Diabetes Ther (2020) 11:1835–1847
https://doi.org/10.1007/s13300-020-00866-2

ORIGINAL RESEARCH

Patient-Reported Outcomes with Insulin Glargine 300 U/mL in People with Type 2 Diabetes: The MAGE Multicenter Observational Study

Ides M. Colin · Kathy Alexandre · Jacques Bruhwyler · André Scheen · Ann Verhaegen

Received: May 28, 2020 / Published online: July 8, 2020

ABSTRACT

Introduction: MAGE was a Multicenter, single-Arm, observational 6-month (plus 6-month extension) study that aimed to assess treatment satisfaction, efficacy, and safety of insulin Glargine 300 U/mL (Gla-300) in people with type 2 diabetes (T2DM) receiving basal-bolus insulin in a rEal-world setting.

Materials and methods: Participants were at least 18 years old, with T2DM for more than 1 year, HbA_{1c} 7.0–10.0%. The primary endpoint was change in Diabetes Treatment Satisfaction Questionnaire status version (DTSQs) total score (baseline to month 6). Secondary endpoints included reasons for starting Gla-300, changes in the DTSQ change version (DTSQc) total score, Hypoglycemia Fear Survey-II (HFS-II) total behavior and worry scores at months 6 and 12, HbA_{1c} changes at months 3, 6, 9, and 12, and safety.

Results: MAGE included 87 adults (mean T2DM duration 17 years). The primary endpoint of DTSQs mean (standard deviation) total score improvement at month 6 was achieved (2.80 [5.46] points; $p < 0.0001$). The main reasons for Gla-300 initiation were to decrease HbA_{1c} (89.7% of participants) and reduce the number of hypoglycemic events (35.6% of participants). Significant improvements were observed in the DTSQc total score and perceived hyperglycemia/hypoglycemia (baseline to month 6, $p < 0.05$). Significant changes in HFS-II behavior, worry, and total scores at 6 and 12 months were also observed ($p < 0.05$). There were no statistically significant changes in HbA_{1c}. Safety outcomes, including hypoglycemia, were comparable to previously reported trials.

Conclusions: The MAGE study indicates that Gla-300, as part of a basal-bolus regimen, results in improved treatment satisfaction and reduced

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s13300-020-00866-2) contains supplementary material, which is available to authorized users.

Digital Features To view digital features for this article go to https://doi.org/10.6084/m9.figshare.12473045.

I. M. Colin (✉)
Endocrino-Diabetology Clinical Research Unit, CHR Mons-Hainaut/Groupe Jolimont, Avenue Baudouin de Constantinople 5, 7000 Mons, Belgium
e-mail: Ides.Michel.COLIN@jolimont.be

K. Alexandre
Sanofi, Airport Plaza, Montreal Building, Leonardo Da Vincilaan 19, 1831 Diegem, Belgium

J. Bruhwyler
Lambda-Plus, Rue Camille Hubert 15, 5032 Gembloux, Belgium

A. Scheen
Division of Diabetes, Nutrition and Metabolic Disorders and Clinical Pharmacology Unit, CHU Liège, 4000 Liège, Belgium

A. Verhaegen
Department of Endocrinology, Diabetes and Metabolism, Antwerp University Hospital, 2650 Egedem/Antwerp, Belgium

hypoglycemia fear in people with advanced T2DM.

Keywords: Basal-bolus insulin regimen; Hypoglycemia; Insulin glargine 300 U/mL; Quality of life; Type 2 diabetes

Key Summary Points

Why carry out this study?

Improved treatment satisfaction is an important factor in the treatment of type 2 diabetes (T2DM) and is required to gain better treatment adherence

The second-generation basal insulin analogue insulin glargine 300 U/mL (Gla-300) provides a longer duration of action and more stable pharmacodynamic profile than the first-generation analogue, Gla-100

The primary objective and endpoint of the real-world observational MAGE study was to assess treatment satisfaction when switching to Gla-300 in people with T2DM receiving basal-bolus insulin

What was learned from the study?

People with advanced T2DM who switched to Gla-300 treatment had a significant improvement in treatment satisfaction and reduced hypoglycemia fear, without a reduction in HbA_{1c}

The improved treatment satisfaction observed with Gla-300 in people with T2DM may improve treatment adherence, thus contributing to long-term stable glucose control

INTRODUCTION

Improving treatment satisfaction and safety are important for treating type 2 diabetes (T2DM) and are required to gain better treatment adherence, thereby improving long-term outcomes [1]. Poor adherence to insulin treatment results from many factors, including a busy lifestyle, travels, stress or psychosocial issues, skipped meals, and treatment-associated burden such as the number of injections, flexibility in injection time, regimen complexity, and hypoglycemia [2]. Hypoglycemia is associated with reduced quality-of-life (QoL) due to its inherent stressful nature and worries regarding individual psychosocial consequences [3]. Hypoglycemia itself also often results in poor treatment adherence [4].

