



ORIGINAL RESEARCH

Real-World Study on Effectiveness of Insulin Glargine U300 After Oral Antidiabetic Drug Failure in Patients with Type 2 Diabetes in the Gulf Region

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ABSTRACT

Introduction: The effectiveness and safety of long-acting insulin glargine U300 (Gla-300), in patients with type 2 diabetes mellitus (T2DM) requiring insulin, has not been reported in the Gulf region.

Methods: Insulin-naïve patients with T2DM, uncontrolled on OADs, and prescribed Gla-300 were followed up in a 12-month prospective observational study. Gla-300 was titrated to glycemic targets. The primary endpoint (achieving glycemic targets) was evaluated at month 6 of treatment. The need for treatment intensification, safety, and patient-reported outcomes (PRO) were also reported.

Results: The study included 412 patients (61.7% men; age 52.2 ± 11.1 years and T2DM duration 10.7 ± 6.8 years). Almost 50% were on more than 3 OADs, mostly biguanides, sulfonylureas, and dipeptidyl-peptidase-4 inhibitors. Baseline HbA1c level was $9.2\% \pm 1.1\%$ and targets were set at $6.9\% \pm 0.4\%$. Baseline fasting plasma glucose was 11.5 ± 3.8 mmol/l. Fifty-seven patients (13.8%) achieved glycemic targets at month 6, hindered by baseline HbA1c $\geq 10\%$, frequent co-morbidities, older age, sub-urban/rural residence, and full-time employment. Levels of HbA1c dropped progressively by $0.96\% \pm 0.07\%$ (month 3), $1.29\% \pm 0.08\%$ (month 6), and $1.76\% \pm 0.06\%$ (month 12). Gla-300 dose was 17.0 ± 9.0 IU/day at baseline, 24.6 ± 9.6 IU/day at month 3,

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28.5 ± 9.9 IU/day at month 6, and 30.7 ± 10.7 IU/day at month 12. Three patients experienced non-severe hypoglycemia and a slight decrease in body weight and PROs improved.

Conclusions: In the Gulf, Gla-300 in patients with T2DM uncontrolled on OADs improved glycemic control, with low rates of hypoglycemia and improved PROs. Gla-300 dose up-titration from baseline to month 6 did not, however, result in a vast proportion of patients achieving their pre-determined HbA1c targets.

Trial Registration: ClinicalTrials.gov identifier: NCT03703869.

Keywords: Gla-300; Gulf region; Individualized HbA1c targets; Insulin-naïve patients; Treatment satisfaction; Type 2 diabetes mellitus

Key Summary Points

Why carry out the study?

Insulin glargine U300 (Gla-300) is long-acting insulin with comparable efficacy with insulin glargine U100 (Gla-100), but lower rates of severe hypoglycemia.

Insulin might be required to achieve glycemic control in patients with type 2 diabetes mellitus; but no data on the use of Gla-300 exist for patients in the Gulf region.

What was learned from the study?

Achieving individualized glycemic targets might be possible in about 14% of patients after 6 months of treatment with Gla-300, and upon up-titration of the baseline Gla-300 dose.

Quality of life is improved and hypoglycemia remains a very rare event upon treatment with Gla-300.

Gla-300 can be prescribed to patients failing to achieve their glycemic targets on oral medications, but up-titration of Gla-300 (insulin intensification) might be required.

INTRODUCTION

In accordance with current international guidelines for the treatment of type 2 diabetes mellitus (T2DM) after failure of oral therapy, the combination of oral anti-diabetes (OAD) treatment with basal insulin is started. Basal insulin can already be used after failure of metformin alone, i.e., when HbA1c value is greater than 7.5% in patients on metformin therapy [1] or greater than 8% on optimal therapy [2]. Recent updates from the American Diabetes Association (ADA 2022) favor the use of the glucagon-like peptide 1 receptor agonist (GLP-1 RA) instead of insulin or in combination with insulin, when possible [3]. However, insulin therapy may be initially considered on diagnosis for patients with HbA1c beyond 10% [2].

For long-acting insulins, several starting doses and titration algorithms have been proposed and used in randomized controlled trials, and proposed for use in clinical practice. In randomized clinical trials, insulin glargine U300 (Gla-300) has demonstrated efficacy and safety in comparison with insulin glargine U100 (Gla-100) [4–6]. HbA1c reduction was equivalent between the two insulin regimens; however, a lower incidence rate of documented and severe hypoglycemia was reported with Gla-300 compared with Gla-100 [4, 7, 8].

While efficacy and safety of Gla-300 have been established in clinical trials [4, 5], data regarding its use outside of the controlled setting of a clinical trial in some countries are limited. The ATOS is a global non-interventional observational study that aimed to provide data evaluating effectiveness and safety under “real-world” conditions of use of Gla-300 in Asia, the Middle East, North Africa, Latin America, and Eastern Europe [9].

