Product registry report

Compound(s): Toujeo® / Insulin Glargine 300 U/mL

A 6-month, Multicenter, single-Arm, observational study with a 6-month extension evaluating patient-reported outcomes of insulin Glargine 300 U/mL (Gla-300) in basal/bolus-treated people with T2 diabetes on therapy in a rEal world setting (MAGE study)

Registry number: GLARGL07973

Registry name: MAGE

Registry initiation date [date first patient in (FPI)]: 02-Jun-2016

Registry completion date [last patient completed/last patient out (LPO)]: 28-Aug-2018

Registry design: 6-month, multicenter, prospective, single-arm observational Belgian study with Gla-300 with a 6-month extension.

Report date: 12-Feb-2019

This registry was performed in compliance with the guidelines for Good Epidemiology Practice. This report has been prepared based on the publication 'Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) – Guidelines for reporting observational studies – Ann Intern Med. 2007'.

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SYNOPSIS

Title of the registry:	A 6-month, Multicenter, single-Arm, observational study with a 6-month extension evaluating patient-reported outcomes of insulin Glargine 300 U/mL (Gla-300) in basal/bolus-treated people with T2 diabetes on therapy in a rEal world setting (MAGE study)
Design:	This was a 6-month, multicenter, prospective, single-arm, observational Belgian study with Gla-300, with a 6-month extension, aiming at evaluating in a real-life setting patient's satisfaction related to the use of Gla-300 and Gla-300 efficacy in people with type 2 diabetes treated with a basal-bolus regimen. Patients served as their own control. Patients were in the study for at least 6 months, after which they were proposed to continue in the study for another 6 months. If a patient discontinued, then the reason was to be documented. Best efforts were made to administer the Diabetes Treatment Satisfaction Questionnaire status version (DTSQs) [24,25] and possibly other Patient Reported Outcomes (PROs) questionnaires at the time of discontinuation. After the baseline visit, two other visits were scheduled by the physician during the first six months, with a possibility to plan two extra visits during a period of six additional months, if the patient agreed to do so by signing a new informed consent. This study being observational, the visits had to be planned every three months according to the current clinical practice in place for type 2 diabetes patients on basal-bolus treatment. Measurements were therefore taken at months 3 and 6 (= the main study) and at months 9 and 12 (= the extension study). Additional contacts, if deemed necessary by the investigator, were allowed.
Objectives:	The primary objective of this study was to demonstrate a change of at least 2 points in the Diabetes Treatment Satisfaction Questionnaire Status Version (DTSQs) total score from baseline to Month 6, in patients with type 2 diabetes treated with insulin glargine 300 U/mL (Gla-300) in routine care. The secondary objectives were: • To document the reason to start Gla-300 in a real life situation in patients with type 2 diabetes: o Hypoglycemia – number of hypoglycemic events or fear of hypoglycemia; o Insulin dose – need for less volume; o Treatment – flexibility in injection time; o Glycated hemoglobin A1c (HbA1c) – not reaching treatment goals (<7%, as defined by the American Diabetes Association [ADA]/ European Association For Study of Diabetes [EASD] position statement); o Any other reason • To document the Gla-300 doses. In that respect, and in the context of an observational study, it should be noted that no specific titration algorithm was suggested to the investigators, the objective being to reflect the real-life conditions of Gla-300 prescription. The investigator was supposed to rely upon the Summary of Product Characteristics (SmPC). • To document the Gla-300 treatment persistency. • To document the effect of Gla-300 administered in a real life situation in patients with type 2 diabetes on: o Weight/Body Mass Index (BMI)/HbA1c at Months 3, 6 (main study) and Months 9 and 12 (extension study) o Other Patient Reported Outcomes measured by the following questionnaires: Diabetes Treatment Satisfaction Questionnaire change version (DTSQc) [24,25] total, hyperglycemia and hypoglycemia perception scores; World Health Organization