Second-generation long-acting basal insulin (BI) analogues, including insulin glargine 300 U/mL (Gla-300), provide a longer duration of action and even more stable pharmacokinetic/pharmacodynamic profiles than the first-generation BI analogue, Gla-100 [5, 6]. The EDITION treat-to-target randomized controlled trial (RCT) program compared Gla-300 with Gla-100 in populations with type 1 and T2DM [7–14]. EDITION 1, which included people with T2DM treated with a basal-bolus treatment regimen, showed that Gla-300 provided similar glycemic control after 6 months, but with significantly less nocturnal hypoglycemia compared with Gla-100, and a more sustained HbA_{1c} reduction for Gla-300 at 12 months [8, 9]. Gla-300 may also reduce insulin treatment burden compared with Gla-100, as it allows more flexibility in the timing of injections, requires a reduced volume of injected insulin, and results in smaller glycemic excursions [15, 16].

Most studies of BI analogues are not specifically designed to evaluate treatment satisfaction. Therefore, MAGE aimed to assess treatment satisfaction, efficacy, and safety of Gla-300 in people with T2DM receiving basal-bolus insulin in a real-world setting, and is distinct from other real-world studies, as treatment satisfaction was the primary endpoint.

METHODS

Study Design

MAGE (a 6-month Multicenter, prospective, single-Arm, observational study with a 6-month extension period, evaluated treatment satisfaction, efficacy and safety of insulin Glargine 300

U/mL in people with T2DM receiving basal-bolus insulin in a rEal-world setting), was conducted in second-line diabetes clinics in Belgium. MAGE was performed in accordance with the principles of the 18th World Medical Assembly (Declaration of Helsinki, 1964) and all subsequent amendments, the European guidelines for Good Epidemiology Practice, and complied with local regulatory requirements [17, 18]. All participants signed an informed consent form before taking part in the study and study extension.

Study Population

Participants were at least 18 years old, with T2DM for more than 1 year, HbA_{1c} 7.0–10.0%, receiving basal and mealtime insulin (with 4–5 daily injections) for at least 6 months, and had not previously used Gla-300. Individuals were excluded if they were taking oral antihyperglycemic drugs (OADs) other than metformin or were receiving corticosteroids. Full inclusion and exclusion criteria are listed in the Supplementary Methods.

Study Endpoints

After the baseline visit, two further visits were scheduled by the physician during the first 6 months (months 3 and 6), with the possibility to plan two extra visits over an additional 6-month period (months 9 and 12). As this study was observational, visits were planned every 3 months according to the current clinical practice in Belgium. Additional visits were allowed if considered necessary by the investigator.

The primary endpoint was a change in the Diabetes Treatment Satisfaction Questionnaire status version (DTSQs) total score from baseline to month 6 in participants with T2DM treated with Gla-300 in routine care (see Supplementary Methods for details of DTSQs methodology). The primary objective was to demonstrate a change of at least 2 points in the DTSQs total score (baseline to month 6), which was deemed as a clinically relevant improvement.

Secondary endpoints included additional Patient-Reported Outcomes (PROs) such as the Diabetes Treatment Satisfaction Questionnaire change version (DTSQc); World Health Organization (WHO)-5 Well-Being Index; Hypoglycemia Fear Survey (HFS)-II; and Pittsburgh Sleep Quality Index (PSQI). See Supplementary Methods for the methodology regarding the secondary PRO analyses. Reasons for starting Gla-300 were also assessed. The study also examined mean changes in bodyweight, body mass index (BMI), HbA_{1c}, and Gla-300 dose. The proportion of participants who continued Gla-300 therapy was also recorded.

Self-reported hypoglycemia (severe, symptomatic, confirmed [$\leq$ 70 mg/dL and $<$ 54 mg/dL]) was recorded according to time (nocturnal [between 00:00 and 05:59] and at any time of day [24 h]). Severe hypoglycemia was defined (per American Diabetes Association guidelines) as an event that required the assistance of another person to actively administer carbohydrates, glucagon, or to take other corrective actions [19].

Safety outcomes including adverse events (AEs), serious adverse events (SAEs), and adverse events of special interest (AESI) were recorded.

Data Analysis and Statistics

The sample size calculation performed prior to the study (paired t test with nQuery Advisor Version 7.0) determined that the recruitment of 82 patients was required to detect a clinically relevant change of at least 2 points in the DTSQs total treatment satisfaction score at month 6 versus baseline (p value set at 0.05, standard deviation [SD] of 5.50, power of 90%). Taking into account an approximate 20% participant dropout rate, it was estimated that 100 patients should be enrolled to achieve the expected 82 completed patients at month 6.

The primary endpoint was assessed in the intent-to-treat (ITT) population (all individuals eligible for Gla-300 treatment at baseline) and in the per-protocol (PP) population (all participants who completed the study). Secondary efficacy endpoints were assessed in the ITT population. All endpoints were summarized by descriptive statistics. The primary endpoint was analyzed using a paired Student's t test with $p < 0.05$ considered statistically significant. The

normality of continuous secondary endpoints was assessed using Kolmogorov–Smirnov testing. For endpoints with more than two time points, mixed models were used, while changes from baseline were assessed with a one-sample *t* test. If normality was not achieved, Friedman's testing was used for outcomes with more than two time points, and paired Wilcoxon's testing was performed on outcomes with two time points. Statistical analysis was performed using IBM SPSS Statistics (Version 21.0) and StatXact (Version 6.0). Missing values were not replaced/extrapolated.

