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Effectiveness and Safety of Initiation and Titration of Insulin Glargine 300 U/mL in Insulin-Naive Patients with Type 2 Diabetes Mellitus Uncontrolled on Oral Antidiabetic Drug Treatment in Turkey: The EASE Study

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ABSTRACT

Objective: The aim of the study was to evaluate the effectiveness and safety of insulin glargine 300 U/mL (Gla-300) in insulin-naive patients with type 2 diabetes mellitus (T2DM) inadequately controlled on oral antidiabetic drug (OADs) treatment in Turkey.

Methods: One hundred eight patients from 20 centers enrolled in the study. Starting from baseline, Gla-300 was self-administered subcutaneously and once daily in the evening. The primary outcome was the mean change in glycated hemoglobin A1c (HbA1c) from baseline to week 24.

Results: The mean (±SD) Hb1Ac level of 9.4% (±0.8) at baseline decreased to 7.5% (±0.9) at week 12 ($P < .1$) and to 7.3% (±0.9) at week 24 ($P < .1$). Although none of the patients were within the target Hb1Ac level of ≤7% at baseline, the percentage of patients who achieved the target Hb1Ac level was 30.4% at week 12 and increased to 42.9% at week 24. Gla-300 treatment achieved the Hb1Ac target in 21 (19.4%) patients without experiencing a hypoglycemic event and in 27 (25.0%) patients who experienced at least one hypoglycemic event. For each self-monitoring blood glucose time point, significant improvements were observed as compared to baseline ($P < .001$). Statistically significant improvement ($P < .001$) was seen in the treatment satisfaction questionnaire – status version scores between baseline and week 24.

Conclusion: This study indicated that Gla-300 is effective to provide a successful glycemic control with low risk of hypoglycemia added to OADs in insulin-naive patients with T2DM, and it has the potential to improve the quality of life of patients.

Keywords: Gla-300, HbA1c, hypoglycemia, insulin, OAD, type 2 diabetes mellitus, insulin-naïve

Introduction

Type 2 diabetes mellitus (T2DM) is a chronic, progressive disease characterized by various microvascular and macrovascular complications, resulting in organ and tissue damage. The primary defects leading to T2DM are insufficient insulin production and insulin resistance. The development of relative insulin deficiency at the early onset of T2DM progresses to absolute insulin deficiency in the late stages of the disease.[1,2]

In progression of the disease, β-cell failure develops along with hyperglycemia and hypoinsulinemia. Data from the United Kingdom Prospective Diabetes Study (UKPDS) revealed that β-cell dysfunction could be detected 15 years before the clinical diagnosis of the disease. At the time of diagnosis, β-cell function is declined by nearly 50%-80%.[2,3] Because of the progressive nature of T2DM, it is estimated that a very high percentage of patients with T2DM will eventually require treatment intensification to achieve adequate glycemic control, despite ongoing treatment with oral antidiabetic drugs (OADs) with/without glucagon-like peptide-1 receptor agonists (GLP-1 RAs). Additionally, clinical evidence shows that the median delay in insulin initiation and intensification varies between 4 and 7 years.[4,5]

Glycated hemoglobin A1c (HbA1c) is recognized as an important marker for glycemic control. The most optimal achievable HbA1c target is defined by the American Diabetes Association (ADA) as less than 6.5% for patients without undue exposure to hypoglycemia or treatment-related adverse events and as less than 8% for patients with previous episodes of severe

hypoglycemia, progressive microvascular and macrovascular complications and comorbidities, and long-term diabetes in which it is difficult to manage blood glucose.[6]

Insulin is considered the most effective blood glucose-lowering therapy in patients with T2DM who are unresponsive to diet, exercise, and OADs with/without GLP-1 RAs treatment and is recommended in patients who have HbA1c levels greater than 10%.[7]

Failure in reaching treatment targets is mainly due to ineffective insulin dose titration.[8] Although the mean total daily dose of basal insulin analogs in Turkey is 25.4 international units,[9] international guidelines recommend that dose optimization and glycemic targets should be individualized by taking into consideration of each patient's age, duration of diabetes, OADs with/without GLP-1RAs usage, body mass index, and risk of hypoglycemia.[10]

