pfohl. Substantial contributions to the conduction of the study and acquisition of data for the work were made by Jochen Seufert, Peter Wiesli, Andreas Fritsche, Stefan Pscherer, Helmut Anderten, Katrin Pegelow and Martin Pfohl. Analysis or interpretation of data for the work were undertaken by Jochen Seufert, Andreas Fritsche, Katrin Pegelow and Martin Pfohl. The work was drafted by Jochen Seufert, Martin Pfohl and Katrin Pegelow and was revised critically for important intellectual content by Peter Wiesli, Andreas Fritsche, Stefan Pscherer and Helmut Anderten. Jochen Seufert, Peter Wiesli, Andreas Fritsche, Stefan Pscherer, Helmut Anderten, Katrin Pegelow and Martin Pfohl 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.

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DATA AVAILABILITY STATEMENT

Data available on request due to privacy/ethical restrictions. The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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