RESULTS

Participant Disposition

The study was conducted between 2 June 2016 and 28 August 2018. Participant disposition is presented in Fig. 1. As the aim of this observational study was to be as close to real life as possible, data are presented primarily from the ITT population of 87 individuals, which included all those who received the allocated intervention. In total, 68 individuals completed the primary study and were included in the PP population; 67 patients completed the 6-month study extension period.

Baseline Characteristics

Baseline characteristics (ITT population) are presented in Table 1. The cohort was composed of people with T2DM with a mean (SD) BMI of 32 (5.5) kg/m^2, mean age of approximately 64 (8.9) years, and diabetes duration of 17 (7.7) years. Approximately one-third of this cohort had microvascular complications and most participants had hypertension, as well as

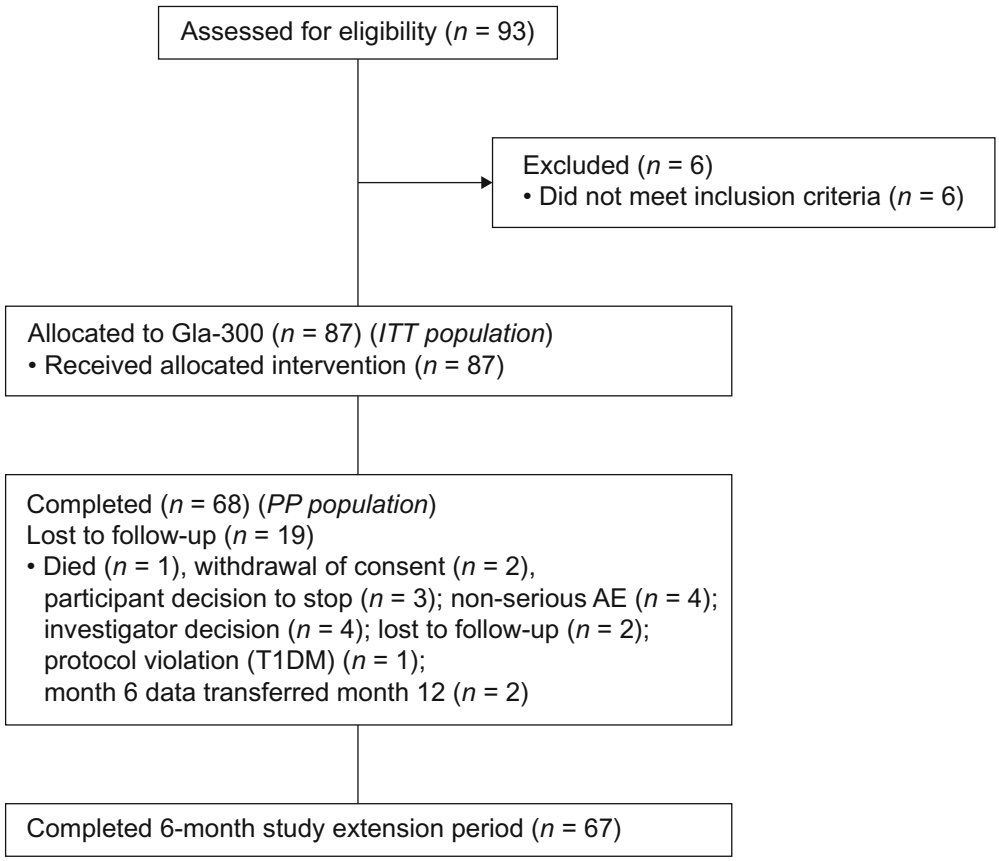

Fig. 1 Participant disposition in MAGE. *AE* adverse event, *ITT* intent-to-treat, *PP* per-protocol, *T1DM* type 1 diabetes

Table 1 Baseline characteristics (ITT population)

Parameter	Baseline characteristics		
	***N* (missing)**	**Mean ± SD**	***n* (%)**
Mean age, years	87 (0)	63.8 ± 8.9	–
Male gender	87 (0)	–	58 (66.7)
Mean diabetes duration, years	87 (0)	17.1 ± 7.7	–
Weight, kg	87 (0)	94.0 ± 18.1	–
BMI, kg/m^2	87 (0)	32.2 ± 5.5	–
HbA_{1c}, %	87 (0)	7.9 ± 0.6	–
Comorbidities			
Retinopathy		–	28 (32.2)
Neuropathy		–	27 (31.0)
Nephropathy		–	30 (34.5)
Hypertension		–	73 (83.9)
Peripheral vascular disease		–	15 (17.2)
Atrial fibrillation		–	5 (5.7)
Transient ischemic attack	87 (0)	–	3 (3.4)
Stroke		–	4 (4.6)
Heart failure		–	7 (8.0)
Angina pectoris		–	9 (10.3)
Myocardial infarction		–	12 (13.8)
Hyperlipidemia/hypercholesterolemia		–	77 (88.5)
Family history of stroke/coronary disease		–	26 (29.9)
Diabetic foot		–	6 (6.9)
Previous basal insulin			
Gla-100		–	74 (85.1)
Detemir	87 (0)	–	8 (9.2)
Isophane		–	5 (5.7)
Previous basal insulin dose, IU			
Gla-100	74 (0)	35.5 ± 18.0	–
Detemir	8 (0)	54.8 ± 26.5	–
Isophane	5 (0)	47.6 ± 23.2	–
Mean baseline Gla-300 dose, IU	87 (0)	38.6 ± 19.0	–