	(WHO)-5 [27] well-being index; Hypoglycemia Fear Survey (also called Adult Low Blood Sugar Survey) (HFS)-II [26] total behavior and worry scores, Pittsburgh Sleep Quality Index (PSQI) [28] sleep quality at Month 6 (the main study) and at Month 12 (the extension study) o Safety
Treatment:	Toujeo®: insulin glargine 300 U/mL subcutaneously
Scientific committee and members:	Dr. Ann Verhaegen (ZNA Jan Palfijn, Merksem, Belgium) Prof. Dr. Ides Colin (CHR Mons-Hainaut, Mons, Belgium)
Publications (reference):	Not applicable
Introduction – Background / rationale:	Diabetes mellitus affects almost 382 million people worldwide (estimated figures) with 90% to 95% having type 2 diabetes.[1] It is associated with a range of serious complications which result in reduced quality of life, increased morbidity, and premature mortality.[2] Type 2 diabetes remains a leading cause of cardiovascular disorders, blindness, end-stage renal failure, amputations, and hospitalizations. Prospective randomized trials have documented reduced rates of microvascular complications in patients with type 2 diabetes treated to lower glycemic targets, with a trend toward reduced rates of myocardial infarction.[3-4] The general recommended glycated hemoglobin A1c (HbA1c) target is 7.0% (53 mmol/mol).[5] A more stringent goal of 6.5% (48 mmol/mol) can be selected for some patients if it can be achieved without significant hypoglycemia or other adverse effects of treatment.[6-7] However, glycemic targets for elderly with long-standing or more complicated disease should be less ambitious than for the younger, healthier individuals.[5-7] There is a wide range of pharmacological agents available to treat hyperglycemia. Oral anti-diabetic drugs (OADs) reduce insulin resistance or facilitate insulin secretion and can be effective early in the course of the disease.[8] Insulin is effective in all stages and often is ultimately necessary to achieve glycemic control in patients poorly controlled with one or more OAD.[5] Insulin therapy is clearly indicated for patients in whom glycemic targets were not reached with 2 or more OADs and for those who have blood glucose levels of ≥300 mg/dL – 350 mg/dL and/or HbA1c levels ≥10% - 12% (≥86–108 mmol/mol).[5,7,9] Long-acting (basal) insulin analogs have contributed significantly to improved management of diabetes over the last decade. The first and most commonly used basal insulin analog is glargine 100 units/mL (Gla-100)[10-11] which has a well-established mode of action and profile of efficacy and safety.[5,12-14] It has advantages compared with human NPH insulin, namely reduction of nocturnal and overall hypoglycemia.[11,15-16] This benefit is clinically relevant because, in addition to concerns about medical risks associated with hypoglycemia, fear of hypoglycemia is a leading barrier to starting and continuing insulin therapy.[17-19] However, hypoglycemia continues to be observed during Gla-100 treatment, suggesting that a basal insulin with an even flatter and longer profile of action might further improve safety and tolerability. The new insulin glargine at 300 units/mL (Gla-300) has a reduced re-dissolution rate following subcutaneous injection when compared with Gla-100 and has thereby the potential for meeting this need. Glucose clamp studies confirm that Gla-300 provides flatter and more prolonged pharmacokinetic and pharmacodynamic profiles than Gla-100.[20-21] The EDITION 1 study showed that Gla-300 controls HbA1c as well as Gla-100 for people with type 2 diabetes treated with basal and mealtime insulin but with consistently less risk of nocturnal hypoglycemia.[22] Three-months flexibility sub-studies embedded in the EDITION-1 and -2 trials furthermore showed that Gla-300 provides flexibility to occasionally adapt the timing of injection to an individual's changing daily lifestyle patterns.[23] From these results, it is worth to think that using Gla-300 could be associated with adequate glycemic control with less

	hypoglycemic episodes. However, randomized clinical trials provide little information about the effectiveness and the safety of this drug in the real world, which implies the need for observational studies. The ADA/EASD position statement stresses that a patient-individualized treatment approach, individual treatment goals and plans should be set in the daily clinical practice. When foreseen goals are not reached, the physician may decide in accordance with the patient to change treatment.[5] The decision to switch to Gla-300 can be supported by the following arguments: not achieving treatment goals, need for more flexibility or lower volume of insulin, fear of hypoglycemia, lack of satisfaction with current therapy or not wanting to gain more weight than for example with Gla-100. A single-arm, observational multi-centric study in secondary care was chosen to evaluate in a real-life setting patient (or treatment) satisfaction related to the use of Gla-300 and Gla-300 efficacy in people with type 2 diabetes treated with a basal-bolus regimen. Patients with type 2 diabetes who, prior to Gla-300 treatment, were already on insulin treatment for at least 6 months, were included. This would help to assign changes in outcomes to Gla-300 instead of other factors, i.e. starting insulin in general. Some exclusion criteria were set up in order to prevent bias in the primary outcome (DTSQs) but in limited number, allowing for a pragmatic observational study. Approximately 100 patients from ~15 sites were to be included. The PRO questionnaires were designed to be easily understandable and therefore not too burdensome for patients, in order to minimize the drop-out at Month 6.
Methodology:	The inclusion criteria of the main study were: • ≥18 years; • T2DM (> 1 year); • HbA1c 7.0–10.0%; • basal-bolus (BB) with 4 or 5 injections for at least 6 months; • metformin (MET) could be used as background OAD; • no prior therapy with Gla-300; • reason identified by physician and/or patient to start Gla-300 (hypoglycemia – nr. of hypoglycemic events or fear of hypoglycemia; insulin dose – need for less volume; treatment – flexibility in injection time; HbA1c – not reaching treatment goals [<7%, as defined by the ADA/EASD position statement]; any other reason); • willingness/capability to self-manage titration algorithm; • willingness to fill in 5 PRO questionnaires; • and signed informed consent The inclusion criteria of the extension period were: patient having participated in the main study and signed informed consent The exclusion criteria (main study and extension period) were: • pregnancy or pregnancy wish within next 7 months; • T1DM; • other types of diabetes than T2DM (ex. secondary to pancreatitis); • oral corticosteroid therapy; • life expectancy < 1 year; • and OAD other than MET. Participating investigators (up to 15 centers) were specialists (e.g. endocrinology, diabetology/metabolism, internal medicine) familiar with the management of diabetes. The data were collected in an electronic case report form (eCRF). The primary endpoint was the change in DTSQs [24,25] total treatment satisfaction

