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A 12-Month Prospective Observational Study Assessing the Real-World Clinical Effectiveness and Safety of Insulin Glargine 300 U/mLInitiation After Oral Antidiabetic Drug Failure in Insulin-Naïve Individuals with Type 2 Diabetes Mellitus in Egypt: A Posthoc Subgroup Analysis [ATOS Study]

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Abstract

Background: Reaching the HbA1c target and keeping the euglycemic state are major challenges in the management of individuals with diabetes. Given the high rate of failure of oral antidiabetic drugs (OADs) to control the glycemic state of individuals with type-2 diabetes mellitus (T2DM), other new options have emerged to replace the traditional treatments in such cases. Second-generation basal insulin glarginehas proven its safety and efficacy in improving glycemic control in individuals with uncontrolled T2DM in multiple randomized clinical trials (RCTs).

Aim of Study: This study aims to assess the effectiveness and safety of insulin glargine 300U/mL (Gla-300) when added to OADs and titrated to individualized goals in real-world practice.

Patient and Methods: The ATOS study was a prospective, observational, international, multicenter study to collect information on 4422 individuals with T2DMinitiating Gla-300 across 18 countries in different geographical regions, and which routinely assessed glycated hemoglobin (HbA1c) at least every 6 months (NCT03703869). Our posthocsub group analysis is a part of this large-scale multinational study that analyzed the data collected from Egypt, one of the countries representing the South African region, to assess the real-world effectiveness of Gla-300 in Egyptian individuals with T2DM. The primary outcomes include an assessment of the effectiveness of Gla-300 in achieving glycemic goals measured by HbA1c after 6 months. The secondary objectives include effectiveness and safety during the extended follow-up period (12 months).

Results: This posthocsubgroup analysis included 216 individuals with T2DM in Egypt with a mean age of 52.7 (±9.8) years. The mean body weight and bodymass index (BMI) were 86.8 (±13.6) and 30.6 (±5.0), respectively. Most included participants were on more than one concomitant OAD (mostly metformin and sulfonylureas). The HbA1c target achievement after 6 months was 27.7%. This figure increased to 51.2% after 12 months. In individuals ≥65 years, the HbA1c target achievement after 6 and 12 months was 36% and 52%, respectively. The mean HbA1c% reduced from a baseline value of 9.45 (0.94) to 7.36 (0.60) after 6 months and 6.97 (±0.55) after 12 months of Gla-300 treatment. No major or serious adverse events (AEs) were reported during the follow-up period. Two participants (0.9%) had hypoglycemic events, with only oneexperiencing severe hypoglycemia.

Conclusion: Insulin treatment with Glar-300 in Egyptian individuals with T2D Muncontrolled on OADs improved glycemic control, and target HbA1c level was achieved in 27.7% after 6 months with a very low risk of hypoglycemia and other treatment-related AEs. People with T2DM who are uncontrolled on OADs may benefit from therapy with Gla-300. Our study results are in line with the results of previously conducted studies.

Key Words: *Diabetes – Type-2 diabetes mellitus – Insulin – Glargine – Oral antidiabetic drugs – Egypt.*

Introduction

DIABETES mellitus (DM) is one of the major public health challenges that carries a heavy burden on the global public healthcare system **[1]**. DM is a chronic metabolic disease characterized by hyperglycemia developed from absent insulin secretion and reduced insulin secretion or action **[2,3]**. According to the American Diabetes Association (ADA), DM can be classified intotype-1, type-2, gestational diabetes mellitus (GDM), and other types **[4]**. Individuals with type-2 diabetes mellitus (T2DM) are characterized by high insulin resistance. Both types of DM (type-1 and type-2) are genetically determined; however, the genetic predisposition revealed a stronger association in type-2 (such as the association between T2DM and TCF7L2 gene) **[5]**. The pathogenesis of T2DM

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starts with the development of insulin resistance on a cellular level; in response, compensatory hyperinsulinemia occurs to control this high blood sugar level [6]. This state of hyperinsulinemia will lead to a progressive degenerationof beta cells that ends up with a drop in insulin secretion and more hyperglycemia. Hyperglycemia inhibits insulin secretion and leads to more insulin resistance [7,8].

The prevalence of DM has been on a rising trend in most developed and developing countries in the last few years [9-11]. As per statistics from the International Diabetes Federation (IDF), nearly 463 million adult individuals worldwide were diagnosed with DM in 2019. These numbers might rise to 693 million by 2030 and 548 million by 2045 if no proper management plans are implemented to prevent or control the progression of the disease [12].

Egypt's diabetes epidemiology data are limited. With a prevalence of 15.2%, Egypt has the ninth-highest rate of DM worldwide, and the number of adult people with diabetes was 8,850,400 as early as 2020, per data from the IDF. Egypt is a member of the Middle East and North Africa (MENA) region of the IDF. Regarding the MENA region, DM affected almost 55 million people in 2019 as per the IDF statistics - the highest prevalence in the world - and this number might uprise to 107.6 million by 2045 [12-14].

Earlyonset of T2DM is characterized by no or mild clinical symptoms, making its diagnosis challengingand might be delayed for years, especially in developing countries. This diagnostic delay increases the risk of long-term complications resulting from untreated hyperglycemia. Common symptoms of T2DM include frequent nocturnal urination, feeling thirsty most of the time, increased hunger sensation, daytime fatigue, decreased visual acuity with blurred vision, and weight loss [15]. Also, individuals with T2DM and insulin resistance may manifestobesity, hypertension, dyslipidemia, polycystic ovary and hyperandrogenism, non-alcoholic fatty liver, and recurrent systemic infections [2,16,17]. Other diabetes complications include microvascular complications (including nephropathy, retinopathy, and neuropathy) and macrovascular complications (including cardiovascular and cerebrovascular comorbidities such as coronary heart disease, arrhythmias, and sudden death) [18].