Table 1 continued

Parameter	Baseline characteristics		
	N (missing)	Mean ± SD	*n* (%)
Previous prandial insulin			
Glulisine		–	18 (20.7)
Lispro	87 (0)	–	11 (12.6)
Aspart		–	54 (62.1)
Human		–	4 (4.6)
Previous prandial insulin dose, IU			
Glulisine	18 (0)	39.8 ± 20.9	–
Lispro	11 (0)	48.3 ± 25.3	–
Aspart	54 (0)	44.1 ± 16.8	–
Human	4 (0)	40.0 ± 10.7	–

BMI body mass index, *Gla-100* insulin glargine 100 U/mL, *Gla-300* insulin glargine 300 U/mL, *HbA_{1c}* glycated hemoglobin, *SD* standard deviation

dyslipidemia. Prior to switching to Gla-300, most participants received Gla-100 as their basal insulin (85.1%) and insulin aspart as prandial insulin (62.1%). Gla-300 was prescribed with the main objectives of decreasing HbA_{1c} (in 89.7%) and reducing hypoglycemic events (in 35.6%). Other objectives included reduced insulin volume (in 6.7%), weight loss (in 4.4%), increased flexibility (in 3.3%), and better glycemic stability (in 3.3%). At least one concomitant medication was taken by all participants, including metformin and statins in 77% and 79% of participants, respectively.

Primary Endpoint

A mean (SD) improvement of 2.80 (5.46) points in the DTSQs total score between baseline and month 6 was achieved in the ITT population ($p < 0.0001$), meeting the primary objective of the study (improvement of at least 2 points) and the primary endpoint (DTSQs total score improvement). A similar improvement (2.69 [5.42]; $p < 0.001$) was achieved in the PP population, and in both the ITT and PP populations the significance of the DTSQs total score improvements was confirmed using paired Wilcoxon's tests ($p < 0.0001$). A sensitivity analysis of the PP population, excluding two participants who received another diabetes drug (liraglutide, a glucagon-like peptide 1 receptor agonist), showed equivalent results (DTSQs improvement 2.67 [5.45] points). Improvement in DTSQs of at least 2 points between baseline and month 12 was also achieved in both the ITT population (DTSQs improvement [SD] 2.10 [5.50] points, $p = 0.004$) and the PP population (DTSQs improvement [SD] 2.10 [5.51] points, $p = 0.004$).

Secondary Endpoints

Patient-Reported Outcomes

The DTSQs total satisfaction score significantly improved between baseline and month 12 (Table 2; $p = 0.004$). Changes in perceived hypoglycemia between baseline and month 6 were also significant (− 0.41, $p = 0.013$). Changes in the DTSQc from baseline in total treatment satisfaction score at month 6, perceived hyperglycemia score at months 6 and 12, and perceived hypoglycemia score at months 6 and 12 were significantly improved (Table 2; $p < 0.05$).

Table 2 Change in patient-reported outcomes between baseline and months 6 and 12 (ITT population)

Patient-reported outcome	*N*		Mean	SD	*p* value
	Valid	Missing			
DTSQs					
Change in total DTSQs score					
Month 6 (primary endpoint)	69	17	2.80	5.46	< 0.0001
Month 12	62	24	2.10	5.50	0.004
Change in perceived hyperglycemia score					
Month 6	69	17	− 0.45	2.05	NS
Month 12	62	24	− 0.27	1.90	NS
Change in perceived hypoglycemia score					
Month 6	69	17	− 0.41	1.31	0.013
Month 12	62	24	− 0.08	1.63	NS
DTSQc					
Change in satisfaction with treatment					
Month 6	68	1	11.28	6.11	0.032
Month 12	63	6	11.00	5.71	NS
Change in perceived hyperglycemia score					
Month 6	68	1	0.59	1.55	0.011
Month 12	63	6	0.51	1.66	0.003
Change in perceived hypoglycemia score					
Month 6	68	1	0.15	1.46	0.001
Month 12	63	6	− 0.25	1.59	0.002
HFS-II					
Change in behavior score					
Month 6	67	19	− 2.38	7.39	0.010
Month 12	62	24	− 3.30	9.58	0.009
Change in worry score					
Month 6	68	18	− 4.41	11.22	0.002
Month 12	63	23	− 4.80	12.33	0.003
Change in total score					
Month 6	67	19	− 6.96	15.11	< 0.0001
Month 12	62	24	− 8.50	18.68	0.001

Table 2 continued

Patient-reported outcome	*N*		Mean	SD	*p* value
	Valid	Missing			
PSQI					
Change in score					
Month 6	68	18	− 0.73	2.94	0.044
Month 12	63	23	− 0.25	3.06	NS