score from baseline to Month 6.

The secondary endpoints were:

- Reason(s) for starting with Gla-300: hypoglycemia – nr. of hypoglycemic events or fear of hypoglycemia; insulin dose – need for less volume; treatment – flexibility in injection time; HbA1c – not reaching treatment goals (<7%, as defined by the ADA/EASD position statement); and any other reason.
- DTSQs hyperglycemia and hypoglycemia perception scores at Month 6
- DTSQs total, hyperglycemia and hypoglycemia perception scores at Month 12
- DTSQc total, hyperglycemia and hypoglycemia perception scores at Months 6 and 12
- WHO-5 [27] well-being index at Months 0, 6 and 12
- HFS-II [26] total, behavior and worry scores at Months 0, 6 and 12
- PSQI [28] sleep quality total score at Months 0, 6 and 12
- Mean Change in HbA1c from baseline to Months 3, 6, 9 and 12
- Percentage of patients reaching a HbA1c target of <7% at Months 0, 3, 6, 9 and 12
- Mean change in body weight and BMI from baseline to Months 3, 6, 9 and 12
- Mean change in Gla-300 dose from baseline to Months 3, 6, 9 and 12
- Percentage of patients who were switched to Gla-300+RAI as their BB therapy at baseline and who remained on this regimen until Month 6 and until Month 12
- Self-reported hypoglycemic events, recorded as follows:
    - according to definitions (severe, symptomatic, confirmed ≤70mg/dL and <54mg/dL)
    - according to the time (nocturnal defined as time between 00:00 and 05:59 am, and at any time of day)
- Adverse events (AEs), serious adverse events (SAEs), adverse events of special interest (AESI)

A Statistical Analysis Plan (SAP) was written and approved by the sponsor and principal investigator(s) (21 Feb 2018) before database lock. It constituted the reference document as far as statistical analyses and methodologies were concerned.

- IBM SPSS Statistics (Version 21.0) was used for the statistical analyses.
- Missing values were not replaced nor extrapolated.
- The normality of each variable was confirmed using Kolmogorov-Smirnov's tests. If normality was achieved, parametric tests were used. If not, non-parametric tests were preferred.
- A p value lower than 5% will be considered statistically significant for the primary endpoint.

Descriptive statistics were used to characterize the patient population at baseline: continuous variables were characterized by the N with valid data, N with missing data, mean, standard deviation (SD), median, minimum and maximum, and discrete variables were characterized by the N for each category with valid data, N with missing data, total N, corresponding percentages and cumulative percentages.

The statistical methods used to analyze the primary and secondary endpoints are summarized in the table below.

Endpoint	Descriptive statistics	Normality achieved → Parametric tests			Normality not achieved for continuous variables or analysis of discrete ordinal variables → Non-parametric tests	
		One sample t test	Mixed model	Mixed model with covariates only in case of subgroup comparisons	Friedman's test	Wilcoxon's test
DTSQs M6 vs M0	●	●				●
Reason(s) for starting with Gla-300	●					
DTSQs hyperglycemia and hypoglycemia perception scores at M0 and M6	●	●				●
DTSQs total, hyperglycemia and hypoglycemia perception scores at M0 and M12	●	●				●
DTSQs total, hyperglycemia and hypoglycemia perception scores at M0, M6 and M12	●	●	●	●	●	●
DTSQc total, hyperglycemia and hypoglycemia perception scores at M0, M6 and M12	●	●	●	●	●	●
WHO-5 well-being index at M0, M6 and M12	●	●	●	●	●	●
HFS-II total, behavior and worry scores at M0, M6 and M12	●	●	●	●	●	●
PSQI sleep quality total score at M0, M6 and M12	●	●	●	●	●	●
Mean Change in HbA1c from baseline to M3, M6, M9 and M12	●	●	●	●	●	●
Percentage of patients reaching a HbA1c target of <7% at M0, M3, M6, M9 and M12	●					