The new formulation of insulin glargine 300 U/mL (Gla-300) has been developed to optimize glycemic control while minimizing the risk of hypoglycemia. Following subcutaneous (SC) injection, the pharmacokinetic and pharmacodynamic profiles of Gla-300 are more constant and prolonged compared with Gla-100 due to a more gradual and extended release of insulin glargine from the SC depot.[11] The 24-week study results from the EDITION 3[12] and the BRIGHT[13] revealed that HbA1c targets of 7.8% and 7.03% were achieved, respectively, in the Gla-300 treatment group, and quality of life (QoL) was improved in insulin-naïve patients who used insulin glargine with their ongoing OAD with/without GLP-1 RAs treatment regimen.

The aim of this study was to evaluate the effectiveness and safety of initiation and titration of Gla-300 and to determine the achievement of HbA1c target values in insulin-naive patients with T2DM inadequately controlled on OADs treatment in Turkey.

Materials and Methods

Study Design and Population

This study was designed as a national, multicenter, prospective, interventional, open-label, single-arm, 24-week, phase IV study to assess the mean HbA1c change from baseline to week 24 with a second-generation basal insulin analogue (Gla-300) in patients with T2DM across 20 study centers from 10 different cities in Turkey. The study consisted of 2 weeks of screening period, 24 weeks of treatment period, and a 2-7 days of follow-up period.

The study was conducted in accordance with the Declaration of Helsinki and the Good Clinical Practice guidelines. Written informed consent was obtained from all participating patients. This study is also registered at clinicaltrials.gov (NCT02954692). This study was approved by the Ethics Committee of Kocaeli University Faculty of Medicine with approval number KİA 2016/149 (date: June 7, 2016).

The inclusion criteria specified adults (aged ≥18 years) diagnosed with T2DM for at least 1 year, a HbA1c level of 8%-11% (insulin-naive), stable antidiabetic treatment for at least 3 months, with more than 1 OAD without insulin for at least 6 months, willingness to adhere to treatment and titration [including self-injection and self-monitoring blood glucose (SMBG)] and a signed informed consent form.

Patients, who had type 1 diabetes mellitus, secondary T2DM, experience hypoglycemia unawareness, alcohol/drug abuse, used of any insulin therapy, including premix, basal plus/basal bolus regimen from the diagnosis; were pregnant or lactating, were excluded from the study.

MAIN POINTS

- After the initiation of insulin treatment with insulin glargine 300 U/mL (Gla-300), the percentage of patients within the defined target glycated hemoglobin A1c (HbA1c) level of ≤7% successfully increased to 42.9% by the 24-week treatment.
- The mean decrease in HbA1c levels was comparatively higher than the changes from previous clinical trials.
- Twenty-four-week once-daily dosing of Gla-300 provided successful targeted glycemic control with a lower risk of hypoglycemia.
- The study findings indicated that Gla-300 was well tolerated with a good safety profile in patients with T2DM.

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Study Intervention

Insulin glargine 300 is a new basal insulin analogue, which is a formulation of insulin glargine that delivers the same amount of Gla-100 in 1/3 volume, and each pen (SoloSTAR®) contains in total 450 U of insulin glargine (1.5 mL of 300 U/mL insulin glargine solution).

All patients were trained by study site staff on how to use the pen correctly, how to store it, and how to change the needle for pen-injector device at visit 0. At visit 1 (day 0), patients were required to demonstrate competence in the unaided use of the injection device, including dose setting, practice injection into a practice pad, and troubleshooting.

Starting from baseline (day 1), patients self-administered Gla-300 SC once daily; the beginning dose was 0.2 U per kg body weight in the evening. The insulin dose was adjusted to a target range for fasting SMBG of 80-130 mg/dL as per the ADA and the European Association for the Study of Diabetes recommendations.[14] The Gla-300 dose was adjusted based on the median of at least 3 fasting SMBG measurements in the days before dose adjustment, including the day of adjustment.