DTSQc Diabetes Treatment Satisfaction Questionnaire change version, *DTSQs* Diabetes Treatment Satisfaction Questionnaire status version, *HFS-II* Hypoglycemia Fear Survey-II, *ITT* intent-to-treat, *NS* not significant ($p > 0.05$), *PSQI* Pittsburgh Sleep Quality Index, *SD* standard deviation

Changes in the WHO-5 Well-Being Index between baseline and months 6 (− 1.12) and 12 (3.17) did not achieve significance ($p = 0.560$ and $p = 0.076$, respectively). By contrast, significant changes in HFS-II behavior (− 2.38 and − 3.30, at 6 and 12 months, respectively), worry (− 4.41 and − 4.80, at 6 and 12 months, respectively), and total (− 6.96 and − 8.50 at 6 and 12 months, respectively) scores were observed (Table 2; $p < 0.05$). Sleep quality was significantly improved between baseline and month 6 (− 0.73, Table 2; $p < 0.05$).

HbA$_{1c}$

The mean (SD) baseline HbA_{1c} was 7.9 (0.6) %. Changes in HbA_{1c} from baseline to month 6 (0.0%, $p = 0.856$) and month 12 (− 0.1%, $p = 0.594$) were not significant. However, more participants reached $HbA_{1c} < 7\%$ at month 12 versus baseline (11.5% versus 0%).

Bodyweight and Gla-300 Dose

The mean (SD) baseline bodyweight was 94.0 (18.1) kg. Bodyweight changes between baseline and months 6 and 12 (0.47 kg and 0.34 kg, respectively) were not significant ($p > 0.05$). At baseline, the mean BI and Gla-300 doses were 38.0 IU and 38.6 IU, respectively. The mean Gla-300 dose increased by 7.9% (3.0 IU) at month 6 and 14.2% (5.5 IU) at month 12 ($p < 0.0001$ for both time points). There were no significant changes in the total prandial insulin doses from baseline to month 12 ($p > 0.05$).

Hypoglycemic Events

Participants experienced a mean of 21 self-reported hypoglycemic events per participant-year, of which two were nocturnal (Table 3). Most events ($n = 17$) required countermeasures and were symptomatic ($n = 19$). Seven events per participant-year were confirmed with a blood glucose reading of below 54 mg/dL (< 3.0 mmol/L) and fewer than one event per participant-year was classified as severe.

Adverse Events

In total, 150 AEs were reported by 55 participants (63.2%). The most frequent non-hypoglycemic AEs were diarrhea (4.6%), bronchitis (4.6%), and myalgia (3.2%). Hypoglycemia was reported as an AE in 9.2% of participants; this should be considered an underestimation given that 49 participants (56% of the ITT population) reported at least one event in the hypoglycemia section of the electronic case report form. Two participants (2.3%) reported AEs considered related to Gla-300 by the investigator: arthralgia ($n = 1$) and myalgia ($n = 2$). Twelve participants (13.8%) reported 18 SAEs, with each type of SAE reported by only one participant; none were considered related to Gla-300 treatment. There was no reported AESI.

DISCUSSION

Participants in MAGE are representative of people with T2DM typically followed in second-line diabetes clinics; however, the mean HbA_{1c}

Table 3 Hypoglycemic events (ITT population)

Hypoglycemic events	*N*		Mean events per participant-year ± SD
	Valid	Missing	
Total	82	0	20.9 ± 41.0
Requiring counter measures	82	0	17.4 ± 38.8
Symptomatic	82	0	18.7 ± 39.7
Nocturnal (00:00 to 05:59)	78	4	2.3 ± 5.2
Confirmed ≤ 70 mg/dL	81	1	21.0 ± 41.1
Confirmed < 54 mg/dL	81	1	6.6 ± 17.5
Severe	82	0	0.2 ± 0.7

ITT intent-to-treat, *SD* standard deviation

value at baseline was slightly higher than reported for the general Belgian population [20], and all participants in MAGE were on basal-bolus insulin regimens, suggesting that the MAGE population in this study was at a more advanced stage of diabetes. Approximately one-third of participants had microvascular complications, as expected in a population of people who have long-term T2DM.

In this real-world population, switching to Gla-300 was associated with a significant improvement in treatment satisfaction at 6 and 12 months (2.8 points [$p < 0.0001$] and 2.1 points [$p = 0.004$], respectively); these improvements are in line with those reported in the EDITION 1 RCT (2.3 points from baseline to month 6) [8]. It is worth noting that the MAGE study evaluated fewer participants over 6 months than planned on the basis of power calculations. However, because the amplitude of the observed difference in treatment satisfaction between baseline and month 6 was greater than the estimated 2 points, power for the primary endpoint remained above 90%. Different approaches have been used to determine minimally important differences (MID) in QoL measures. An empirical method based on a systematic review of 38 studies suggests using a cutoff of half of the SD [21]. Hence, for the 7-point DTSQs scale, the MID should likely be approximately 3.5. A second group suggests a more stringent MID of 0.3 SD (i.e., a 2.1-point difference on the 7-point DTSQs scale) [22]. Of note, the baseline DTSQs score was 27.93 points on a scale of 36 points, suggesting an already high treatment satisfaction prior to switching.