The diagnostic criteria of DM comprise a combination of clinical symptoms and laboratory findings. The laboratory diagnosis depends on either blood glucose [including fasting blood glucose (FPG) or oral glucose tolerance test (OGTT)] or HbA1c level. In order to diagnose a patient with DM, the patient must have symptoms of hyperglycemia alongside FPG ≥126mg/dL, plasma glucose after 2-h of OGTT ≥200mg/dL, HbA1c ›_6.5%, or a random plasma glucose level ›_200mg/dL [2].

Lifestyle modifications (i.e., diet therapy and physical exercise) are the cornerstone of the management plan for both T1DM and T2DM and should be started initially for all cases with DM [19,20]. The main goal of non-pharmacological therapy in individuals with T2DM is to lose weight in order to decrease insulin resistance. Pharmacological treatment comprises mainly oral antidiabetic drugs (OADs). The available pharmacological options for individuals with T2DM include metformin (considered the first-line therapy), dipeptidyl peptidase-4 (DPP-4) inhibitors, sulfonylureas, glucagon-like peptide-1 (GLP-I) receptor agonists, sodium-glucose co-transporter-2 (SGLT2) inhibitors, thiazolidinedione (as pioglitazone), and insulin in some cases [15]. Choosing the appropriate OAD for people with diabetesrelies mainly on associated comorbidities and types of developed complications. For instance, pioglitazone is reported to improve individuals' lipid profile - it decreases triglycerides, low-density lipoprotein, and serum fatty acids and increases the level of high-density lipoproteins - so it is better prescribed for individuals with fatty liver disease [21,22]. Also, in individuals with cardiovascular disorders (CVDs), SGLT2 inhibitors (such as empagliflozin) and the GLP-1 receptor agonist (such as liraglutide) should be considered due to their effects on CV events and mortality rate [23].

Despite the availability of many therapeutic options for individuals with diabetes, in some cases, they fail to achieve the required treatment goals. Therefore, a combination of two or more treatment options (OADs and insulin) are prescribed in order to achieve the therapeutic target and decrease the risk of complications. Insulin is one of the treatment options that has been used in combinations or alone in individuals with T2DM. Long-acting forms of insulin are preferred over short-acting forms as theyproject a lower frequency of injections, higher patient compliance, and higher diabetic control. Insulin glargine 300U/mL (Gla-300) is one ofthe long-acting insulin forms that has proven its efficacy in lowering HbA1c levels, providing an effective replacement for basal insulin, and protecting from the risk of hypoglycemia [24,25].

This non-interventional observational study aims to assess the effectiveness and safety of Gla-

300 when added to OADs and titrated to individualized goals in daily clinical practice. The primary endpoints were analyzed at 6 months; however, the study was extended to 12 months in order to assess long-term effectiveness, safety, and patient-reported outcomes (PROs).

Patients and Methods

Study design and procedures:

The ATOS studywas a prospective, observational, international, multicenter study to collect information on 4422 individualswith T2DM initiating Gla-300 across 18 countries in different geographical regions (Colombia, Egypt, India, Indonesia, Israel, Jordan, Kuwait, Lebanon, Mexico, Peru, Philippines, Russian Federation, Saudi Arabia, Singapore, Taiwan, Thailand, Ukraine, and the United Arab Emirates), to assess the real-world effectiveness of Gla-300 in individuals with T2DM (NCT03703869) **[26]**.

Our posthocsub group analysis is a part of this large-scale multinational study that analyzed the data collected from Egypt, one of the countries representing the South African region, to assess the real-world effectiveness of Gla-300 in Egyptian individuals with T2DM. The study protocol was approved by the Research and Ethics Committee of the included centers. All participants wereasked to givetheir written informed consent prior to study enrollment. Also, the study methodology and objectives were explained to all study participants before enrollment.

Included participants planned to use Gla-300 for their T2DM and were under routine assessment of their HbA1c at least every 6 months. Study participants were assessed at 4 visits at study sites: baseline, 3, 6, and 12 months. Baseline data were collected regardingparticipants' demography, diabetes medical history, andother medical conditions.

Eligibility criteria:

Eligibility criteria were minimized to include almost all participants who would otherwise be treated according to the local prescribing information. Individuals who previously used insulin were not allowed in the study as the intention was to collect data on individuals initiated on insulin therapy.

In order to replicate real-world conditions, no interventions and no study-specific observations were proposed. The study applied a “new-user” design, enrolling participants at the moment when they commenced treatment. This design is the recommended approach to minimize patient selection bias **[27]**. It is similar to that of an interventional clinical trial, thereby allowing a reasonable comparison of the observational data collected with clinical trial data.

Inclusion criteria:

Participating physicians proposed participation in the study to all individuals with T2DM initiated on basal insulin after OAD failure at their sites if they potentially met the eligibility criteria. The study inclusion criteria include the following: The patient is willing to give a signed informed consent, has a diagnosis of T2DM, treatment with at least 1 OAD for at least 6 months, and is above thelegal age of adulthood (at least $\geq$ 18 years), HbA1c >7.0% and $<$ 11% within 3 months of study baseline, and physician's decision in accordance with the local Egyptian guidelines to add basal Gla-300 to the existing OAD regimen.

Exclusion criteria:

Individuals with the following characteristics were excluded: DM other than type 2, existing or previous treatment with insulin or other injectable antidiabetic drugs, contraindications to Gla-300 according to local product labeling (including hypersensitivity during the attacks of hypoglycemia, low potassium level, liver problems, and decreased renal functions), drug or alcohol abuse within the past year, a concomitant disease with a life expectancy of less than 1 year, and concomitant participation in other clinical trials. Also, pregnant females, breastfeeding or planning pregnancy were excluded, as the present study did not aim to evaluate these populations.

