

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

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To cite: Wieringa TH, de Wit M, Twisk JWR, *et al*. 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 Diab Res Care* 2018;**6**:e000548. doi:10.1136/bmjdr-2018-000548

► Additional material is published online only. To view please visit the journal online (<http://dx.doi.org/10.1136/bmjdr-2018-000548>).

Received 4 May 2018

Revised 24 July 2018

Accepted 13 August 2018



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ABSTRACT

Objective Insulin glargine 300 (Gla-300) provides less hypoglycemia risk and more flexibility in injection time. The extent to which these effects translate into improved patient-reported outcomes (PROs) is unknown, and is the subject of this observational study.

Research design and methods Adults with type 2 diabetes treated with basal insulin for at least 6 months initiating Gla-300 were included. Data were collected at baseline (start Gla-300) and at 3-month and 6-month follow-up. Patients and physicians gave reasons for switching to Gla-300 at baseline and the extent to which Gla-300 fulfilled their expectations at 6 months. Mixed model analyses examined PRO changes over time, with emotional well-being (WHO-5 Well-Being Index) as the primary outcome. The secondary outcomes were hypoglycemia incidence, hemoglobin A1c (HbA1c), hypoglycemia worries (worry subscale of the Hypoglycemia Fear Survey), diabetes distress (short form of the Dutch version of the Problem Areas In Diabetes Scale), diabetes medication convenience (Diabetes Medication System Rating Questionnaire (DMSRQ)), sleep quality and duration (Pittsburgh Sleep Quality Index), and adherence (Summary of Diabetes Self-Care Activities).

Results 162 patients participated: 53.70% were men, the mean age was 65.54 years (9.05), baseline mean HbA1c was 7.87% (1.15) (62.48 mmol/mol (12.61)), and mean diabetes duration was 15.14 years (6.65). Mean WHO-5 Well-Being Index scores improved non-significantly from 61.94 (19.52) at baseline (T0) to 63.83 (19.67) at 6 months (T2). Mean DMSRQ scores improved significantly from 32.96 (9.02) (T0) to 36.70 (8.85) (T2) ($p<0.001$). Dose (less volume) was a switching reason in 69.60% of patients and 63% of physicians, and flexibility in 33.30% and 24.70%, respectively. Gla-300 fulfilled the expectations or even better than expected in 92.30% of patients and 88.90% of physicians.

Conclusion In a relatively well-controlled sample of adults with type 2 diabetes, switching to Gla-300 improves diabetes medication convenience.

INTRODUCTION

Long-acting (basal) insulin analogs have contributed to improved management of

Significance of this study

What is already known about this subject?

► Clinical trials have shown that in type 2 diabetes glargine 300 U/mL (Gla-300) results in a flatter profile and less risk of hypoglycemia compared with glargine 100 U/mL, with comparable glycemic control (hemoglobin A1c), but the effects on quality of life are unknown.

What are the new findings?

► Switching to Gla-300 has no pronounced effects on quality of life, but does improve diabetes medication convenience, possibly because of volume reduction and more flexibility in injection time.

How might these results change the focus of research or clinical practice?

► The results of this study may inform shared decision-making practices in which Gla-300 is one of the available options to reduce glucose variability, and provide a basis for future research to identify which patients may benefit most from Gla-300.

diabetes over the last decade. The first and most commonly used analog is insulin glargine 100 U/mL (Gla-100),^{1,2} with a well-established mode of action and profile of efficacy and safety.³⁻⁵ It has advantages compared with human neutral protamine Hagedorn (NPH) insulin, notably reduction of nocturnal and overall hypoglycemia.^{1,6} 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.⁷⁻⁹ However, hypoglycemia continues to be observed during Gla-100 treatment,^{1,4,6,10} suggesting that a basal insulin with an even flatter and longer action profile might further improve safety and tolerability. Research to date shows that the new insulin glargine 300 U/mL (Gla-300) provides

a flatter and more prolonged pharmacokinetic and pharmacodynamic profiles as compared with Gla-100,¹¹ thereby meeting this need. With regard to hemoglobin A1c (HbA1c), Gla-300 appears to perform as well as Gla-100 in patients with type 2 diabetes, but with less risk of hypoglycemia and more flexibility in injection time.¹¹ It is unknown if these benefits of Gla-300 relative to Gla-100 translate into improved patient-relevant outcomes. We could hypothesize that Gla-300 may improve patients' well-being due to a reduction in glycemic variability and hypoglycemia, and perhaps more convenience due to more flexibility in injection time. Patient-reported outcomes (PROs) are subjective reports and represent what is most important to patients about a condition and its treatment.¹² These reports come directly from patients about how they feel and function in relation to a health condition and its therapy, without interpretation by healthcare professionals or anyone else. PROs are becoming increasingly important in weighing the pros and cons of a particular medication or treatment regimen incorporating the patient's perspective. The American Diabetes Association and the European Association for the Study of Diabetes advocate for patient-centeredness, which is defined as an approach to 'providing care that is respectful of and responsive to individual patient preferences, needs and values and ensuring that patient values guide all clinical decisions'.⁵ While the glycemic benefits of Gla-300 have been studied extensively before, evidence from clinical practice whether these benefits translate into PROs is lacking and is the primary focus of the current OPTIN-D (Optimizing Patient-relevant outcomes with Toujeo (insulin glargine 300 U/mL) IN Routine Diabetes care) study. The following are the two research questions underpinning OPTIN-D: (1) Do PROs improve following switching to Gla-300? (2) What reasons do patients and physicians see for switching to Gla-300 and are these expectations met? Well-being may be expected to increase as a result of reduced hypoglycemia and/or more injection time flexibility. Hypoglycemia reduction may lead to less hypoglycemia worry,^{13 14} less diabetes distress,¹⁵ and improved sleep quality and duration in case of nocturnal hypoglycemia reduction.¹⁶ Flexibility may favor well-being indirectly through an increase of convenience and ease to be adherent. Patients and physicians may have different perspectives on why switching to Gla-300 might be relevant and what is expected. Weighting the harms and benefits of treatment options is critical in the process of shared decision making when initiating a new medication. Therefore, insight into (differences between) patients' and physicians' reasons to switch to Gla-300, as well as the extent to which Gla-300 meets expectations, may inform future shared decision-making practices in which Gla-300 is one of the available options.^{17–19}