Insulin doses were adjusted twice weekly, no more often than every 3 days. Titration was followed by telephone visits. Patients were allowed to decrease doses by more than 3 U if median fasting SMBG was <80 mg/dL, or ≥2 symptomatic or one severe hypoglycemia events occurred in the preceding week, and increase doses by more than 3 U if median fasting SMBG was >130 mg/dL. In order to achieve the glycemic target (80-130 mg/dL), patients continued their current regimen without any change. Insulin glargine 300 dose wasn't up-titrated if hypoglycemia occurred during the period when fasting SMBGs were measured.

Gla-300 was administered daily in the evening, which was defined as the time period from immediately prior to the evening meal until bedtime. It was defined at the start of the study and maintained as a reference time for the whole duration of the study. If necessary, a flexibility of ±3 hours was allowed.

Patients were allowed to use their noninsulin OADs concomitantly (except thiazolidinediones) until the end of the study unless safety concerns necessitate an OAD dose adjustment or discontinuation. Any change to OADs was based on a comprehensive assessment of the patient's glycemic control.

Study Outcomes

The primary outcome of this study was the mean change in HbA1c from baseline to week 24. The secondary outcomes included the percentage of patients achieving target fasting SMBG (80-130 mg/dL) at weeks 12 and 24 without experiencing severe and/or confirmed hypoglycemia, percentage of patients experiencing hypoglycemia, and the number of hypoglycemic events per patient per year during the treatment period, as well as the percentage of patients reaching target fasting SMBG (80-130 mg/dL) at week 12 and week 24 and mean changes in HbA1c from baseline to week 12 and fasting plasma glucose (FPG) from baseline to weeks 12 and 24.

Patients were asked to complete a diabetes treatment satisfaction questionnaire (DTSQ) at baseline and at the end of the study (week 24). The DTSQ has been specifically designed to measure treatment satisfaction scores in patient with diabetes. Diabetes treatment satisfaction questionnaire also evaluates the patients' willingness to maintain prescribed treatment regimen.

Hypoglycemia categories were defined as confirmed [≤3.9 mmol/L (≤ 70 mg/dL)] or severe hypoglycemia (requiring external assistance for recovery) and confirmed [<3.0 mmol/L (<54 mg/dL)] or severe hypoglycemia. The hypoglycemic episodes were recorded in the patient diary throughout the study period by measuring 7-point SMBG with a glucose meter.

The other exploratory outcome was continuous glucose monitoring (CGM) data, which was measured at the screening visit and visit 4 only in 12 patients. Glycemic data were obtained over 24 hours [area under the curve (AUC) mean 24 hours] and separately for the daytime period [(AUC) mean daytime; 06:00-23:59 hours] and the nocturnal period [(AUC) mean nocturnal; 00:00-05:59].

Determination of Sample Size

The sample size estimation was based on the precision of the mean change estimate in HbA1c (the distance from mean to the upper or lower limit of 95% CI). With an expected standard deviation of 1.4% for HbA1c change between baseline and week 24, a total of 88 evaluable patients would allow to estimate the HbA1c change with a precision of at least 0.29%. The level of precision was hypothetically selected. Taking into account a dropout rate of 20%, it was planned to include a total of 110 patients.

Statistical Analysis

Statistical analysis was performed by using STATA, Multivariate Statistics (release version 14.0). Continuous data were summarized using the number of available data, mean, standard deviation, median, minimum, and maximum for the study group. Categorical and ordinal data were summarized using the number and percentage of patients in the study group.

Comparisons were performed by using paired sample *t*-test or one-way repeated measures analysis of variance (ANOVA) (if continuous data were normally distributed), Wilcoxon signed-rank test, or Friedman test (if continuous data were non-normally distributed). For post hoc tests of repeated measures ANOVA, Tukey test with Bonferroni correction was used. For post hoc tests of Friedman test, Wilcoxon signed-rank test with Bonferroni correction was used. No multivariate testing was performed for the detection of confounding factors that may have attributions to safety and efficacy outcomes of the study.

Results

Baseline Characteristics

A total of 144 patients were screened, and 112 were found eligible according to the inclusion/exclusion criteria. Four patients were excluded from the efficacy population due to nonattendance at follow-up visits. Efficacy analysis was performed with 108 patients' data (Figure 1). Patient demographics and distributions are summarized in Table 1.