Mean change in body weight and BMI from baseline to M3, M6, M9 and M12	●	●	●	●	●	●
Mean change in Gla-300 dose from baseline to M3, M6, M9 and M12	●	●	●	●	●	●
Percentage of patients who were switched to Gla-300+ RAI as their BB therapy at baseline and who remained on this regimen until M6 and M12	●					
Self-reported hypoglycemic events	●					
AEs	●					
SAEs	●					
AESI	●					

On-site verification of 100% of signed informed consent forms was performed. A data quality control of minimum 25% of patient data was performed at each active site. The methodology of Quality Control (site monitoring and/or phone QC) and appropriate consecutive corrective actions has been detailed in the Study Manual. A Data Management/Data Cleaning Plan was written by Lambda-Plus. Five full data cleaning processes were conducted and corresponding reports were produced and reviewed. Manual queries were generated in the eCRF until all data were cleaned. The distribution of the patients into the different analysis cohorts was discussed and approved during a database pre-lock meeting and a report (21 Sep 2018) corresponding to this meeting was approved by Lambda-Plus and the sponsor.

RESULTS

Participants (actual):

The main milestones of the study were as follows: first patient enrolled on 02 June 2016, last patient enrolled on 31 July 2017, first patient finalizing the main study (up to Month 6) on 10 November 2016, last patient finalizing the main study (up to Month 6) on 19 February 2018, first patient finalizing the extension study (up to Month 12) on 09 May 2017, and last patient finalizing the extension study (up to Month 12) on 28 August 2018. The inclusion period had been prolonged to enroll a sufficient number of patients.

A total of 93 patients were enrolled and signed the informed consent, among which 6 had an inclusion failure status and were not considered further in the analysis. The inclusion failure reasons of these 6 patients were as follows:

- 4 patients had an HbA1c outside the range of 7-10%;
- 1 patient did not have a basal bolus with 4-5 injections for at least 6 months and presented another type of diabetes than type 2 diabetes mellitus;
- 1 patient did not have a basal bolus with 4-5 injections for at least 6 months and received a treatment with canagliflozine.

A total of 87 patients (100.0%) were included in the ITT cohort by 10 investigators in 10 centers.