The effectiveness and safety of Gla-300 was assessed when added to OADs and titrated to individualized goals in daily clinical practice. The primary endpoint was analyzed at 6 months; however, data were collected for 12 months in order to assess earlier and later effectiveness endpoints, requirement for treatment intensification, safety outcomes of

interest in T2DM, as well as patient-reported outcomes and healthcare resource utilization.

The study applied a “new-user” design, enrolling patients at the moment when they commenced treatment. This design is the recommended approach to minimize patient selection bias [10] and is similar to that of an interventional clinical trial, thereby allowing reasonable comparison of the observational data collected with clinical trial data.

The current chapter reports on data in countries of the Gulf region, namely Kuwait, Saudi Arabia, and the United Arab Emirates (UAE). The regional setting of this study was meant to facilitate data analysis on a regional basis, with the aim to enhance the significance of the results, as diabetes management can vary depending on the healthcare system, resources, and patient-support activities.

METHODS

Study Design

The global A Toujeo Observational Study (ATOS) was a prospective, observational, regional, multicenter study to collect information on patients with T2DM initiating basal insulin (Toujeo®; Gla-300) in countries across the world. The present manuscript reports data in three countries of the Gulf region: Kuwait, Saudi Arabia, and the UAE. This was a sub-analysis of an international study carried out in countries outside the United States (US) and Western Europe [9]. Patients initiating Gla-300 and enrolled in the study were assessed at four visits (observations) at the study site: baseline and months 3, 6, and 12. The visits were scheduled and performed according to clinical practice and the observation closest to the study schedule was recorded as a study visit. Insulin titration was performed at the discretion of the treating physician.

The study was conducted in accordance with the principles laid down by the 18th World Medical Assembly (Helsinki, 1964), and its latest amendments. Each participating country locally ensured that all necessary regulatory submissions were performed in accordance with

local regulations including local data protection regulations. The Institutional Review Board of King Abdulaziz University in Saudi Arabia (Reference number 17-18) has approved this study. All patients signed an informed consent form before any study-related activity.

Study Participants

Participating investigators (endocrinologists, diabetologists, internal medicine or general practitioners) who routinely prescribe Gla-300 and evaluate HbA1c every 6 months proposed participation in the study to all patients with T2DM who potentially met eligibility criteria.

Eligibility criteria were minimized to include almost all insulin-naïve patients who were prescribed insulin for the first time, according to the local prescribing information. Patients had to be at least 18 years old, treated with at least one OAD for at least 6 months, with HbA1c levels comprised between 7.0% and 11.0% in the 3 months leading up to study start and prescribed Gla-300. Pregnant or nursing women as well as patients with substance abuse problems and life expectancy below 1 year were excluded.

Study Endpoints

The primary endpoint was the percentage of participants achieving their pre-defined individualized HbA1c target (as determined by their treating physician) at month 6. Secondary efficacy endpoints included the percentage of participants achieving their pre-defined individualized HbA1c target at months 3 and 12 and changes in HbA1c, fasting plasma glucose (FPG), and self-monitored blood glucose (SMBG) from baseline to months 3, 6, and 12. Other study endpoints included changes in insulin dose, body weight and hypoglycemia incidence and rates, as well as incidence of adverse events (AEs).

Patient-Reported Outcomes

Patient-reported outcomes (PRO) were reported at each visit. The perception of blood glucose

control was measured using Diabetes Treatment Satisfaction Questionnaire on status (DTSQs). Health status was measured by EuroQol 5-dimension scale version 3L (EQ-5D-3L; treatment persistence and dosing time flexibility). The EQ-5D-3L was valued by the visual analogue scale (VAS) and the time trade-off (TTO) methods [11]. The VAS recorded the respondent's health on a vertical scale from 0 (worst imaginable health state) to 100 (best imaginable health state). The TTO values are anchored at 1 (full health) and 0 (dead), reflecting the estimation of Quality Adjusted Life Years and the person's perception of how 'livable' their condition is.

Statistical Considerations

Sample Size

The Gulf countries were included with other countries in the region (Western Asia) for sample size calculation.

The precision calculation was based on the two-sided 95% confidence interval (CI) for the percentage of patients reaching the predefined individualized HbA1c goal at month 6, assuming an expected percentage of patients at HbA1c goal at month 6 of 25%. Therefore, assuming a drop-out rate during the first 6 months of around 10% and for a precision of at least 3.8%, a sample size of 500 patients was to be enrolled. Collectively, 701 patients were evaluable in the Western Asia region, 288 of which were from the Gulf countries.