Included sites:

Sites using or planning to use Gla-300 and routinely assessing HbA1c at least every 6 months were invited to participate in the study. Treating physicians were either specialists in endocrinology, diabetology, internal medicine, or general practitioners (GPs) working in centers with expertise in these specialties. Overall, 17 participating sites were randomly selected based on a list of sites provided for Egypt.

We took all reasonable measures to minimize the impact of funding sources on the outcomes. In particular, the selection process was randomized in order to minimize site selection bias. In addition, all potentially eligible individuals at a study site were offered to participate in the study to minimize patient-selection bias. With the measures implemented to minimize these possible sources of bias, the study aimed to obtain real-world information on the use of Gla-300.

Treatment plan:

Participants enrolled in the study were selected among individuals for whom the treating physician had decided to prescribe Gla-300 independently from the study entry. Therefore, study treatment was not provided by the Sponsor for the study. The individual patient's HbA1c glycemic goal was set by the treating physician, and the titration was performed using the locally applicable titration algorithm. Participants must have been treated with at least one OAD for at least 6 months before initiating the basal insulin treatment. Other antidiabetics were given as treatment intensification for individuals with poor glycemic control.

Study objectives:

The primary objective of the ATOS study is to assess the effectiveness of Gla-300 in achieving the glycemic goal measured by HbA1c after 6 months. Whereas the secondary objectives include efficacy-related objectivesand safety-related objectives. Efficacy objectives were targeted to assess the following: Treatment effectiveness in achieving glycemic goal measured by HbA1c at 3 and 12 months; treatment effectiveness on change in HbA1c, FPG, and fasting self-measured plasma glucose (SMPG) after 3, 6, and 12 months; and requirements for therapeutic intensification by additional antidiabetics. Safety objectives include assessment of the incidence of hypoglycemia, any change in the body weight, and other safety endpoints [including adverse events (AEs) and severe adverse events (SAEs)].

Data collection:

Data collection schedule:

Data collection was performed on scheduled individuals' visits to the included centers (four planned visits: At baseline, 3, 6, and 12 months). Individuals' visits to the included study site were scheduled and performed according to clinical practice. Observations closest to the study schedule were recorded as a study visit. If there was no observation within ± 1 month of the planned visit, the closest observation was recorded as a visit if this visit occurred before the end of data collection for the study.

Data collected:

Baseline characteristics data:

Baseline characteristics data were collected from each included patient, which includes demographic data, diabetes medical history, HbA1c goal as set by the treating physician at the baseline, determinant factors for HbA1c goals, and history of diseases other than diabetes. Individuals' demographic data include gender, age (year of birth), and socioeconomic status (i.e., living in the urban-rural or sub-urban area; educational level: Illiterate, primary, secondary, or university /higher education). The details of diabetic history were collected, including duration of diabetes, concomitant antidiabetic drugs, and diabetes-associated comorbidities. Also, other factors that determine HbA1c goals such as body mass index (weight and height), history of severe hypoglycemia, limited life expectancy, and advanced microvascular or macrovascular complications.

Efficacy data were recorded at each visit:

Data related to treatment efficacy were recorded at each visit, including the following:

1- HbA1c: Prior to or at each visit.

2- FPG: Prior to or at each visit.

3- Fasting SMPG: the mean of the 3 most recent readings prior to each visit and the mean of the last 3 consecutive readings each month of the study (e.g., the last 3 readings 1 month after baseline and 2 months after the baseline).

4- Gla-300 dose and time of injection at every visit. Only the dose of the last visit or the most recent dose just prior to each visit.

5- Treatment intensification by additional antidiabetics and the reason for their administration.

Safety data recorded at each post-baseline visit:

We collected the safety data related to the study treatment in order to ensure the high safety profile of the Gla-300. The collected safety data include hypoglycemia (either documented symptomatic hypoglycemia or severe hypoglycemia), body weight changes, and other safety-related data (such as AEs and SAEs).

Sample size calculation and statistical analysis plan:

The sample size was calculated based on the primary objective and statistical analysis plan of the whole ATOS study (NCT03703869); however, our posthocsubgroup analysis shared only the data related to the Egyptian participants. Our analysis shared data from 216 Egyptian individuals with T2DM from 17 investigational sites across Egypt. For more details on sample size justification and statistical analysis plan of the whole study, please refer to Supplementary File No 1.

Results

Demographics and baseline characteristics:

A total of 216 participants with T2DM (123 females, 56.9%) were included in our study and

completed the 12-month follow-up period. The mean age (SD) was 52.7 (9.8), with 191 (88.4%) of the included participants below 65 years of age. Mean weight (SD) was 86.8 (13.6), and mean BMI (SD) was 30.6 (5), with the majority of participants (43.3%) being obese (i.e., 25-30 BMI). Most included participants were from urban areas (92.1 %) and had health insurance coverage (56.9%) - mostly public health insurance. Mostparticipants had long-standing diabetes [mean duration (SD) was 9.8 (6.7)], with 44% of them having had diabetes for more than 10 years. The mean (SD) HbA1c % among the included participants at the baseline was 9.4 (0.9); withonly 3 participants (1.4%)having HbA1c of 7-7.5%, 18 (8.3%) had HbA1c of 7.5-8%, 46 (21.3%) had HbA1c of 8-9%, 76 (35.2%) had HbA1c of 9-10%, and 73 (33.8%) had HbA1c% ≥10. Full details of participants' demographics and baseline characteristics are presented in Table (1).

Table (1): Demographics, patient characteristics, and treatment characteristics at baseline.