Primary Outcome

The mean (±SD) HbA1c level of 9.4% (±0.8) at baseline decreased to 7.3% (±0.9) at week 24. The mean change of HbA1c in 12 weeks was −1.8% (±1.3) and −2.0% (±1.1) after 24 weeks. There was a significant difference between HbA1c levels at baseline as compared to week 24 ($P < .1$; Table 2).

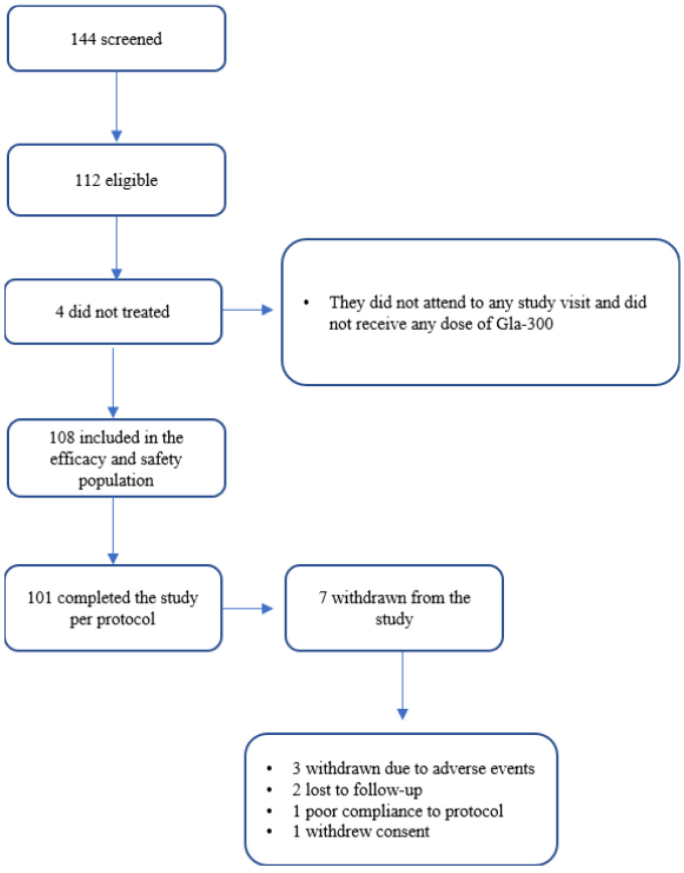

Figure 1. Consort diagram. Gla-300, glargine 300 U/mL.

Secondary Outcomes

The mean HbA1c (±SD) level significantly decreased from 9.4% (±0.8) to 7.5% (±0.9) at week 12 as compared to baseline ($P <$ .001; Table 2). The percentage of patients who achieved the target HbA1c level of ≤7% was 30.4% at week 12 and increased to 42.9% at week 24.

The mean FPG level of 194.7 (±51.4) mg/dL at baseline significantly decreased to 126.5 (±32.8) mg/dL at week 12 ($P <$ .001) and increased to 131.0 (±36.1) mg/dL at week 24 ($P <$ .001; Table 2). The mean decrease in FPG levels was −71.7 (±53.7) mg/dL at week 12 and −67.2 (±61.9) mg/dL at week 24 as compared to baseline.

At baseline, only 8.9% of the patients were within the target fasting SMBG level of 80-130 mg/dL. This ratio increased to 65.7% at week 12 and remained above 63% at week 24. Twenty-nine (28.4%) patients without experiencing any hypoglycemic events and 34 (33.3%) patients with at least one hypoglycemic event reached the target fasting SMGB levels at week 24 (Table 2).

The starting dose of Gla-300 was 0.2 (±0.11) U per kg at baseline. The mean daily Gla-300 dose increased from baseline to 0.33 (±0.10) U per kg at week 12, and 0.36 (±0.11) U per kg at week 24 ($P <$ .001).

After the initiation of Gla-300 treatment, the proportion of patients who reached the target prebreakfast SMBG levels was 41.7% at week 4, 25.9% at week 12, and 13.9% at week 24. Approximately one-fifth of patients (18.5%) could not reach to the target prebreakfast SMBG during the study.