	In the ITT cohort, 19 patients presented major protocol violations. The reasons for excluding these patients from the analysis (major protocol deviations) are summarized in the Pre-Lock Database Meeting Report (dated 21 September 2018): • Three (N=3) patients discontinued the study between the baseline visit (V0) and the Month 3 visit (V1): one patient died, one patient decided to stop the study and one patient withdrew his/her consent. • Fourteen (N=14) patients discontinued the study between Month 3 (V1) and Month 6 (V2) for the following reason: 4 for a non-serious AE (headache and sensation of hypoglycemia but not objectivated; myalgia; muscle and joint pain; vomiting), 4 following the decision of the investigator (conflict between investigator and one patient who was aggressive before the consultation; insufficient glycemic control and too many hypoglycemia with Toujeo; lack of efficacy in 2 patients), 1 for consent withdrawal, 2 following the decision of the patient, 2 were lost to follow-up and 1 had a protocol deviation (type 1 diabetes). • Two (N=2) patients had their data of Visit 2 (Month 6) transferred to Visit 4 (Month 12). A total of 68 patients (78.2%) (87-19) completed the primary study and were included in the PP cohort. Three patients discontinued the study between Month 6 (V2) and Month 9 (V3) and for one additional patient the data of Visit 3 (Month 9) were transferred to Visit 4 (Month 12). No additional patient discontinued the study between Month 9 (V3) and Month 12 (V4). A total of 67 patients (77.0%) completed the study extension up to Month 12 (V4).
Participant characteristics and primary analyses:	The 87 patients of ITT cohort (58 males [66.7%] and 29 females [33.3%]) were 63.8 ± 8.9 years-old with a median of 65 years (min-max = 41-82 years). Their disease had lasted for 17.1 ± 7.7 years on average. Their mean BMI was 32.2 ± 5.5 kg/m². Their mean HbA1c was 7.9 ± 0.6 %. Gla-300 (Toujeo®) was prescribed with the objective to decrease HbA1c in 78 (89.7%) patients, to decrease hypoglycemic events (HEs) in 31 (35.6%) patients and/or for another objective in 20 (23.0%) patients. The following microvascular complications were reported: retinopathy in 28 (32.2%) patients, neuropathy in 27 (31.0%) patients, and nephropathy in 30 (34.5%) patients. The following macrovascular complications were reported: peripheral vascular disease in 15 (17.2%) patients, transient ischemic attack in 3 (3.4%) patients, stroke in 4 (4.6%) patients, angina pectoris in 9 (10.3%) patients, and myocardial infarction in 12 (13.8%) patients. The following other comorbidities were reported: hypertension in 73 (83.9%) patients, with a treatment required for all of them, atrial fibrillation in 5 (5.7%) patients, heart failure in 7 (8.0%) patients (not requiring hospitalization), and hyperlipidemia/hypercholesterolemia in 77 (88.5%) patients, with a treatment required in 75 (86.2%) patients. A family history of stroke or coronary disease was reported in 26 (29.9%) patients. Diabetic foot was present in 6 (6.9%) patients. Allergy was recorded in 11 (12.6%) patients. A relevant surgery was reported in 38 (43.7%) patients. The 68 patients of PP cohort (44 males [64.7%] and 24 females [35.3%]) were 64.2 ± 8.8 years-old with a median of 66 years (min-max = 41-82 years). Their disease had lasted for 16.7 ± 7.5 years on average. Their mean BMI was 32.5 ± 5.9 kg/m². Their mean HbA1c was 7.8 ± 0.6 %. Gla-300 (Toujeo®) was prescribed with the objective to decrease HbA1c in 63 (92.6%) patients, to decrease HEs in 20 (29.4%) patients and/or for another objective in 18 (26.5%) patients. The following microvascular complications were reported: retinopathy in 19 (27.9%) patients, neuropathy in 20 (29.4%) patients, and nephropathy in 22 (32.4%) patients. The following macrovascular complications were reported: peripheral vascular disease in 11 (16.2%) patients, transient ischemic attack in 3 (4.4%) patients, stroke in 2 (2.9%) patients, angina pectoris in 5 (7.4%) patients, and myocardial infarction in 11

(16.2%) patients. The following other comorbidities were reported: hypertension in 56 (82.4%) patients, with a treatment required for all of them, atrial fibrillation in 4 (5.9%) patients, heart failure in 7 (10.3%) patients (not requiring hospitalization), and hyperlipidemia/hypercholesterolemia in 62 (91.2%) patients, with a treatment required in 60 (88.2%) patients. A family history of stroke or coronary disease was reported in 19 (27.9%) patients. Diabetic foot was present in 4 (5.9%) patients. Allergy was recorded in 11 (16.2%) patients. A relevant surgery was reported in 33 (48.5%) patients.

In the ITT cohort, 74 (85.1%) patients took insulin glargine (Lantus), 5 (5.7%) patients took insulin isophane (Insulatard or Insuman Basal) and 8 (9.2%) took insulin determir (Levemir) at baseline. The mean ± SD total basal insulin dose at baseline was 38.0 ± 19.9 IU. In the PP cohort, 57 (83.8%) patients took insulin glargine (Lantus), 4 (5.9%) patients took insulin isophane (Insulatard or Insuman Basal) and 7 (10.3%) took insulin determir (Levemir) at baseline. The mean ± SD total basal insulin dose at baseline was 39.0 ± 20.4 IU.

In the ITT cohort, 18 (20.7%) patients took insulin glulisine (Apidra), 11 (12.6%) took insulin lispro (Humalog), 54 (62.1%) took insulin aspart (Novorapid) and 4 (4.6%) took human insulin (Actrapid or Insuman Rapid) as prandial insulin at baseline. The mean total prandial insulin daily dose at baseline was 43.6 ± 18.6 IU. In the PP cohort, 14 (20.6%) patients took insulin glulisine (Apidra), 6 (8.8%) took insulin lispro (Humalog), 45 (66.2%) took insulin aspart (Novorapid) and 3 (4.4%) took human insulin (Actrapid or Insuman Rapid) at baseline. The mean total prandial insulin daily dose at baseline was 43.8 ± 19.3 IU.

In the ITT cohort, the mean time between the baseline visit and the start of Gla-300 (Toujeo) was 0.74 ± 1.61 day. The mean dose of Gla-300 was 38.6 ± 19.0 IU. In the PP cohort, the mean time between the baseline visit and the start of Gla-300 (Toujeo) was 0.85 ± 1.78 day. The mean dose of Gla-300 was 38.7 ± 19.1 IU.