Endpoint Analyses

The primary endpoint was the percentage of patients achieving the predefined individualized HbA1c goal at month 6, as determined by their treating physician. If a predefined individual goal was not specified at baseline, a general HbA1c goal of < 7.0% was used. To identify any predictive baseline factors for HbA1c target achievement at month 6, univariate and multivariate logistic regression analyses were performed. A sensitivity analysis was performed on the primary efficacy endpoint to assess the impact of patients with missing HbA1c at month 6 by considering patients with missing 6-month HbA1c values as failures for

reaching the predefined individualized HbA1c target.

Continuous data were summarized using the number of observations available (N), mean, standard deviation (SD), minimum, median, maximum, and quartiles 1 and 3 (Q1 and Q3). Categorical data were summarized using counts and percentages. In general, descriptive statistics of quantitative effectiveness and safety parameters by scheduled visits were provided on observed cases. The baseline value of patients was defined as the last available value before the signature of the consent form.

All secondary analyses were performed on the evaluable population. Statistical tests were two-sided at a nominal 5% significance level. For continuous secondary effectiveness endpoints (HbA1c, FPG, and fasting SMPG) a mixed-model repeated measurement (MMRM) was used to estimate changes from baseline to months 3, 6, and 12. This model provided baseline-adjusted least square (LS) mean estimates and 95% CI on the changes at months 3, 6, and 12. Categorical endpoints were presented using descriptive statistics (number, percentages of patients and their 95% CI); patients with missing values at scheduled visits were considered as failures.

RESULTS

Study Participants

The study was carried out in 32 centers, most of which were private secondary healthcare institutions (12 [37.5%]), mostly located in urban areas (29 [90.6%]). Among participating physicians, 11 (34.4%) were endocrinologists, 11 (34.4%) were internal medicine specialists, nine (28.1%) were diabetologists, and one (3.1%) was a general practitioner.

Out of 446 patients screened for eligibility, 412 qualified to be enrolled in the study. Of those, only 289 patients had an HbA1c value at month 6. Over 50% of study patients were university graduates; 170 out of 289 patients held full-time jobs; 87% were urban dwellers and a total of 274 patients had medical insurance. Most patients (379 [92.0%]) lived with

Table 1 Patient characteristics

Study population
***N* = 412**

Male sex	254 (61.7%)		
Age, in years		BMI, in kg/m ²	
Mean ± SD	52.2 ± 11.1	Mean ± SD	30.3 ± 5.6
Median (range)	52.0 (26–82)	Median (range)	29.3 (19–64)
Age groups, <i>n</i> (%)		BMI categories, <i>n</i> (%)	<i>N</i> = 396
< 65	361 (87.6%)	< 25	57 (14.4%)
[65–75[	37 (9.0%)	[25–30[	157 (39.6%)
≥ 75	14 (3.4%)	[30–35[	114 (28.8%)
		≥ 35	68 (17.2%)
Educational level		Employment status	
Incomplete primary	14 (3.4%)	Full time	255 (61.9%)
Primary	40 (9.7%)	Not employed	99 (24.0%)
Secondary	111 (26.9%)	Retired	34 (8.3%)
University	211 (51.2%)	Part time	2 (0.5%)
Unknown	36 (8.7%)	Incapacity	1 (0.2%)
		Unknown	21 (5.1%)
Housing situation		Health insurance	<i>N</i> = 387
Urban area	366 (88.8%)	Public	155 (40.1%)
Rural area	30 (7.3%)	Private	203 (52.5%)
Sub-urban area	Sub-urban area	Public + private	29 (7.5%)
Unknown	3 (0.7%)		

BMI body mass index, *SD* standard deviation

another adult. Table 1 provides patient characteristics.

DESCRIPTION OF T2DM AT STUDY ENTRY

The history of T2DM was described for the study population at baseline. Table 2 summarizes the history of the disease, glycemic parameters and OADs at baseline, as well as T2DM-related complications and co-morbidities.

Around 50% of the 412 patients were also on a non-T2DM medication (208 [50.5%]); mainly

treatments for cardiovascular conditions (197 [47.8%]) and blood-related conditions (51 [12.4%]). Treatment with Gla-300 was taken by all 412 patients, for an average of 9.5 ± 4.5 months, with a median of 11.5 months (0.03–16.2 months).