One of the main drawbacks of DTSQs is the "ceiling" effect, as individuals tend to score their current baseline treatment satisfaction at a high level, possibly precluding further improvements by the end of the study [23]. The DTSQc was developed to overcome this bias by asking individuals to compare their new treatment versus their old treatment by the end of the trial. DTSQc results confirmed those from the DTSQs as they also showed a significant improvement in treatment satisfaction. Additionally, DTSQc identified significant improvements in both perceived frequency of hyperglycemia and hypoglycemia at both 6 and 12 months, suggesting improved perception of glucose control with the new treatment. This may be linked to a more stable glycemic profile when treated with Gla-300, compared with older BIs [5, 6, 24].

Improvement in treatment satisfaction scores may potentially be biased, as participants may be tempted to answer PRO questionnaires positively. However, as no improvements were observed in the other non–diabetes-specific QoL measures (such as the WHO-5 Well-Being Index measure), one may conclude that this bias was avoided in MAGE. This is in accordance with another real-world observational study of Gla-300 in adults with T2DM, which demonstrated a non-significant improvement in the

non–diabetes-specific WHO-5 measure, alongside a significant improvement in the Diabetes Medication System Rating Questionnaire measure [15].

Gla-300 was associated with significant improvements in hypoglycemia fear scores (HFS-II total scores were in the range of MID: 2.0–5.8 or 3.6–3.9, depending on the methodology) [25]. Reductions in the hypoglycemia behavior and worry subscales also suggested participants were less likely to adopt damaging behaviors (e.g., insulin dose reduction or deliberately maintaining hyperglycemia during social events/important tasks), or have hypoglycemia-related worries (e.g., failing to recognize low blood glucose, losing control, or public embarrassment) [26]. Sleep quality improved between baseline and month 6, which may also be associated with improved QoL [27].

The overall annualized hypoglycemia rate in MAGE was comparable to that seen in EDITION 1 for Gla-300 (21 versus 26 events per participant-year, respectively), as was the rate of severe events (0.2 versus 0.3 events per participant-year) [8]. Comparing other categories of hypoglycemia between these two studies is confounded by different definitions, but the rates of hypoglycemia confirmed at either the $\leq$ 70 mg/dL or $<$ 54 mg/dL thresholds in MAGE (21 and 6.6 events per participant-year, respectively) also appear similar to the rates seen in EDITION 1 for hypoglycemia, defined as "confirmed" ($\leq$ 70 mg/dL or $<$ 54 mg/dL) or "severe" (25 and 3.8 events per participant-year, respectively). Although this latter definition in EDITION 1 includes severe events, these were rare and so would not have a substantial impact on the rates reported; any differences may be due to differences in study design (real-world study versus RCT with treat-to-target approach, in EDITION 1). The frequency of overall AEs was low in this study, and the most commonly experienced non-hypoglycemic AEs of diarrhea, bronchitis, and myalgia are in line with those reported in the 6-month EDITION 1 study, where the most common AEs in both treatment groups were infections, gastrointestinal events, or musculoskeletal complaints [8].

Improvements in treatment satisfaction and reduction in hypoglycemia fear occurred without reduction in HbA_{1c} between baseline and months 6 or 12. This is in agreement with other studies using DTSQs, which showed that, while improvements in treatment satisfaction were not associated with improved glycemic control, they were likely to improve treatment adherence and the perception individuals have about control of the disease [1]. Thus, improvements in treatment satisfaction may contribute to long-term stable glucose control.

There was an increase in Gla-300 dose between baseline and months 6 and 12 of up to 14%, which is in line with the EDITION trial program [8]. However, an insulin dose increase has not been seen in all studies [28, 29]. In this study, the dose increase occurred in parallel with clinically relevant benefits in PROs, such as increased treatment satisfaction and reduced hypoglycemia fear.

A strength of the MAGE study is the length of the study; the 6-month extension period confirmed the positive diabetes-specific PRO results from the 6-month study period. When interpreting the results of MAGE, consideration should be given to the open-label, non-interventional design of the study. Although the results are in accordance with the EDITION 1 RCT, they should be considered as complementary to the RCT data and deserve to be confirmed by additional trials. It is possible that the participants of MAGE may have decided to switch to Gla-300 as a result of dissatisfaction with their prior insulin therapy, which could have biased their perception of treatment satisfaction in favor of Gla-300. As individuals were unblinded and aware that they were receiving a "newer" and more advanced insulin, they may have been influenced to be more positive in treatment satisfaction and QoL scoring. However, the MAGE cohort appeared typical of those who attend second-line outpatient clinics, and the absence of improvement in non–diabetes-specific measures (e.g., WHO-5 Well-Being Index) makes a bias in favor of Gla-300 unlikely. Other limitations include the limited participant numbers, and the absence of a control group; however, this is reflective of the nature of this real-world study.

CONCLUSION

In a real-world population of people with advanced T2DM and comorbidities, the inclusion of Gla-300 as part of their basal-bolus insulin regimen resulted in clinically relevant improvements in treatment satisfaction and reduced hypoglycemia fear.