For both the ITT and the PP cohorts, the one sample t test for the improvement of DTSQs total treatment satisfaction score between baseline and Month 6 was significant ($p<0.0001$) and this was confirmed by paired Wilcoxon's test which was also significant ($p<0.0001$). The results in the ITT cohort are shown in the table below.

Baseline, Month 6 and change between baseline and Month 6 in the DTSQs total treatment satisfaction score (ITT cohort)

	N		Mean	Median	SD	Min	Max
	Valid	Missing					
Baseline score	*86*	*0*	*27.93*	*29.00*	*5.608*	*15*	*36*
Month 6 score	*69*	*17*	*30.39*	*31.00*	*4.404*	*17*	*36*
Change satisfaction score between baseline and Month 6	*69*	*17*	*2.80*	*3.00*	*5.46*	*-12*	*18*

Other analyses:

All the other analyses are presented in the ITT cohort only, which is the most important cohort for an observational study aiming to provide a real-life picture of the use of Toujeo®. The results obtained in the PP cohort are available in the Statistical Analysis Report (dated 24 October 2018).

The improvement change in the DTSQs total satisfaction score between baseline and Month 12 was 2.10 ± 5.51 ($p=0.004$).

The improvement in the perceived hypoglycemia score between baseline and Month 6 was -0.40 ± 1.32 ($p=0.016$). Between baseline and Month 12 it was -0.08 ± 1.63 ($p>0.05$).

The improvement in the perceived hyperglycemia score between baseline and Month 6 was -0.41 ± 2.02 (p>0.05). Between baseline and Month 12 it was -0.27 ± 1.90 (p>0.05).

The chi-square tests comparing the actual scores distributions to a theoretical distribution equal in all categories revealed a statistically significant improvement of the total satisfaction score at Month 6 (p=0.032), of perceived hyperglycemia at Month 6 and at Month 12 (p=0.011 and p=0.003, respectively), and of perceived hypoglycemia at Month 6 and at Month 12 (p=0.001 and p=0.002, respectively).

DTSQc change in the satisfaction with treatment perceived hyperglycemia and perceived hypoglycemia scores at Month 6 and Month 12 (ITT cohort)

	N		Mean	Median	SD	Min	Max
	Valid	Missing					
DTSQc satisfaction with treatment at Month 6	***68***	***1***	***11.28***	***13.50***	***6.113***	***-7***	***18***
DTSQc satisfaction with treatment at Month 12	***63***	***6***	***11.00***	***12.00***	***5.714***	***-9***	***18***
DTSQc perceived hyperglycemia at Month 6	***68***	***1***	***.59***	***1.00***	***1.548***	***-3***	***3***
DTSQc perceived hyperglycemia at Month 12	***63***	***6***	***.51***	***1.00***	***1.655***	***-3***	***3***
DTSQc perceived hypoglycemia at Month 6	***68***	***1***	***.15***	***.00***	***1.459***	***-3***	***3***
DTSQc perceived hypoglycemia at Month 12	***63***	***6***	***-.25***	***.00***	***1.586***	***-3***	***3***

The modification of the WHO-5 score between baseline and Month 6 was -1.12 ± 15.7 (p=0.560) and the modification of the score between baseline and Month 12 was 3.17 ± 14.0 (p=0.076).

The improvement of the HFS-II behavior score was equal to -2.38 ±7.39 between baseline and Month 6 (p=0.010) and -3.30 ± 9.58 between baseline and Month 12 (p=0.009). The improvement of the HFS-II worry score as equal to -4.41 ± 11.22 between baseline and Month 6 (p=0.002) and -4.80 ±12.33 between baseline and Month 12 (p=0.003). The improvement of the HFS-II total score was equal to -6.96 ±15.11 between baseline and Month 6 (p<0.0001) and -8.50 ± 18.68 between baseline and Month 12 (p=0.001).

The improvement of the PSQI total score between baseline and Month 6 was statistically significant (p=0.044) (-0.73 ± 2.94) but the change between baseline and Month 12 was not statistically significant (p=0.525) (-0.25 ± 3.06).

There was no significant modification of HbA1c between baseline and all the other time points (-0.06 ± 0.60 [median = -0.1] at Month 3; 0.01 ±0.64 [median = 0.0] at Month 6, -0.01 ± 0.59 [median = -0.05] at Month 9 and -0.05 ± 0.82 [median = -0.2] at Month 12). The number and percentage of patients with a value of HbA1c <7% was equal to 0 (0%) at baseline, 7 (8%) at Month 3, 7 (8%) at Month 6, 4 (4.6%) at Month 9, and 10 (11.5%) at Month 12.