DESCRIPTION OF GLYCEMIC PARAMETERS OVER TIME

Levels of HbA1c, FPG, and SMPG were recorded at each study visit, to reflect changes from baseline upon the introduction of treatment

Table 2 Characteristics of T2DM at baseline**Study population**
N = 412

Duration of T2DM, in years		Age at onset	
Mean $\pm$ SD	10.7 $\pm$ 6.8	Mean $\pm$ SD	43.5 $\pm$ 9.1
Median (range)	9.0 (1–39)	Median (range)	43.0 (21–80)
Intervals, n (%)		History of gestational diabetes	
< 1	0 (0.0%)		N = 158
[1–5[	71 (17.2%)		40 (25.3%)
[5–10[	143 (34.7%)		
$\geq$ 10	198 (48.1%)		
Oral anti-diabetes therapy			
<i>Duration, in years</i>	N = 406	<i>OAD class</i>	
Mean $\pm$ SD	10.3 $\pm$ 6.7	Biguanides	355 (86.2%)
Median (range)	9.0 (1–39)	Sulfonylureas	260 (63.1%)
<i>Number of OADs</i>		DDP-4 inhibitors	255 (61.9%)
One	68 (16.5%)	SGLT-2 inhibitors	103 (25.0%)
Two	151 (36.7%)	Thiazolidinediones	21 (5.1%)
		Glinides	3 (0.7%)
$\geq$ Three	193 (46.8%)	α -glucosidase inhibitors	2 (0.5%)
Glycemic parameters			
<i>HbA1c, in %</i>		<i>HbA1c categories, n (%)</i>	
Mean $\pm$ SD	9.2 $\pm$ 1.1	[7%–7.5%[	25 (6.1%)
Median (range)	9.0 (7–11)	[7.5%–8%[	24 (5.8%)
<i>HbA1c, in mmol/mol</i>		[8%–9%[	126 (30.6%)
Mean $\pm$ SD	77.0 $\pm$ 11.5	[9%–10%[	123 (29.9%)
Median (range)	75.0 (53–97)	$\geq$ 10%	114 (27.7%)
<i>FPG, in mmol/l</i>	N = 393	<i>Fasting SMPG, in mmol/l</i>	N = 340
Mean $\pm$ SD	11.5 $\pm$ 3.8	Mean $\pm$ SD	11.1 $\pm$ 3.0
Median (range)	10.8 (4–27)	Median (range)	10.3 (5.4–23.5)
Glycemic targets		<i>HbA1c target categories</i>	
<i>HbA1c target, in %</i>		< 7%	102 (24.8%)
Mean $\pm$ SD	6.9 $\pm$ 0.4	6.9 $\pm$ 0.4	288 (69.9%)
Median (range)	7.0 (6–8)	[7.5%–8%[	12 (2.9%)
		$\geq$ 8%	10 (2.4%)

Table 2 continued**Study population** $N = 412$

Conditions motivating HbA1c target > 7% (less stringent target)	$N = 310$
Extensive co-morbid conditions	20 (6.5%)
Age	18 (5.8%)
Long-standing diabetes in which the general goal is difficult to attain	14 (4.5%)
Advanced microvascular or macrovascular complications	11 (3.5%)
Patient attitude and expected treatment efforts	11 (3.5%)
Limited life expectancy	10 (3.2%)
Resources and support system availability to the particular patient	10 (3.2%)
History of severe hypoglycemia	8 (2.6%)
T2DM complications and co-morbidities in > 20% of patients	
Any complication and comorbidity history	274 (66.5%)
Dyslipidemia	234 (56.8%)
Hypertension	182 (44.2%)
Diabetic neuropathy	135 (32.8%)
Diabetic retinopathy	86 (20.9%)
Renal function impairment	85 (20.6%)
Microalbuminuria	59 (14.3%)
Macroalbuminuria	18 (4.4%)
Advanced kidney disease	7 (1.7%)

DPP-4 dipeptidyl peptidase 4, *HbA1c* glycated hemoglobin, *FPG* fasting plasma glucose, *OAD* oral anti-diabetes drugs, *SD* standard deviation, *SGLT-2* sodium-glucose co-transporter 2, *SMPG* self-monitored plasma glucose, *T2DM* type 2 diabetes mellitus

with Gla-300. Figure 1 presents changes in glycemic parameters throughout the study duration.

Achievement of the Primary Endpoint

The primary endpoint of achieving individually set HbA1c target (average of $6.9\% \pm 0.4\%$) by month 6 of treatment with Gla-300 was fulfilled by 57 patients (13.8% with 95% CI 10.6;17.6). To identify any predictive baseline factors for HbA1c target achievement at month 6, regression analyses were performed. Achievement of the primary endpoint milestone was not

significantly determined by most demographic or lifestyle characteristics reported in this study. Results of the univariate analysis showed that, albeit not statistically significant, a baseline HbA1c $\geq 10\%$ was associated with a lower likelihood of achieving HbA1c target at month 6: i.e., baseline HbA1c of [8–9% [(OR = 0.839; 95% CI 0.352;1.995), [9–10% [(OR = 0.665; 95% CI 0.272;1.625), and $\geq 10\%$ (OR = 0.523; 95% CI 0.205;1.336), when compared with a baseline HbA1c of [7–8%]. Additionally, a higher number of co-morbid conditions halved the likelihood of achieving HbA1c target (OR = 0.508; 95% CI 0.111;2.332). Age beyond 75 years