	N (%)	Total
Age (years), Mean (SD)	52.7 (9.8)	216
Age Group (years) [n (%)]:		
<65	191 (88.4%)	216
65-75	24 (11.1%)	
>=75	1 (0.5%)	
Sex, n (%):		
Male	93 (43.1%)	216
Female	123 (56.9%)	
Weight (kg), Mean (SD)	86.8 (13.6)	171
Height (cm), Mean (SD)	168.0 (6.4)	216
BMI (kg/m2), Mean (SD)	30.6 (5.0)	171
BMI (kg/m ^{2}) [n (%)]:		
<25	15 (8.8%)	171
25-30	74 (43.3%)	
30-35	54 (31.6%)	
>=35	28 (16.4%)	
Work disability due to diabetes [n (%)]#:		
Yes	0 (0.0%)	58
No	58 (100.0%)	
Patient's location [n (%)]:		
Urban area	199 (92.1%)	216
Rural area	8 (3.7%)	
Suburban area	4 (1.9%)	
Unknown	5 (2.3%)	
Lifestyle [n (%)]:		
Alone	10 (4.6%)	216
With another adult	197 (91.2%)	
In an institution or a community	0 (0.0%)	
Other	9 (4.2%)	
Health insurance cover [n (%)]:		
Yes	93 (43.1%)	216
No	123 (56.9%)	
Type of health insurance [n (%)]##:		
Public Health Insurance	59 (63.4%)	93
Private Health Insurance	20 (21.5%)	
Public + Private Health Insurance	14 (15.1%)	
Duration of diabetes (years), Mean (SD)	9.8 (6.7)	216
Duration of diabetes (years) [n (%)]:		
<1	0 (0.0%)	216
1-5	59 (27.3%)	
5-10	62 (28.7%)	
>=10	95 (44.0%)	
Age of onset of diabetes in years, Mean (SD)	44.9 (8.8)	216
History of gestational diabetes [n (%)]:		
Yes	9 (7.3%)	123
No	114 (92.7%)	
Duration of OAD in years, Mean (SD) ###	9.5 (6.6)	216
OAD use at baseline [n (%)]:		
1 OAD use	37 (17.1%)	216
2 OADs use	121 (56.0%)	
3 or more OADs use	58 (26.9%)	
OAD at baseline classification [n (%)]:		
Biguanides	172 (79.6%)	216
Sulfonylureas	171 (79.2%)	
Glinides	2 (0.9%)	
Thiazolidinediones	16 (7.4%)	
DDP-4 inhibitors	79 (36.6%)	
SGLT-2 inhibitors	21 (9.7%)	
Alpha-glucosidase inhibitors	1 (0.5%)	

If "Part-time," or "Not employed," or "Incapacity" answered in employment status.
If "Yes" answered in the Health insurance cover.
Duration calculated based on the participants who have reported at least one OAD in the concomitant CRF form; Note: the answers as "Not Applicable" in history of gestational diabetes has been considered as No; Note: OAD use at baseline is defined as the medications taken within 6 months of screening (i.e., taken in any time from the 6 months previous to informed consent (IC) date until the IC date).

Treatment characteristics:

OADs were received for a mean (SD) period of 9.5 (6.6.) years, with 37 participants (17.1%) on one OAD, 121 (56%) on two OADs, and 58 (26.9%) on three or more OADs use. OADs used at the baseline were Biguanides by 172 participants (79.6%), Sulfonylureas by 171 (79.2%), DDP-4 inhibitors by 79 (36.6%), SGLT-2 inhibitors by 21 (9.7%), Thiazolidinediones by 16 (7.4%), and Glinides by 2 (0.9%), Table (1). Basal insulin was initiated on a mean dose (SD) of 16.7 (6.5), which was increased at 3 months to 20.3 (7.6), 6 months to 22.1 (8.0), and at 12 months to 23.6 (9.0) as shown in Table (2). Bodyweight did not significantly change after Gla-300 dose adjustments across visits

(mean weight at baseline = 86.8, at 3 months = 87.3, at 6 months = 87.3, andat 12 months = 87.6).

Table (2): Basal insulin dose change from baseline across visits.

		Basal insulin dose (U) change across visits
Baseline	Mean (SD)	16.7 (6.5)
Month 3 (visit 2)	Mean (SD)	20.3 (7.6)
Month 6 (visit 3)	Mean (SD)	22.1 (8.0)
Month 12 (visit 4)	Mean (SD)	23.6 (9.0)

Treatment effectiveness outcomes:

The hbA1c target was achieved by 59 participants (27.7%) [95% CI = 21.8 to 34.2] after 6 months. After 12 months, the HbA1c target achievement was increased to 109 participants (51.2%) [95% CI = 44.3 to 58.1], Table (3). At 6 months, five participants achieved an HbA1c target of <7%, 49 achieved an HbA1c target of 7%-7.5%, four achieved an HbA1c% target of 7.5%-8%, and one patient achieved an HbA1c target of ›_8%, Table (3).

Table (3): Summary of individuals achieving different HbA1c targets by baseline HbA1c value and by each visit.