Table 1. Demographics and Baseline Characteristics*

Patient distribution (n)	
Eligible	112
Excluded patients	4
Male, n (%)	52 (48.1)
Female, n (%)	56 (51.9)
Age, mean (SD) (years)	55.9 (8.1)
Weight, mean (SD) (kg)	83.5 (15.9)
Height, mean (SD) (cm)	162.4 (10.5)
BMI, mean (SD) (kg/m^2)	31.8 (6.0)
Diabetes duration, mean (SD) (years)	8.8 (5.3)
HbA1c, mean (SD) (%)	9.4 (0.8)
FPG, mean (SD) (mg/dL)	199.2 (55.0)
Total bilirubin, mean (SD) (mg/dL)	0.5 (0.2)
AST, mean (SD) (U/L)	21.3 (10.4)
ALT, mean (SD) (U/L)	24.9 (13.3)
ALP, mean (SD) (U/L)	86.5 (29.6)
GGT, mean (SD) (U/L)	31.1 (19.0)
Creatinine, mean (SD) (mg/dL)	108 (0.2)
Systolic blood pressure, mean (SD) (mmHg) (n = 107)	135.2 (21.9)
Diastolic blood pressure, mean (SD) (mmHg) (n = 107)	80.7 (11.6)
Heart rate, mean (SD) (bpm) (n = 106)	83.7 (12.2)
Oral antidiabetic drugs, n (%)	
Metformin	98 (90.7)
Sulfonylureas	66 (61.1)
DPP-IV inhibitors	39 (36.1)
Alpha-glucosidase inhibitor	11 (10.2)
Meglitinides (glinides)	10 (9.3)
Thiazolidinediones	8 (7.4)
GLP-1 receptor agonist	2 (1.9)
SGLT-2 inhibitors	2 (1.9)
Diabetes complications at screening	
Diabetic neuropathy, n (%)	38 (35.2)
Diabetic retinopathy, n (%)	12 (11.1)
Diabetic nephropathy, n (%)	10 (9.3)
Nicotine consumption	
No, n (%)	80 (74.1)
Alcohol consumption	
No, n (%)	105 (97.2)
Diet regimen	
No, n (%)	83 (76.9)

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; DPP-IV, dipeptidyl peptidase IV; FPG, fasting plasma glucose; GGT, gamma-glutamyl transferase; GLP, glucagon-like peptide; HbA1c, glycated hemoglobin; SD, standard deviation; SGLT, sodium−glucose cotransporter.
*All (n = 108).

Seven-point SMBG values were measured at prebreakfast, postbreakfast, prelunch, postlunch, predinner, postdinner, and bedtime timepoints at baseline, week 12, and week 24. Improvements observed at each SMBG time point were significant compared to baseline ($P <$ .001).

There was a minor increase in mean body weight, from 83.1 (±15.9) kg at baseline to 83.6 (±16.1) kg at week 12 ($P = .3$) and 84.0 (±15.5) kg

Table 2. Mean Glycated Hemoglobin (%), Fasting Plasma Glucose (mg/dL) Levels, and insulin glargine 300 (units/day) at Baseline vs. Week 12 and Week 24, Target Glycated Hemoglobin Levels (≤7%), and Self-Monitoring Blood Glucose Levels at Week 24

	n	Mean (%)	Median	SD	Minimum Maximum	P[1]
Mean Hb1Ac levels (%)						
Baseline	108	9.4	9.3	0.8	7.5-11.0	
Week 12	108	7.5	7.4	0.9	6.0-10.5	<.001
Week 24	108	7.3	7.2	0.9	5.8-10.2	<.001
Mean FPG levels (mg/dL)						
Baseline	108	194.7	183.5	51.4	106.0-396.0	
Week 12	103	126.5	120.0	32.8	66.0-245.0	<.001
Week 24	103	131.0	125.0	36.1	48.0-243.0	<.001

	Patients with hypoglycemia		Patients with no hypoglycemic event		Total	
SMBG levels at week 24	**n**	**%**	**n**	**%**	**n**	**%**
Achieved target (80-130 mg/dL)	34	33.3	29	28.4	63	61.7
Above target (>130 mg/dL)	13	12.7	24	23.5	37	36.2
Below target (<80 mg/dL)	1	1.0	1	1.0	2	2.0
Total	48	47.0	54	52.9	102	100.0

HbA1c, glycated hemoglobin; FPG, fasting plasma glucose; Gla-300, insulin glargine 300 U/mL; N, number of patients; SMBG, self-monitoring blood glucose; SD, standard deviation.
[1]Compared to baseline (Wilcoxon test).

at week 24 ($P = .042$). Treatment with Gla-300 resulted in a statistically significant increase in mean body weight at week 24 as compared to baseline.