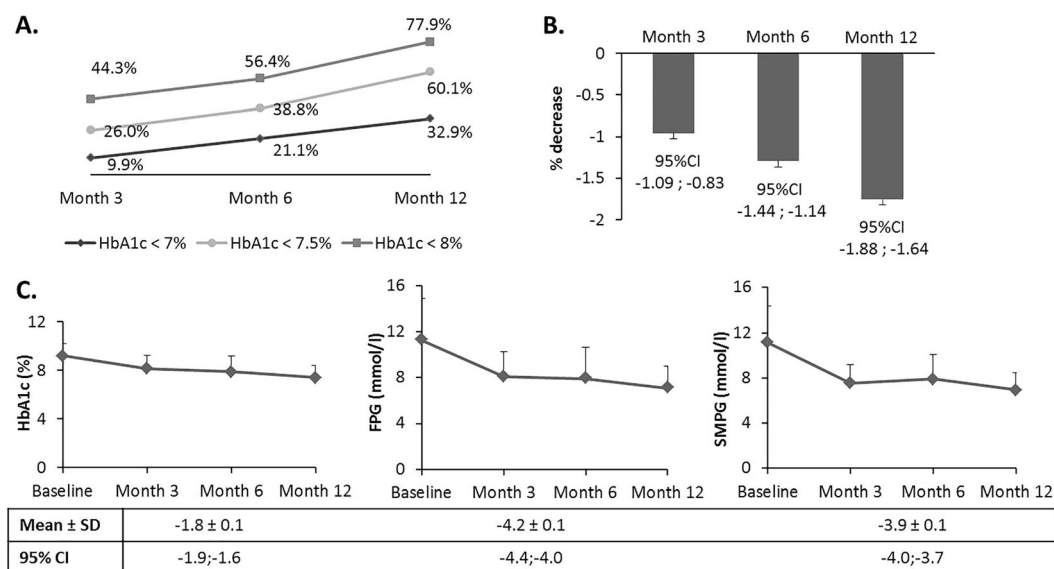


Fig. 1 Change in glycemic parameters from baseline over time ($N = 289$). **A** Progressively more patients reached their HbA1c target throughout the study duration. **B** The drop of HbA1c from baseline to each of the data points was consistent and significant with tight 95% CI. **C** Levels of HbA1c, FPG, and SMPG decreased over the study

duration. Overall drops from baseline until month 12 are displayed in the lower panel table. *CI* confidence interval, *FPG* fasting plasma glucose, *HbA1c* glycated hemoglobin, *SD* standard deviation, *SMPG* self-monitoring plasma glucose

resulted in around 49% lower likelihood of achieving the primary endpoint ($P = 0.138$; probably owing to the small group size). Achievement of predefined individualized HbA1c target at month 6 trends towards an association with the geographical area, since patients located in a suburban area ($OR = 0.492$; 95% CI 0.063; 3.864) or in a rural area ($OR = 0.656$; 95% CI 0.192; 2.240) were associated with a lower probability of achieving the HbA1c target at month 6 when compared with urban dwellers. Other parameters factored into the univariate analysis, such as BMI, number of comorbid conditions, prior use of OAD, as well as health insurance status, showed some trend of influencing HbA1c target achievement, without reaching the significance threshold.

Employment status was the only parameter that significantly modified the likelihood of HbA1c target achievement at month 6 ($P = 0.021$). Compared to full-time employees or students, retired patients ($n = 35$) were 2.893 times more likely to achieve HbA1c target ($P = 0.016$) and those with unknown

occupation status ($n = 21$) had 3.857-fold higher odds of achieving the primary endpoint of the study ($P = 0.007$).

Evolution of HbA1c Over Time

Out of the 412 patients included in the study, 289 had HbA1c levels reported beyond baseline. HbA1c levels dropped from $9.2\% \pm 1.0\%$ at baseline to $7.9\% \pm 1.13\%$ at month 6 of treatment. The proportion of patients achieving their HbA1c target increased over the study duration, with over 75% of patients reaching HbA1c < 8% at the end of the study (Fig. 1A).

Levels of HbA1c dropped progressively more over time, by -1.0 ± 0.1 on month 3, -1.3 ± 0.1 on month 6 and -1.8 ± 0.1 on month 12 (Fig. 1B). Briefly, all three parameters consistently decreased over 12 months (Fig. 1C).