	Summary of All individuals achieving different HbA1c targets by baseline HbA1c value and by visit n (%), 95% CI	Summary of individuals aged >=65 years achieving different HbA1c targets by baseline HbA1c value and by visit
Month 3 (visit 2):		
HbA1c target achievement	22 (10.4%), 6.7 to 15.4	2 (8.3%), 1.0 to 27.0
HbA1c value <7%	19 (9.0%), 5.5 to 13.7	2 (8.3%), 1.0 to 27.0
HbA1c value <7.5%	48 (22.7%), 17.3 to 29.0	5 (20.8%), 7.1 to 42.2
HbA1c value <8%	92 (43.6%), 36.8 to 50.6	9 (37.5%), 18.8 to 59.4
N	211	24
Month 6 (visit 3):		
HbA1c target achievement	59 (27.7%), 21.8 to 34.2	9 (36.0%), 18.0 to 57.5
HbA1c value <7%	53 (24.9%), 19.2 to 31.2	10 (40.0%), 21.1 to 61.3
HbA1c value <7.5%	124 (58.2%), 51.3 to 64.9	16 (64.0%), 42.5 to 82.0
HbA1c value <8%	180 (84.5%), 78.9 to 89.1	22 (88.0%), 68.8 to 97.5
HbA1c target achievement according to baseline HbA1c value:		
<8%	10 (50.0%), 27.2 to 72.8	2 (66.7%), 9.4 to 99.2
8%-10%	43 (35.5%), 27.0 to 44.8	7 (50.0%), 23.0 to 77.0
>=10%	6 (8.3%), 3.1 to 17.3	0 (0.0%), NA
HbA1c target achievement according to HbA1c goal:		
<7%	5 (7.7%), 2.5 to 17.0	0 (0.0%), NA
7%-7.5%	49 (36.0%), 28.0 to 44.7	6 (42.9%), 17.7 to 71.1
7.5%-8%	4 (40.0%), 12.2 to73.8	2 (50.0%), 6.8 to 93.2
>=8%	1 (50.0%), 1.3 to 98.7	1 (100.0%), NA
N	213	25
Month 12 (visit 4):		
HbA1c target achievement	109 (51.2%), 44.3 to 58.1	13 (52.0%), 31.3 to 72.2
HbA1c value <7%	100 (46.9%), 40.1 to 53.9	13 (52.0%), 31.3 to 72.2
HbA1c value <7.5%	182 (85.4%), 80.0 to 89.9	21 (84.0%), 63.9 to 95.5
HbA1c value <8%	206 (96.7%), 93.3 to 98.7	23 (92.0%), 74.0 to 99.0
HbA1c target achievement according to baseline HbA1c value:		
<8%	15 (75.0%), 50.9 to 91.3	3 (100.0%), NA
8%-10%	67 (55.4%), 46.1 to 64.4	7 (50.0%), 23.0 to 77.0
>=10%	27 (37.5%), 26.4 to 49.7	3 (37.5%), 8.5 to 75.5
N	213	25

The mean (SD) HbA1c was reduced significantly after 6 months of Gla-300, initiating from 9.45% (0.94) to 7.36% (0.60) and further to 6.97% (0.55) after 12 months of the treatment (Table 4). Absolute changes in HbA1c from baseline at 3 months, 6 months, and 12 months were -1.37% (0.69), -2.09% (0.82), and -2.48% (0.94), respectively. Also, HbA1c, FPG, and FSMPG showed a significant reduction from baseline values at follow-up visits (Table 4).

Adverse events and treatment safety:

During the 12-month follow-up period, hypoglycemic events showed a rare incidence with Gla-300 treatment (Table 5). Only two hypoglycemic events (0.93%) occurred in the first 6 months, with one event (0.46%) considered severe hypoglycemia. Also, treatment-emergent adverse events (TEAEs) occurred in 21 participants (9.7%), with only 2 (0.9%) experiencing serious TEAEs. Out of those 21 participants, one participant (0.5) had a nervous system disorder and passed through severe hypoglycemia during the follow-up period. Moreover, no treatment discontinuation event due to TEAE was reported during the follow-up period (Table 5).

Table (4): Summary of change from baseline across visits in terms of HbA1c (%), HbA1c (mmol/mol), FPG (mmol/L), and SMPG (mmol/L).

	HbA1c (%) change from baseline across visits	HbA1c (mmol/mol) change from baseline across visits	FPG (mmol/L) change from baseline across visits	FSMPG (mmol/L) change from baseline across visits
Baseline:				
Mean (SD)	9.45 (0.94)	79.82 (10.32)	12.45 (3.06)	12.33 (2.81)
N	213	213	188	186
Month 3 (visit 2):				
Mean (SD)	8.09 (0.80)	64.90 (8.72)	8.13 (2.04)	8.59 (1.96)
Absolute change from baseline	–1.37 (0.69)	–14.98 (7.59)	–4.50 (2.94)	–3.34 (2.42)
N	211	211	176	135
Month 6 (visit 3):				
Mean (SD)	7.36 (0.60)	56.93 (6.55)	7.29 (1.78)	7.49 (1.77)
Absolute change from baseline	–2.09 (0.82)	–22.89 (8.93)	–4.95 (3.03)	–4.91 (2.79)
N	213	213	178	173
Month 12 (visit 4):				
Mean (SD)	6.97 (0.55)	52.73 (5.96)	6.55 (1.30)	6.81 (1.24)
Absolute change from baseline	–2.48 (0.94)	–27.09 (10.22)	–5.87 (3.28)	–5.52 (2.79)
N	213	213	188	170
Change from baseline to Month 3 (visit 2) (MMRM):				
LS Mean (SE), 95% CI	–1.37 (0.04), (-1.46 to -1.29)	–14.98 (0.47), (-15.91 to -14.05)	–4.30 (0.14), (-4.58 to -4.01)	–3.77 (0.16), (-4.08; -3.46)
Change from baseline to Month 6 (visit 3) (MMRM):				
LS Mean (SE), 95% CI	–2.10 (0.04), (-2.16 to -2.03)	–22.90 (0.39), (-23.66 to -22.14)	–5.05 (0.13), (-5.30 to -4.80)	–4.82 (0.12), (-5.06; -4.58)
Change from baseline to Month 12 (visit 4) (MMRM):				
LS Mean (SE), 95% CI	–2.48 (0.04), (-2.55 to 2.41)	–27.10 (0.40), (-27.90 to -26.31)	–5.86 (0.10), (-6.05 to -5.67)	–5.44 (0.09), (-5.63; -5.26)

Note: Relative change = ((Value at specific visit - Value at baseline)/Value at baseline); MMRM= Mixed model for repeated measurements; MMRM model with fixed categorical effects of time point (V2, V3, and V4) and the continuous fixed covariate of the baseline value of HbA1c; Least-squares (LS) means and standard errors (SE) taken from MMRM analysis.