ACKNOWLEDGEMENTS

The authors thank the study participants, the trial staff, particularly Elke Meyssen and Frank Stessens, and the investigators for their participation.

Funding. The study was sponsored by Sanofi Belgium. Sanofi was involved in designing the trials, conducted the trials, and analyzed the data. The *Diabetes Therapy* Rapid Service Fee was also funded by Sanofi.

Medical Writing Assistance. Editorial assistance was provided by Vicky Hinstridge, B. Pharm, and Jennina Taylor-Wells, PhD, of Fishawack Communications Ltd, funded by Sanofi.

Authorship. All authors had full access to all the data in this study and take complete responsibility for the integrity of the data and accuracy of the data analysis. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Disclosures. Ides M. Colin has received an honorarium from Sanofi and is a member of the advisory board and/or speakers bureau at Sanofi. Kathy Alexandre is a Sanofi employee. Jacques Bruhwyler is an external contractor for data management, biostatistics, and medical writing. André Scheen is a member of the advisory board and/or speakers bureau at Sanofi. A.V., Novo Nordisk, Eli Lilly, Merck, AstraZeneca, and Boehringer Ingelheim. Ann Verhaegen has received an honorarium from Sanofi and is a member of the advisory board and/or speakers bureau at Sanofi, Novo Nordisk, Eli Lilly, Amgen, Merck, and Boehringer Ingelheim.

Compliance with Ethics Guidelines. MAGE was performed in accordance with the principles of the 18th World Medical Assembly (Declaration of Helsinki, 1964) and all subsequent amendments, the European guidelines for Good Epidemiology Practice, and complied with local regulatory requirements. The study was approved by Comité d'éthique hospital-facultaire universitaire de Liège (707) under reference number 2016–114. All participants signed an informed consent form before taking part in the study and study extension.

Data Availability. Qualified researchers may request access to patient-level data and related study documents, including the clinical study report, study protocol with any amendments, blank case report form, statistical analysis plan, and dataset specifications. Patient-level data will be anonymized and study documents will be redacted to protect the privacy of trial participants. Further details on Sanofi's data sharing criteria, eligible studies, and process for requesting access can be found at https://www.clinicalstudydatarequest.com.

REFERENCES

1. Saisho Y. Use of Diabetes Treatment Satisfaction Questionnaire in diabetes care: importance of patient-reported outcomes. Int J Environ Res Public Health. 2018;15(5):947.

2. Peyrot M, Barnett AH, Meneghini LF, Schumm-Draeger PM. Insulin adherence behaviours and barriers in the multinational Global Attitudes of Patients and Physicians in Insulin Therapy study. Diabet Med. 2012;29(5):682–9.

3. Wieringa TH, de Wit M, Twisk JWR, Snoek FJ. Does hypoglycaemia affect the improvement in QoL after the transition to insulin in people with type 2 diabetes? J Endocrinol Invest. 2018;41(2):249–58.

4. Lopez JM, Annunziata K, Bailey RA, Rupnow MF, Morisky DE. Impact of hypoglycemia on patients with type 2 diabetes mellitus and their quality of life, work productivity, and medication adherence. Patient Prefer Adher. 2014;8:683–92.

5. Becker RH, Dahmen R, Bergmann K, Lehmann A, Jax T, Heise T. New insulin glargine 300 Units mL^{-1} provides a more even activity profile and prolonged glycemic control at steady state compared with insulin glargine 100 Units mL^{-1}. Diabetes Care. 2015;38(4):637–43.

6. Heise T, Mathieu C. Impact of the mode of protraction of basal insulin therapies on their pharmacokinetic and pharmacodynamic properties and resulting clinical outcomes. Diabetes Obes Metab. 2017;19(1):3–12.

7. Bolli GB, Riddle MC, Bergenstal RM, et al. New insulin glargine 300 U/ml compared with glargine 100 U/ml in insulin-naive people with type 2 diabetes on oral glucose-lowering drugs: a randomized controlled trial (EDITION 3). Diabetes Obes Metab. 2015;17(4):386–94.

8. Riddle MC, Bolli GB, Ziemen M, et al. New insulin glargine 300 units/mL versus glargine 100 units/mL in people with type 2 diabetes using basal and mealtime insulin: glucose control and hypoglycemia in a 6-month randomized controlled trial (EDITION 1). Diabetes Care. 2014;37(10):2755–62.

9. Riddle MC, Yki-Jarvinen H, Bolli GB, et al. One-year sustained glycaemic control and less hypoglycaemia with new insulin glargine 300 U/ml compared with 100 U/ml in people with type 2 diabetes using basal plus meal-time insulin: the EDITION 1 12-month randomized trial, including 6-month extension. Diabetes Obes Metab. 2015;17(9):835–42.

10. Yki-Jarvinen H, Bergenstal R, Ziemen M, et al. New insulin glargine 300 units/mL versus glargine 100 units/mL in people with type 2 diabetes using oral agents and basal insulin: glucose control and hypoglycemia in a 6-month randomized controlled trial (EDITION 2). Diabetes Care. 2014;37(12):3235–43.

11. Home PD, Bergenstal RM, Bolli GB, et al. New insulin glargine 300 units/mL versus glargine 100 units/mL in people with type 1 diabetes: a randomized, phase 3a, open-label clinical trial (EDITION 4). Diabetes Care. 2015;38(12):2217–25.