At month 6, the highest proportion of patients achieving their HbA1c targets was among those whose baseline HbA1c was below 8% (29.0%, compared to 19.5% for patients in

the 8%-to-10% HbA1c range and to 16.4% for patients who baseline HbA1c was greater than 10%). By month 12, however, the highest proportion of patients achieving their HbA1c target was among those with baseline HbA1c between 8 and 10%. Treatment intensification by the addition of concomitant anti-T2DM medications was required in 40 patients (13.8%).

Secondary efficacy results showed that, at Month 6, the greater the predefined individualized HbA1c goal, the greater the percentage of patients achieving that goal. Thus at month 6 predefined individualized HbA1c goals of < 7%, 7–7.5%, 7.5–8%, and $\geq$ 8% were achieved in 11.8%, 17.6%, 66.7%, and 87.5% of patients, respectively.

COMPLIANCE WITH INSULIN DOSING SCHEDULE

Over 85% of patients in the evaluable population administered Gla-300 within one hour of schedule (219 [86.6%]). The 34 patients who deviated from the 24-h dosing regimen blamed it on forgetting the dose (22 [64.7%]) or on being away from home (12 [35.3%]) at the exact time. Only three patients deviated by more than 3 h. The proportion of patients abiding by dosing schedule increased to 90.8% at month 6 and to 92.9% at month 12. Gla-300 dose increased over the study period: 17.0 ± 9.0 IU/day at baseline, 24.6 ± 9.6 IU/day at month 3, 28.5 ± 9.9 IU/day at month 6 and 30.7 ± 10.7 IU/day at month 12.

DESCRIPTION OF SAFETY PARAMETERS

Adverse events (AEs) were described for the eligible population ($N = 412$). Over the first 6 months, four (1.0%) patients presented at least one AE and this number did not increase over the 12-month study period. A total of three patients only (0.7%) reported experiencing hypoglycemia during the study, without instances of severe hypoglycemia. Overall, treatment-emergent AEs (TEAEs) were reported in 1.0% of patients, while SAEs were reported in

0.2% of patients, TEAEs leading to discontinuation of study treatment were reported in 0.5% of patients, and there were no TEAEs leading to death reported.

On the 3-month data point, 15 visits to healthcare professionals were reported, down to seven visits on month 6 and to four by month 12.

CHANGE IN BODY WEIGHT

There were no significant changes in mean body weight over the 12-month study period. In the eligible population, the mean body weight evolved as follows: 83.3 ± 15.8 kg at baseline; 84.5 ± 14.3 kg at month 3, 83.5 ± 14.5 kg at month 6, and 83.0 ± 13.6 kg at month 12.

The decrease in body weight, albeit slight, was meaningful at month 6 with a change of -0.9 ± 0.2 kg (95% CI $-1.3; -0.5$) and at month 12 with a change of -1.5 ± 0.3 kg (95% CI $-2.0; -1.0$).

TREATMENT WITH GLA-300 IMPROVED PROS

Patients with data available throughout the study visits ($N = 289$) were asked to complete questionnaires that quantify their satisfaction from T2DM treatment, perceived hyperglycemia and hypoglycemia rates, and quality of life with the disease. Figure 2 shows that all PROs strongly improved upon the introduction of Gla-300 at baseline. In particular, the DTSQs scores improved sharply starting the third month of treatment, and kept increasing throughout the study duration (Fig. 2A). A closer analysis reveals a 7.7 ± 0.2 point increase from baseline to month 3 (95% CI 7.2; 8.2), a 9.8 ± 0.2 point increase by month 6 (95% CI 9.3; 10.2) and a 11.3 ± 0.2 point increase by month 12 (95% CI 11.0; 11.7). The perceived frequency of hypoglycemia and of hyperglycemia also increasingly dropped by two reported instances on month 3 and by 3.1 reported instances on month 12 for hyperglycemia and by 1.4 reported instances on month 3 and by 1.9 reported instances on