Table (5): Overview of adverse events and drug safety profile.

	Eligible population (N=216)	Included population (N=219)
Any hypoglycemia event*	2 (0.93%)	2 (0.93%)
Severe hypoglycemia**	1 (0.46%)	1 (0.46%)
TEAE on-treatment period:		
Any TEAE	21 (9.7%)	22 (10.0%)
Any serious TEAE	2 (0.9%)	2 (0.9%)
Any related TEAE	1 (0.5%)	1 (0.5%)
Any serious related TEAE	1 (0.5%)	1 (0.5%)
Any treatment-emergent AESI	0 (0.0%)	0 (0.0%)
Any TEAE leading to premature treatment discontinuation	0 (0.0%)	0 (0.0%)
Any TEAE leading to death	0 (0.0%)	0 (0.0%)
Number (%) of individuals with related TEAE(s) by Primary SOC and PT:		
Any related TEAE	1 (0.5%)	1 (0.5%)
Nervous system disorders	1 (0.5%)	1 (0.5%)
Severe hypoglycemia	1 (0.5%)	1 (0.5%)
Number (%) of individuals with related serious TEAE(s) by Primary SOC and PT:		
Any serious related TEAE	1 (0.5%)	1 (0.5%)
Nervous system disorders	1 (0.5%)	1 (0.5%)
Severe hypoglycemia	1 (0.5%)	1 (0.5%)
Number (%) of individuals with pre-treatment AE(s) by Primary SOC and PT:		
Any pre-treatment AE	1 (0.5%)	1 (0.5%)
General disorders and administration site conditions	1 (0.5%)	1 (0.5%)
Non-cardiac chest pain	1 (0.5%)	1 (0.5%)

* All hypoglycemic events occurred in the first 6 months of the follow-up period.
* The severe hypoglycemic event occurred in the first 6 months of the follow-up period.

Note: TEAE = treatment-emergent adverse events, AESI = Adverse event of special interest, SOC = System organ class, PT = preferred term, AEs = adverse events.

Discussion

Insulin glargine is basal injectable insulin that comes in two formulations: Glar-100and Glar-300. Gla-100 is the most used form due to its well-established efficacy and safety profiles **[28,29]**. However, in order to achieve better glycemic control and avoid the risk of hypoglycemia, a more concentrated formulation of glargine with a smoother and longer PK-PD profile, glargine 300U, was investigated in people living with T1D and T2DM. The main idea behind shifting from Glar-100 to Glar-300 is to get a prolonged and gradual insulin-release from the subcutaneous deposit, therefore achieving glycemic control over an extended period (lasting more than 24 hours) **[30]** and a flatter profile of glucose-lowering action decreasing the risk of hypoglycemia.

The multinational ATOS observational study aimed to assess the real-world effectiveness and safety profile of Glar-300 in a wider range of countries than the previously conducted clinical trials outside the US and counties of western Europe. Our posthoc subgroup analysis was a part of this international study that analyzed only data collected from Egyptian individuals to investigate the real-world effectiveness in Egypt as one of the Northern African countries. Our analysis revealed a significant improvement in glycemic control with the use of Gla-300 during the follow-up period, with a very rare incidence of hypoglycemic events or other TEAEs.

Baseline characteristics regarding age, gender distribution, weight, BMI, duration of diabetes, HbA1c, percentage of participants reaching HbA1c targets, FPG, and SMPG were comparable with participants of the EDITION 3 trial, BRIGHT trial, and Toujeo-1 study **[31-33]**. However, participants in our study were younger than Toujeo-1, EDITION, and BRIGHT studies (52.7 vs. 64.9, 58.2, and 60.6, respectively). Likewise, participants recruited from Egypt were relatively younger compared to the eligible population in the ATOS overall study (52.7 vs. 57.2 years old). The baseline HbA1c (%) and FPG (mmol/mol) were higher among our study

participants compared to previous studies; 9.45 (0.94) and 12.4 (3) vs. 8.49 (1.04) and 9.9 (2.86) in the EDITION trial, 8.5 (0.8) and 10.3 (2.5) in the Toujeo-1 study], as well as the ATOS overall study population; 9.28 (1.0) and 11 (3.1).The initial Gla-300 dose in our study period was comparable with the Toujeo-1 study (16.6 vs. 14.7). However, a higher increase in Gla-300 dose was reported in Toujeo-1 across the study period (22.1 vs. 24.2 at 6 months and 23.6 vs. 26.3 at 12 months). Our study participants received metformin and sulfonylureas (79.6 and 79.2) approximately as inthe BRIGHT trial (91.8 and 64.6) and EDITION trial (90.6 and 59.1), but significantly higher than in the Toujeo-1 study (21.1 and 2.7) **[31-33]**. Although this high rate of OADs use, we observed a low hypoglycemia rate during our follow-up period.