The bodyweight changes between baseline and the other time points were not statistically significant (p>0.05) at the exception of the increase between baseline and Month 9 which was statistically significant (p=0.028) (1.00 ± 3.29 kg).

Similarly, the BMI changes between baseline and the other time points were not statistically significant (p>0.05) at the exception of the increase between baseline

	and Month 9 which was statistically significant (p=0.024) (0.37 ± 1.16 kg/m²). The Gla-300 dose change between baseline and Month 3 was not statistically significant (p=0.745). However, the changes between baseline and the other time points were statistically significant (p<0.0001 for the three other time points) (+3.04 ± 5.11 IU at Month 6 [+7.9%]; +4.42 ± 7.50 IU at Month 9 [+11.4%] and +5.48 ± 9.79 IU at Month 12 [+14.2%]). The statistical tests did not reveal any statistically significant modifications of the total prandial insulin dose from the baseline to Month 12 (p>0.05). A total of 1,509 hypoglycemic events (HEs) were reported in 49 patients (56.3%) from the ITT cohort. This corresponds to a mean ± SD of 30.8 ± 49.6 HEs per patient and to a mean ± SD of 35.0 ± 48.3 HEs per patient-year. A total of 1,244 HEs necessitated counter measures. This corresponds to a mean ± SD of 25.4 ± 47.1 HEs with counter measures per patient and to a mean ± SD of 29.2 ± 46.8 HEs with counter measures per patient-year. A total of 1,346 HEs were symptomatic. This corresponds to a mean ± SD of 27.5 ± 48.5 symptomatic HEs per patient and to a mean ± SD of 31.3 ± 47.5 symptomatic HEs per patient-year. A total of 140 HEs were nocturnal. This corresponds to a mean ± SD of 3.1 ± 4.6 nocturnal HEs per patient and to a mean ± SD of 4.1 ± 6.4 nocturnal HEs per patient-year. A total of 1,497 HEs were confirmed by glucose concentrations below or equal to 70 mg/dL. This corresponds to a mean ± SD of 31.2 ± 49.8 confirmed HEs per patient and to a mean ± SD of 35.4 ± 48.5 HEs confirmed by glucose concentrations below or equal to 70 mg/dL per patient-year. A total of 493 HEs were severe and confirmed by glucose concentrations below 54 mg/dL. This corresponds to a mean ± SD of 10.3 ± 22.1 severe and confirmed HEs per patient and to a mean ± SD of 11.1 ± 21.7 severe and confirmed (glucose concentrations below 54 mg/dL) HEs per patient-year. A total of 150 AEs were reported in 55 patients (63.2%) of the ITT cohort. The most frequent AEs were hypoglycemia (9.2%), diarrhea (4.6%), bronchitis (4.6%) and myalgia (3.2%). Two patients (2.3%) reported three AEs considered related to Gla-300 by the investigator: 1 case of arthralgia and 2 cases of myalgia. Twelve patients (13.8%) reported 18 SAEs. Each SAE type was reported only by 1 (1.1%) patient. None of these SAEs was considered related to Gla-300 by the investigator. There were no reported adverse events of specific interest (AESI): pregnancy, symptomatic overdose (accidental or intentional) or increase in alanine transaminase (ALT). All patients (100.0%) of the ITT took at least one concomitant medication. A total of 776 medications were taken.
Discussions:	The primary objective to demonstrate a change of at least 2 points in the total DTSQs score from baseline to Month 6, in patients with type 2 diabetes, treated with insulin glargine 300 U/mL (Gla-300) in routine care, was achieved both clinically and statistically with a mean decrease of 2.8 points (p<0.0001). According to the investigators, Gla-300 (Toujeo®) was prescribed with the objective to decrease HbA1c in 78 (89.7%) patients, to decrease hypoglycemic events (HEs) in 31 (35.6%) patients and/or for another objective in 20 (23.0%) patients. A total of 68 patients (78.2%) completed the primary study up to Month 6 and 67 patients (77.0%) completed the study extension up to Month 12. The mean dose of Gla-300 was 38.6 ± 19.0 IU. The Gla-300 dose change between baseline and Month 3 was not statistically significant (p=0.745). However, the changes between baseline and the other time points were statistically significant (p<0.0001 for the three other time points) (+3.04 ± 5.11 IU at Month 6 [+7.9%]; +4.42 ± 7.50 IU at Month 9 [+11.4%] and +5.48 ± 9.79 IU at Month 12 [+14.2%]).