At least one hypoglycemia event was reported in 48 patients (44.4%), with a total of 193 hypoglycemic events. Four events were considered severe hypoglycemia, which required the assistance of another person. The majority of the hypoglycemic events (91.8%) occurred during the daytime (between 06:00 and 23.59). Distribution of hypoglycemic events according to event severity and time is presented in Table 3.

Almost one in every 5 patients (19.4%) reached the target HbA1c level without experiencing a hypoglycemic event, whereas one in every four (25.0%) who achieved the target HbA1c level experienced at least one hypoglycemic event. Hypoglycemia and the distribution of hypoglycemic events in patients within or out of the target range of HbA1c levels according to time and event severity are summarized in Table 3.

The mean DTSQ-status version scores significantly improved from baseline to week 24 in overall patients (from 24.76 to 30.08; $P < .001$). The mean DTSQs score of perceived frequency of hyperglycemia significantly improved from 4.6 at baseline to 2.3 at week 24 ($P < .001$). However, the mean hypoglycemia scores remained almost unchanged ($P = .681$; Table 4).

Continuous glucose monitoring was planned in a subgroup of 15 patients and was performed with 12 patients from two study centers. According to CGM data, percentage (%) of time where glucose concentrations were within the target range of 80-130 mg/dL for each visit increased from 11.7% at baseline to 35% at visit 4 (Table 5).

Safety Evaluation

Hypoglycemia (0.9%) was the most frequent serious adverse event (SAE). During the study, 1 case of symptomatic overdose was reported as an adverse event of special interest (AESI). Sixty-nine nonserious AEs, 13 SAEs, and one AESI were reported in 42 patients during the treatment period. The most common adverse events were infections and infestations (influenza, 4.6%), administration site conditions (injection site hemorrhage, 1.9%), and gastrointestinal events (diarrhea, 1.9%).

Seven patients did not complete the treatment period as per protocol. Three patients discontinued their treatments due to adverse events, whereas poor compliance with protocol, lost to follow-up, and withdrawal of consent were other recorded reasons for discontinuation.

Discussion

In our study, all patients were out of target HbA1c levels (≤7%) at baseline despite their ongoing treatment with different OADs. The results from the IDMPS[15] and the PURE[16] studies showed that the percentage of patients achieving the target HbA1c of 7% was found to be 28% and 25%, respectively. In EDITION 3[12] and BRIGHT[13] studies, 43.1% and 48.7% of the patients, respectively, reached this HbA1c target, very close to the percentage observed in our study.

The study findings of HbA1c reductions are in general agreement with those obtained in other real-world evidence studies with Gla-300, such as EDITION 3, GOAL_RO, and the RESTORE-2 Naive Study.[12,17,18] Recently, Yu et al[19] in a randomized, 20-week, 2-titration algorithms of insulin detemir in insulin-naïve patients with T2DM found very similar HbA1c reductions with our results. On the contrary, in a noninterventional prospective study by AlMalki et al,[20] insulin degludec provided statistically significant and clinically meaningful improvements in HbA1c, with a mean change reduction of −1.6% points from baseline to 26-week in insulin-naïve T2DM patients.