The proportion of individuals achieving the HbA1c target after 6 months of Gla-300 (27.7%) was higher than the overall participants of the ATOS main study (25.2%) and less than inthe Toujeo-1 study (33.4%), BRIGHT trial (48.7%), and EDITION trial (43.1%). However, the absolute reduction of mean HbA1c from the baseline after 6 months was significantly higher in our study compared to the ATOS main study and other studies [–2.09 (0.82) vs. –1.50 (1.15), –1.02 (1,09), –1.64 (0.04), and -1.42 (0.05)]. The mean HbA1c level in our study continued to decrease from month 7 to month 12 to a final level of 6.97%, while it slightly increased in EDITION 3 (7.08% to 7.13%) **[31]**. This led to a double mean reduction in HbA1c (–2.48 % vs. –1.29%) observed 12 months after starting Gla-300 treatment in our study and EDITION 3 trial. Furthermore, glycemic improvement in clinical practice was shown in our study by a significant reduction in the mean FPG (SD) of –4.95 (3.03) mmol/L after 6 months and –5.87 (3.28) mmol/L after 12 months of Gla-300 treatment. However, the reduction was lower in the ATOS overall study population after 6 and 12 months [–3.42 (2.97) mmol/L and –3.95 (3.04) mmol/L]. Likewise, a lower FPG reduction in EDITION 3 was reported after 6 and 12 months (–3.39mmol/L and –3.16 mmol/L) **[31]**. These results reflect better glycemic control and strict adherence of our study participants to the prescribed treatment, which is remarkable in an observational study. The highest glycemic control level and HbA1c target achievement (51.2%) were achieved with a final Gla-300 dose of 23.6 (9) U/day after 12 months, which was less than half of the final dose used in EDITION 3 study 59.4 (32.3) U/day and final Gla-300 dose used in Touejo-1, 26.2 (17.2) U/day **[31,33]**. Our final Glar-300 dose is even less than half of the final dose used after only 6 months in the BRIGHT trial [50.5 (25.6) U/day] **[32]**. These low Gla-300 doses used in our study may also contribute to rare hypoglycemic events (only 2 events) that occurred with our study participants compared to other studies, despite the improved glycemia.

Regarding body weight change, the mean body weight/kg showed a very limited fluctuation during the follow-up period [86.8 in the baseline, 87.3 after 3 months and 6 months, and 86,8 after 12 months]. A similar fluctuation was observed in the ATOS overall study population [80.7, 81.4, 81.3, and 81.4 in the baseline and after 3, 6, and 12 months, respectively]. These results align with treatment outcomes observed in EDITION 3 and BRIGHT trials **[31,32]**. Moreover, a 1.2kg loss was observed over the 12 months of Gla-300 treatmentin a real-world study in Switzerland **[33,34]**. Contrary to popular belief and data observed in first-generation basal insulin, therapy with Gla-300 did not affect body weight significantly and even resulted in slight weight loss in some cases.

Hypoglycemia is another AE that usually both physicians and individuals with T2DM are concerned about when using insulin therapy and may lead to treatment discontinuation or severe complications. Among our 216 included participants, only two (0.9%) experienced hypoglycemic episodes. Regarding the ATOS main study population, the documented hypoglycemia incidence was less than 2%. In comparison to DELIVER Naïve D real-world retrospective study - in which hypoglycemic events occurred in 10.3% of participants- our study provided better real-world safety data for Gla-300 **[35]**. Moreover, the hypoglycemia incidence is much lower than the incidence reported in randomized controlled trials (RCTs), such as EDITION 3 (46%) and BRIGHT (66%). However, most of these reported hypoglycemic episodes are mild and non-complicated. Severe hypoglycemia only occurred in one patient (0,002%) in BRIGHT and 4 participants (1%) in EDITION 3 **[31,32]**.

Strength points and limitations:

Our study is the first prospective non-interventional real-world study to collect data related safety and effectiveness of basal Gla-300 use in insulin naïve T2DM individuals in Egypt. Our study reflects the actual efficacy of Gla-300 and supportsthe results of previously published studies in other populations. Also, the relatively long period of follow-up (12 months) enables us to detect HbA1c fluctuations and any AEs related to drug use. Most of our included participants completed the follow-up without any treatment

discontinuation. On the other hand, major limitations of our study include a lack of randomization due to the descriptive nature of the study and the relatively small number of included participants. Also, our study's absence of a comparator arm may insert some selection bias and limit our conclusion. However, applying a "new-user" design in our recruitment method reduces the risk of selection bias. The narrow scope of our included participants- individuals with T2DM initiating Glar-300 after the failure of OADs - limited the ability to generalize our results to individualswith more advanced diabetes. Another limitation to be considered is the possibility of underreporting of hypos. Underreporting of hypos is recognized to be a challenging prevalent issue that can arise for several reasons. Some individualsmay not disclose they have hypos for fear of revoking their license, while others may not know when or if they are suffering hypos, and others may believe their healthcare team cannot help. The danger of severe hypos may increase when hypos are not acknowledged, as the underlying issues can only worsen without action.

Conclusion:

Our posthoc subgroup analysis results from Egypt are consistent with those of previously published studies, including the EDITION 3 trial, BRIGHT trial, and Toujeo-1 study. All of these positive outcomes, along with the drug's safety profile, make second-generation basal insulin Gla-300 an effective treatment option when OADs fail to control the hyperglycemic state of T2DM individuals. This is in line with the primary data published in the ATOS study that Gla-300 use demonstrated a high level of improvement in HbA1c level and high effectiveness in controlling the euglycemic state of individuals with T2DM uncontrolled on OADs, with a very low risk of AEs.

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Conflict of interest:

All authors confirm no financial or personal relationship with a third party whose interests could be positively or negatively influenced by the article's content.