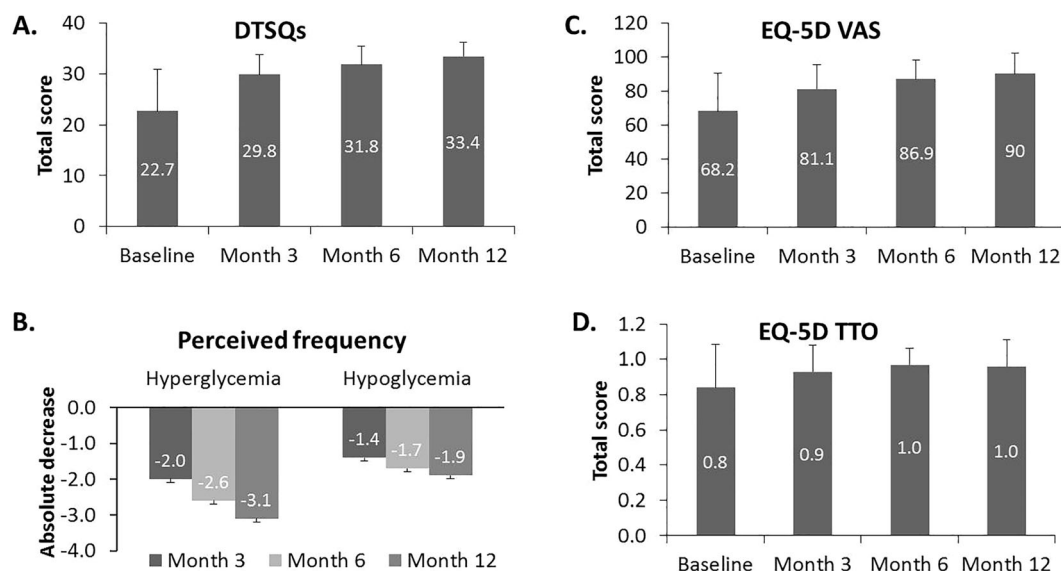


Fig. 2 Improved patient-reported outcomes over time. **A** DTSQs total score increased consistently from baseline to month 12 of treatment with Gla-300. **B** Perceived frequency of hyperglycemia and of hypoglycemia (both components of the DTSQs) dropped. **C** The EQ-5D VAS

improved over time. **D** The EQ-5D TTO improved as early as month 3 and was maintained throughout the study. *DTSQs* diabetes treatment satisfaction questionnaire on status, *VAS* visual analog scale, *TTO* time trade-off

month 12 for hypoglycemia (Fig. 2B). There was a robust increase in the EQ-5D VAS score from 68.2 ± 22.0 points at baseline to 90.0 ± 12.3 by month 12 (Fig. 2C). This was reflected by the patients' perception of their quality of life and their 'willingness' to live longer with T2DM, with EQ-5D TTO of 0.8 ± 0.3 at baseline to 1.0 ± 0.2 at month 12 (Fig. 2D).

DISCUSSION

The rationale for this sub-analysis of the global ATOS was to assess the real-world effectiveness and safety of Gla-300 in countries of the Gulf region. This recent formulation was developed to have a more extended time-action profile than its predecessor, Gla-100, for a better sustained glycemic control over a 24-h dosing interval [6]. Insulin-naïve adults (≥ 18 years) with T2DM and with uncontrolled HbA1c ($> 7\%$ to $\leq 11\%$) on more than one OAD, and in whom the treating physician had decided to add Gla-300 to existing OAD treatment, were enrolled in the study (412 eligible patients).

The primary endpoint of the study was fulfilled. Close to 14% of the 412 patients achieved their predefined individualized HbA1c target at month 6. The results were not aligned with the estimates for the primary endpoint per protocol, i.e., 25% of evaluable patients would reach their predefined individualized HbA1c goal at month 6. Moreover, another study reported even higher proportions of HbA1c target achievement after 6 months of Gla-300 treatment (34.8%) [12]. Further investigation is warranted to identify gaps in treatment of patients with T2DM in the Gulf region.

Of particular interest in long-term T2DM management, HbA1c percentage levels dropped progressively more over time, with tight 95% CI, indicating that the HbA1c percent decrease is robust, reliable, and generalizable to populations with similar profile and healthcare systems. A very recent study reported a 2.1% decrease in HbA1c levels after 6 months of treatment with Gla-300 [13]; this slightly higher percent decrease might be due to a much larger sample size ($N = 1095$ patients). However, a study in the Czech Republic reported similar drops in HbA1c levels by $0.9\% \pm 1.1\%$ at

month 6 [14]. The ORBIT registry reported on the use of basal insulin in a large cohort of patients with T2DM, whose glycemia was uncontrolled on OADs and who were insulin-naïve; mean HbA1c was 9.6% at baseline and 7.4% at 6 months [15], comparable to HbA1c drop achieved in the ATOS Gulf chapter. In a 6-month follow-up study in 2019, the mean HbA1c went from $9.2 \pm 1.4\%$ at baseline to $7.9 \pm 1.1\%$ ($P < 0.001$) after addition of basal insulin to OAD treatment [16]. Treatment of insulin-naïve Japanese patients with T2DM with a biosimilar basal insulin resulted in a 1.5% decrease in HbA1c after 12 months of treatment [17], with Gla-300 in the current study achieving a 1.8% drop by month 12 of treatment.