In patients with HbA1c remaining above target on basal insulin, ADA suggests that fixed ratio combination products containing basal insulin plus a GLP-1 RA, such as insulin glargine plus lixisenatide and insulin degludec plus liraglutide, may help to improve the management of T2DM. Insulin intensification is recommended by adding prandial insulins to basal insulin regimen.[21]

Table 3. Distribution of Hypoglycemic Events by Time, Severity, and Frequency (Glycated Hemoglobin Level, Assistance Requirement, and Time) and Hypoglycemia Events of Patients with Target Glycated Hemoglobin Levels

	Daytime		Nocturnal		Total	
	n	%	n	%	n	%
Nonsevere hypoglycemia	163	84.5	15	7.8	178	92.2
Unknown severity	11	5.7	0	0.0	11	5.7
Severe hypoglycemia (required assistance)	3	1.6	1	0.5	4	2.1
Total	177	91.8	16	8.3	193	100.0

	HbA1c			
	Out-of-Target Range (>7%)		Within-Target Range (≤7%)	
	n*	%	n*	%*
No hypoglycemic event	34	61.8	21	38.2
Hypoglycemic event experienced	21	43.8	27	56.3
Assistance not required	20	44.4	25	55.6
Severe hypoglycemia (required assistance)	1	33.3	2	66.7

	Daytime		Nocturnal	
	n	%	n	%
Nonsevere hypoglycemia	163	100.0	15	100.0
Out-of-target range (>7%)	57	35.0	2	13.3
Within-target range (≤7%)	106	65.0	13	86.7
Severe hypoglycemia (required assistance)	3	100.0	1	100.0
Out-of-target range (>7%)	1	33.3	0	0.0
Within-target range (≤7%)	2	66.7	1	100.0
Total	166		16	

Nocturnal: 00:00-05:59, Daytime: 06:00-23:59.
HbA1c, glycated hemoglobin; N, number of patients.
*Some patients experienced both severe and nonsevere hypoglycemia. Number of patients who experienced at least 1 event was provided. Percentage within all patients (n = 108) is provided.

Improvement of glycemic control with insulin is the most effective treatment modality for T2DM. Early insulinization provides tighter and long-term glycemic control than OAD treatment and may, therefore, help restoring β-cell function, lower insulin resistance, and reducing glucose toxicity and lipotoxicity.[22] Since hypoglycemia is the most common adverse event in insulin therapy and is closely related to the dose intensity, many patients and their physicians are willing to start insulin therapy.[23,24] Thus, it becomes critical achieving favorable glycemic control while preventing hypoglycemia. A dose adjustment or discontinuation of OADs may have to be taken into account due to increasing risk of hypoglycemia.[25]

In the present study, approximately half (44.4%) of the patients experienced at least one hypoglycemic event, while reporting 193 hypoglycemic events altogether. Only 4 events were considered as severe hypoglycemia that required assistance. Majority of the hypoglycemic events (91.8%) occurred during daytime (between 06:00-23:59). The risk of experiencing at least one nocturnal event was low, only 8.3% of patients had any nocturnal hypoglycemia. A report that reviewed a total of 307 publications on patients with T2DM experiencing hypoglycemia indicated that incidence of nocturnal hypoglycemia ranged from 12% to 56%.[26] Thus, in our study the prevalence of nocturnal hypoglycemia with Gla-300 treatment was comparatively lower than the previous publications that presented data on T2DM.

Table 4. Comparison of Mean Treatment Satisfaction Score at Baseline Versus Week 24

	DTSQs Score		
Item Scores	Baseline	Week 24	*P**
Total treatment satisfaction (items: 1, 4, 5, 6, 7, 8)	24.76	30.08	<.001
Perceived frequency of hyperglycemia (item: 2)	4.6	2.3	<.001
Perceived frequency of hypoglycemia (item: 3)	1.6	1.7	.681

DTSQs, diabetes treatment satisfaction questionnaire—status version

In our study, with Gla-300 treatment, approximately 19.4% of the patients reached the HbA1c target without experiencing hypoglycemic events, which was is in line with that (21.9%) observed in the DELIVER naïve cohort study conducted in 1004 patients with T2DM treated with Gla-300.[27] However, one in every 4 patients (25.0%) reaching the target HbA1c level reported at least 1 hypoglycemic event. A possible explanation for this controversial finding could be an underlying medical condition since reaching target levels of HbA1c does not ensure to reduce hypoglycemia risk. Most importantly, the risk of hypoglycemia due to various OADs used in this study should not be underestimated. Data obtained from international studies also advocates the fact that initiation of insulin therapy almost always results in an increase incidence of hypoglycemia in T2DM patients. This hypothesis is highly corroborated with the result of the UKPDS trial, which demonstrated an increment in reported hypoglycemia events in newly diagnosed patients randomized to insulin therapy from a rate of 33% in the first year to 43% at year 10.[28]