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ATOS دراسة رصدية استطلاعية مدتها ١٢ شهراً لتقييم الفعالية الإكلينيكية فى العالم الواقعى وأمان بدء الأنسولين جلارجين القاعدى ٣٠٠ U بعد فشل العقاقير الفموية المضادة لمرض السكرى فى الأفراد المصابين بداء السكرى من النوع فى مصر تحليل مجموعة فرعية بعد انتهاء فترة العلاج

الخلفية : يعُد الوصول إلى المستوى المستهدف من الهيموجلوبين السكرى (HbA1c) والحفاظ على حالة سوانية لسكر الدم من التحديات الرئيسية التى تواجه علاج المصابين بمرض السكرى. نظراً لارتفا ع معدل فشل العقاقير الفموية المضادة لمرض السكرى (OADs) فى التحكم فى مستوى الكسر فى الدم لدى المصابين بمرض السكرى من النوع الثانى (T2DM)، ظهرت خيارات أخرى جديدة لتحل محل العلاجات التقليدية فى هذه الحالات. فقد أثبت الأنسولين جلارجين القاعدى من الجيل الثانى أمانه وفعاليته فى تحسين التحكم فى مستوى السكر فى الدم لدى المصابين بمرض السكرى من النوع الثانى غير المنضبط / غير المتحكم به فى تجارب سريرية متعددة عشوائية التوزيع. من ثم، فإننا نهدف إلى تقييم فعالية وأمان الأنسولين جلارجين بمقدار ٣٠٠ وحدة / مللى لتر (Gla-300) عند إضافته إلى العقاقير الفموية المضادة لمرض السكرى ومعايرته حسب أهداف كل فرد على حدة فى الممارسة الواقعية.

الطرائق الوسائل : كانت دراسة (ATOS) عبارة عن دراسة استطلاعية، رصدية، دولية، متعددة المراكز، لجمع معلومات حول ٤٤٢٢ فرداً مصاباً بمرض السكرى من النوع الثانى ممن يبدأون العلاج بالأنسولين جلارجين ٣٠٠ وحدة / مللى لتر فى ١٨ دولة فى مختلف المناطق الجغرافية، وممن كانوا يخضعون لتقييم الهيموجلوبين السكرى بشكل روتينى كل ٦ أشهر على الأقل (NCT03703869). يمثل تحليلنا اللاحق للمجموعة الفرعية جزءاً من هذه الدراسة واسعة النطاق ومتعددة الجنسيات التى حللت البيانات التى جرى جمعها من مصر، وهى إحدى الدول التى تمثل المنطقة الجنوبية من قارة إفريقيا، لتقييم الفعالية الواقعية لأنسولين جلارجين ٣٠٠ وحدة / مللى لتر لدى الأفراد المصريين المصابين بمرض السكرى من النوع الثانى. تشمل النتائج الأولية تقييم فعالية الأنسولين جلارجين ٣٠٠ وحدة / مللى لتر فى تحقيق الأهداف المتعلقة بمستوى السكر فى الدم المقاسة بالاستعانة باختبار قياس مستوى الهيموجلوبين السكرى بعد ٦ أشهر. تشمل الأهداف الثانوية الفعالية والأمان أثناء فترة المتابعة المتتدة (١٢ شهراً).

النتائج :شمل هذا التحليل اللاحق للمجموعة الفرعية ٢١٦ فرداً مصابين بمرض السكرى من النوع الثانى فى مصر بمتوسط سن ٥٢.٧ (±٩.٨) عاماً بلغ متوسط وزن الجسم ومؤشر كتلة الجسم ٨٦.٨ (±١٣.٦) و ٣٠.٦ (±٥.٠)، على التوالى. كان أغلب المشاركين الملتحقين /المشمولين يخضعون لأكثر من علاج فموى مضاد لمرض السكرى بالتزامن (فى أغلب الأحيان الميتفورمين والسفونيل يوريا) بلغت نسبة تحقيق مستوى الهيموجلوبين السكرى المستهدف بعد ٦ أشهر ٢٧.٧٪. ارتفع هذا الرقم إلى ٥١.٢٪ بعد ١٢ شهراً. فى الأفراد أصحاب الأعمار ≤ ٦٥ عاماً، بلغت نسبة تحقيق مستوى الهيموجلوبين السكرى المستهدف بعد ٦ أشهر و ١٢ شهراً ٣٦٪و ٥٢٪، على التوالى. انخفض متوسط النسبة المئوية لمستوى الهيموجلوبين السكرى عن إحدى قيم بدء الدراسة البالغة ٩.٤٥ (٠.٩٤) إلى ٧.٣٦ (٠.٦٠) بعد ٦ أشهر و ٦.٩٧ (±٠.٥٥) بعد ١٢ شهراً من العلاج بالأنسولين جلارجين ٣٠٠ وحدة مللى / لتر. لم يتم الإبلاغ عن أية أحداث عكسية كبرى أو خطيرة أثناء فترة المتابعة. أصيب مشاركان (٠.٩٪) بانخفاض مستوى السكر فى الدم، مع تعرض مشارك واحد فقط لنقص شديد فى مستوى السكر فى الدم.

الاستنتاجات : أدى العلاج بالأنسولين جلارجين ٣٠٠ وحدة مللى / لتر لدى المصريين بمرض السكرى من النوع الثانى غير المتحكم به بالعقاقير الفموية المضادة لمرض السكرى إلى تحسين التحكم فى مستوى السكر فى الدم، وتحقق مستوى الهيموجلوبين السكرى المستهدف فى ٢٧.٧٪ بعد ٦ أشهر مع انخفاض كبير فى احتمالية التعرض لخطر الإصابة بنقص مستوى السكر فى الدم وأحداث عكسية أخرى متعلقة بالعلاج. قد يستفيد الأشخاص المصابون بمرض السكرى من النوع الثانى غير المتحكم فى حالاتهم بالعقاقير الفموية المضادة لمرض السكرى من العلاج بالأنسولين جلارجين بمقدار ٣٠٠ وحدة مللى/لتر. جدير بالذكر أن نتائج دراستنا تتماشى مع نتائج الدراسات التى أجريت سابقاً.