The secondary efficacy results showed that, at month 6, the greater the predefined individualized HbA1c goal, the greater the percentage of patients achieving that goal. This underscores the importance of setting individualized HbA1c targets, which are attainable.

In an attempt to uncover determinants of HbA1c target achievement after 6 months of Gla-300 treatment, regression analysis reported on the likelihood of achieving individual targets based on sex, age, BMI, number of comorbid conditions, prior use of OAD, as well as place of residence and health insurance status. Some of these parameters showed trends of influencing HbA1c target achievement without, however, reaching the significance threshold. A larger sample size might allow for more rigorous determination of trends and factors that collectively dictate response to Gla-300 treatment and glycemic target achievement. A 2019 study found that male sex, being insulin-naïve, and lower Gla-300 starting dose are potential predictors of HbA1c target achievement [18].

Patients whose baseline HbA1c levels ranged between 8 and 10% more frequently achieved their HbA1c targets by the end of the first year of treatment. In fact, while the current study did not find a significant association between baseline HbA1c and target achievement, analyses from the REALI pooled database point at baseline HbA1c as the major predictive factor of achieving HbA1c target $< 7.5\%$ [18]. Results from the Gulf chapter of the ATOS suggest that

patients with HbA1c of 8–10% will likely benefit from a year-long treatment with Gla-300. In addition, reductions in mean HbA1c levels, in FPG and fasting SMPG levels were observed over the 12-month period, reflecting an improvement in glycemic control [14].

Gla-300 is not bioequivalent to Gla-100, and dose adjustment is needed when patients are switched from Gla-100 or other basal insulins to Gla-300 [19, 20]. In insulin-naïve patients, and given the novelty of Gla-300, dose adjustment needs to be tailored on a case-by-case basis, after treatment initiation. The mean Gla-300 daily dose by month 6 (28.5 ± 9.9 U/day) was lower than the reported dose of 59.4 ± 32.3 U/day in a randomized trial [4]. Patients with prior insulin exposure achieved daily Gla-300 doses of 103 ± 42 U/day and 91 ± 37 U/day, respectively [7, 8]. This suggests that with improved insulin dose titration, more patients may achieve their target HbA1c in a real-life setting.

Treatment of T2DM entails a fine balancing act between achieving glycemia control, avoiding insulin resistance and preventing safety issues, such as hypoglycemia [6, 21]. The frequency of documented symptomatic and severe hypoglycemic events reported during night and at any time of day or night was low, and weight followed a decreasing pattern. The safety profile for Gla-300 indicated no unexpected safety findings, matching reports in the literature [5, 7, 12, 13, 22, 23]. A recent study comparing Gla-300 to a fixed-dose combination of insulin degludec/aspart (IdegAsp) reported on similar effectiveness of both formulations in a basal-bolus regimen, but greater and more significant decrease in hypoglycemia rates upon Gla-300 use for over 12 months [24]. Upon requiring healthcare, patients mostly visited endocrinologists, educators, dieticians, and ophthalmologists.

The DTSQs results indicated improvement in patient treatment satisfaction and a decrease in the perceived frequency of hypoglycemia and hyperglycemia. The results of the EQ-5D-3L indicated patients considered they had an improvement in health status over the course of the study. These findings are in agreement with the literature [12, 14, 25]. In addition, Gla-300 has been associated with medication

convenience in terms of smaller volume for injection [26]. This study reflected dosing convenience, with large proportions of patients complying with their insulin dosing schedule.

Despite the relatively small sample size, exacerbated by the shortcomings of losing 30% of eligible patients for primary analysis (due to lack of HbA1c values at month 6, reflecting the local and regional patient behavior), this observational study demonstrated promising effectiveness and safety of Gla-300 in countries with diverse healthcare systems.

CONCLUSIONS

In a real-life global setting in countries of the Gulf region, the initiation of Gla-300 in patients with T2DM uncontrolled on OADs resulted in improved glycemic control, low rates of reported and perceived hypoglycemia and increasingly improved PROs throughout the study duration; reflecting treatment satisfaction and better health status.

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Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflict of Interest. Amr M. Hassan and Yasser A. Akil are Sanofi employees, with financial interests in the Company. Authors Niaz E. Khan, AbdulRahman A. M. Al Shaikh, Ahmed A. K. Hassoun, Mona M. Salah, Nabeela A. Al Abdella, Saher S. M. Safarini, and Waleed A. Al Dahi declare no conflict of interest.

Ethical Approval. The Institutional Review Board of King Abdulaziz University in Saudi Arabia (Reference number 17-18) has approved this study. All patients signed an informed consent form before any study-related activity. The study was conducted in accordance with the principles laid down by the 18th World Medical Assembly (Helsinki, 1964), and its latest amendments.

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