Table 5. Percentage of Time Glucose Concentrations Within the Target Range of 80-130 mg/dL—Analyses on All-Time (24-hour) Continuous Glucose Monitoring Data

	Screening Visit			Visit 4		
	Number of Measurements (n)	Time (minutes)	%	Number of Measurements (n)	Time (minutes)	%
In-target range	202	168.5	11.7	591	504	35.0
Out-of-target range	1526	1271.5	88.3	1099	936	65.0
Total	1728[a]	1440	100.0	1690[b]	1440	100.0

Measurements were performed every 10 minutes.
[a]Number of patients = 12.
[b]Number of patients = 11. One patient's (1-10) visit 4 measurements were not done; therefore, last measurements data were missing.

A recent published study highly recommends considering the use of 2 glycemic measurement tools, SMBG and CGM, to improve glycemic control and patients' QoL in combination with HbA1c value.[29] In a previous study examining the daily 7-point SMBG profiles, glycemic control has been shown to significantly improve in each time-point throughout 12 months,[30] which is compatible with our study results.

At present, CGM can be considered more favorable over SBMG due to its ability to measure glycemic fluctuations during a 24-hour period.[31] In our study, the mean percentage of time within-the-target glucose range of 80-130 mg/dL in 24 hours increased from 11.7% to 35.0%, and Gla-300 has been observed to reduce AUC values over the 24-hour time period, including daytime and nocturnal time-points.

The assessment of patient-reported outcomes including treatment satisfaction, wellbeing, and QoL are becoming more important during the insulin therapy. Our results indicated a significant increase in mean treatment satisfaction score and a noticeable decrease in mean hyperglycemia score at week 24 as compared to baseline, whereas there was no significant reduction in hypoglycemia score. On the contrary, in a Hong Kong-based study which consisted of 24-week treatment period, perceived frequency of hypoglycemia has been shown to reduce from 2.2 at baseline to 1.5 at the end of insulin glargine treatment ($P = .079$).[32] The EDITION 3 study also showed improvements in total DTSQ scores from baseline (27.2) to week 24 (31.9).[12]

Poor glycemic control almost always results in diabetes-related microvascular and macrovascular complications, and in the long run, due to these irreversible structural complications patients with T2DM become prone to risk of developing cardiovascular diseases since T2DM is diagnosed in the later stages of disease with a progressive nature. Cardiovascular events were rarely seen, and only 4 patients experienced severe hypoglycemia in our study, which supports the results of EDITION 3, where severe hypoglycemia was reported by 4 patients.[12]

The current study is subject to some limitations that should be considered when interpreting its findings, including the lack of a control group and its open-label nature. All patients received Gla-300, and thus, any comparison with other treatment alternatives was not possible. The use of various OADs in combination with insulin therapy has been permitted, but the effect of OADs on glycemic control has not been assessed. The study was also limited by the short duration of 24 weeks. Although a significant improvement was shown in DTSQs scores, changes in treatment satisfaction might be seen in the course of time. Therefore, a longer time evaluation of treatment outcomes would likely be of interest. Finally, the number of patients was very limited for CGM data, and the results did not represent the overall population.

In conclusion, we found that a 24-week of once-daily dosing of Gla-300 provided successful targeted glycemic control with a lower risk of hypoglycemia, and these findings indicated that Gla-300 was well tolerated with a good safety profile in patients with T2DM uncontrolled with OADs.

Ethics Committee Approval: This study was approved by the Ethics Committee of Kocaeli University Faculty of Medicine with thapproval no: KİA 2016/149 (date: June 7, 2016). All procedures performed were in accordance with the 1964 Helsinki Declaration (as revised in 2013) and the ICH Guidelines for Good Clinical Practice.

Informed Consent: Written informed consent was obtained from the patients who agreed to take part in the study.

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