	The increase of Gla-300 dose means that the patient was likely encouraged by the physician to further titrate, alternatively the physicians could have just adapted the dose to fasting glycaemia levels. However this did not result in a change in HbA1c. Interestingly this dose increase did not result in a clinically and statistically significant increase in bodyweight. The number and percentage of patients with a value of HbA1c <7% was equal to 0 (0%) at baseline, 7 (8%) at Month 3, 7 (8%) at Month 6, 4 (4.6%) at Month 9, and 10 (11.5%) at Month 12, showing improvement in HbA1c in a subgroup of patients. The improvement change in the DTSQs total satisfaction score between baseline and Month 12 was 2.10 ± 5.51 (p=0.004). The improvement in the perceived hypoglycemia score between baseline and Month 6 was -0.40 ± 1.32 (p=0.016). Between baseline and Month 12 it was -0.08 ± 1.63 (p>0.05). The improvement in the perceived hyperglycemia score between baseline and Month 6 was -0.41 ± 2.02 (p>0.05). Between baseline and Month 12 it was -0.27 ± 1.90 (p>0.05). The chi-square tests comparing the actual scores distributions to a theoretical distribution equal in all categories revealed a statistically significant improvement of the total satisfaction score at Month 6 (p=0.032), of perceived hyperglycemia at Month 6 and at Month 12 (p=0.011 and p=0.003, respectively), and of perceived hypoglycemia at Month 6 and at Month 12 (p=0.001 and p=0.002, respectively). Clinical and statistical improvements were also measured for the majority of PROs and health-related quality of life scales. However, p values, particularly when they are borderline versus the 0.05 level, should be interpreted cautiously taking into account the multiplicity of endpoints and time points. WHO-5 is not specific of diabetes. Gla-300 improved the specific diabetes related QoL but not the generic questionnaires. The decrease in fear of hypoglycemia did not translate into an improvement of HbA1c. This is strange but real life. A total of 1,509 hypoglycemic events (HEs) were reported in 49 patients (56.3%) from the ITT cohort. This corresponds to a mean ± SD of 30.8 ± 49.6 HEs per patient and to a mean ± SD of 35.0 ± 48.3 HEs per patient-year. A total of 1,346 HEs were symptomatic. This corresponds to a mean ± SD of 27.5 ± 48.5 symptomatic HEs per patient and to a mean ± SD of 31.3 ± 47.5 symptomatic HEs per patient-year. A total of 140 HEs were nocturnal. This corresponds to a mean ± SD of 3.1 ± 4.6 nocturnal HEs per patient and to a mean ± SD of 4.1 ± 6.4 nocturnal HEs per patient-year. In the study EDITION 1 [22], the overall mean number of HEs per patient-year was equal to 26.37 and the mean number of nocturnal HEs per patient-year was equal to 3.32. These two values are relatively similar to the results of the current study. The results of this study attest that a 2nd generation of basal insulin with a flatter and longer pharmacodynamics/pharmacokinetic profile (Gla-300) provides a higher patient's satisfaction. In an open label study, the patients could be tempted to answer more positively to the PRO questionnaires. But, as there is an improvement for all the questionnaires, it means that this bias is not likely. An increase in the QoL is important for the patients and certainly justifies the 15% dose increase. The improvement in the DTSQs was maintained until the end of the study and was therefore not simply an effect of novelty. The applicability (external validity) to other circumstances and the generalizability of this registry are limited due to the intrinsic open, uncontrolled and observational characteristics of its design.

Conclusions:	The primary objective of this study was to demonstrate a change of at least 2 points in the total DTSQs score from baseline to Month 6, in patients with type 2 diabetes, treated with insulin glargine 300 U/mL (Gla-300) in routine care. This objecitve was achieved both clinically and statistically with a mean decrease of 2.8 points (p<0.0001). According to the investigators, Gla-300 (Toujeo®) was prescribed with the objective to decrease HbA1c in 78 (89.7%) patients, to decrease hypoglycemic events (HEs) in 31 (35.6%) patients and/or for another objective in 20 (23.0%) patients. The number and percentage of patients with a value of HbA1c <7% increased gradually from baseline to Month 12, and was equal to 0 (0%) at baseline, 7 (8%) at Month 3, 7 (8%) at Month 6, 4 (4.6%) at Month 9, and 10 (11.5%) at Month 12. Improving HbA1c was the objective expressed by health care providers. Clinical and statistical improvements were also measured for the majority of PROs and health-related quality of life scales. A total of 1,509 hypoglycemic events (HEs) were reported in 49 patients (56.3%) from the ITT cohort. This corresponds to a mean ± SD of 30.8 ± 49.6 HEs per patient and to a mean ± SD of 35.0 ± 48.3 HEs per patient-year. In the study EDITION 1 [22], the overall mean number of HEs per patient-year was equal to 26.37.
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