12. Yki-Jarvinen H, Bergenstal RM, Bolli GB, et al. Glycaemic control and hypoglycaemia with new insulin glargine 300 U/mL versus insulin glargine 100 U/mL in people with type 2 diabetes using basal insulin and oral antihyperglycaemic drugs: the EDITION 2 randomized 12-month trial including 6-month extension. Diabetes Obes Metab. 2015;17(12):1142–9.

13. Matsuhisa M, Koyama M, Cheng X, et al. Sustained glycaemic control and less nocturnal hypoglycaemia with insulin glargine 300 U/mL compared with glargine 100 U/mL in Japanese adults with type 1 diabetes (EDITION JP 1 randomised 12-month trial including 6-month extension). Diabetes Res Clin Pract. 2016;122:133–40.

14. Terauchi Y, Koyama M, Cheng X, et al. Glycaemic control and hypoglycaemia with insulin glargine 300 U/mL compared with glargine 100 U/mL in Japanese adults with type 2 diabetes using basal insulin plus oral anti-hyperglycaemic drugs (EDITION JP 2 randomised 12-month trial including 6-month extension). Diabetes Metab. 2017;43(5):446–52.

15. Wieringa TH, de Wit M, Twisk JW, Snoek FJ. Improved diabetes medication convenience and satisfaction in persons with type 2 diabetes after switching to insulin glargine 300 U/mL: results of the observational OPTIN-D study. BMJ Open Diabetes Res Care. 2018;6(1):e000548.

16. Bergenstal RM, Bailey TS, Rodbard D, et al. Comparison of insulin glargine 300 units/mL and 100 units/mL in adults with type 1 diabetes: continuous glucose monitoring profiles and variability using morning or evening injections. Diabetes Care. 2017;40(4):554–60.

17. World Medical Association. WMA Declaration of Helsinki—ethical principles for medical research involving human subjects. 1964. https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/. Accessed 10 Dec 2018.

18. International Epidemiologcial Association (IEA) European Federation. Good Epidemiological Practice (GEP) proper conduct in epidemiology research. 2007. http://alraziuni.edu.ye/book1/Health%20and%20Society/Good%20Epidemiological%20Practice%20(GEP)%20Proper%20Conduct%20in%20Epidemiologic%20Research.pdf. Accessed 10 Dec 2018.

19. Seaquist ER, Anderson J, Childs B, et al. Hypoglycemia and diabetes: a report of a workgroup of the American Diabetes Association and the Endocrine Society. Diabetes Care. 2013;36(5):1384–95.

20. Lavens A, Krzentowski G, Mathieu C, et al. Initiatief voor Kwaliteitsbevordering en Epidemiologie bij Diabetes IKED. 2011. https://www.wiv-isp.be/epidemio/epinl/iked/iked11nl.pdf. Accessed 7 Dec 2018.

21. Norman GR, Sloan JA, Wyrwich KW. Interpretation of changes in health-related quality of life: the remarkable universality of half a standard deviation. Med Care. 2003;41(5):582–92.

22. Norman GR, Sloan JA, Wyrwich KW. The truly remarkable universality of half a standard deviation: confirmation through another look. Expert Rev Pharmacoecon Outcomes Res. 2004;4(5):581–5.

23. Bradley C, Plowright R, Stewart J, Valentine J, Witthaus E. The Diabetes Treatment Satisfaction Questionnaire change version (DTSQc) evaluated in insulin glargine trials shows greater responsiveness to improvements than the original DTSQ. Health Qual Life Outcomes. 2007;5:57.

24. Bergenstal RM, Rosenstock J, Bastyr EJ 3rd, Prince MJ, Qu Y, Jacober SJ. Lower glucose variability and hypoglycemia measured by continuous glucose monitoring with novel long-acting insulin LY2605541 versus insulin glargine. Diabetes Care. 2014;37(3):659–65.

25. Stargardt T, Gonder-Frederick L, Krobot KJ, Alexander CM. Fear of hypoglycaemia: defining a minimum clinically important difference in patients with type 2 diabetes. Health Qual Life Outcomes. 2009;7:91.

26. Gonder-Frederick LA, Schmidt KM, Vajda KA, et al. Psychometric properties of the Hypoglycemia Fear Survey-II for adults with type 1 diabetes. Diabetes Care. 2011;34(4):801–6.

27. Luyster FS, Dunbar-Jacob J. Sleep quality and quality of life in adults with type 2 diabetes. Diabetes Educ. 2011;37(3):347–55.

28. Gupta S, Wang H, Skolnik N, et al. Treatment dosing patterns and clinical outcomes for patients with type 2 diabetes starting or switching to treatment with insulin glargine (300 units per milliliter) in a real-world setting: a retrospective observational study. Adv Ther. 2018;35(1):43–55.

29. Sauriol L, Glass J, Zhang Y, Milson B. Longitudinal analysis of real world basal insulin utilization for patients with type 1 and 2 diabetes patients switching to insulin glargine 300 U/mL. Can J Diabetes. 2017;41:S70.