RESEARCH DESIGN AND METHODS

Design and setting

We carried out a prospective observational study with three repeated measurements and a follow-up period of 6 months.

Participants

Physicians involved in the management of type 2 diabetes in primary and secondary care were invited to participate. The prescription of therapies remained under the responsibility of the specialist or general practitioner. Only persons for whom the physician decided recently (0–1 week) to prescribe Gla-300 independently from study entry were enrolled in the study.

The following were the inclusion criteria: diagnosed with type 2 diabetes, started Gla-300 within 1 week before study entry, treated with basal insulin for at least 6 months prior to the start of Gla-300, 18 years or older, able to read and write in Dutch, and signed a written informed consent. Patients were excluded when pregnant at baseline and/or diagnosed with a psychiatric disorder.

Data collection

Data were collected at baseline (start Gla-300; T0) and at 3 months (T1) and 6 months (T2) after Gla-300 initiation at regular visits. Patients with type 2 diabetes signed written consent after the study was explained to them by their physician and before any study-related procedure. Checks at regular visits were performed in accordance with the Guideline of the Dutch College of General Practitioners²⁰ and the Clinical Guideline of the Dutch Diabetes Federation.²¹

Measures

Reason(s) for starting Gla-300 (at T0) and *evaluation of experiences with Gla-300* (at T2) were asked from both patients and physicians, independently, using a self-developed topic list. A maximum of three reasons out of seven could be given by patients and physicians. Options were quality of life, (fear of) hypoglycemia, treatment satisfaction, dose (less volume), flexibility, adherence, and HbA1c. Evaluation of Gla-300 (extent to which Gla-300 met the expectations) was assessed by checking one of five categories, namely worse than expected, slightly worse than expected, as expected, slightly better than expected and better than expected.

At every visit *emotional well-being* (WHO-5 Well-Being Index (WHO-5), 5 items), *worries about hypoglycemia* (worry subscale of the Hypoglycemia Fear Survey (HFS-W), 18 items), *diabetes distress* (short form of the Dutch version of the Problem Areas In Diabetes Scale (PAID-SF), 5 items), *diabetes medication convenience* (Diabetes Medication System Rating Questionnaire (DMSRQ), 17 items), *sleep quality and duration* (Pittsburgh Sleep Quality Index (PSQI), 3 items) and *treatment adherence* (Summary of Diabetes Self-Care Activities (SDSCA), 1 item) were assessed by self-report. Below are a brief description of the measures and their psychometric properties.

Emotional well-being was assessed with the WHO-5, a well-validated instrument assessing emotional well-being pertaining to the past 2 weeks.²² The WHO-5 consists of five positively stated items including positive mood, vitality and general interests. Scores are transformed to 0–100, with higher scores representing better emotional

well-being. A score <50 is considered indicative of low mood and a score ≤ 28 indicative of clinical depression.^{22,23}

The number of *hypoglycemic episodes* (symptomatic, nocturnal, and severe) during the last 3 months was based on self-report using standardized questions asked by the physician. Symptomatic hypoglycemia is defined as symptoms due to low blood glucose levels during daytime that the participant can correct independently from others. A nocturnal hypoglycemic episode was defined as a symptomatic episode taking place during the night. Severe hypoglycemia was defined as a low blood glucose level during which the participant is in need of another person (not necessarily medical professional) in order to recover. A severe hypoglycemic episode taking place during the night was defined as a severe episode, not as nocturnal.

Worries about hypoglycemia experienced in the 3 months prior to filling out was assessed using the validated HFS-W.²⁴ The HFS-W consists of 18 items and the scores range from 0 to 72, with higher scores indicating more worries about hypoglycemia. An elevated score (≥ 3) on more than one HFS-W item is indicative of clinically relevant fear of hypoglycemia.²⁵

Diabetes distress was measured using the well-validated five-item PAID-SF.²⁶ The PAID-SF measures diabetes-specific emotional distress on a 5-point Likert scale (not a problem – a serious problem). Total scores were transformed to a 0–100 range, with higher scores indicating more diabetes distress. PAID scores of ≥ 40 are indicative of severe diabetes-specific emotional problems.^{26–28}

Diabetes medication convenience was assessed with a selection of 17 items from four subscales (convenience, interference, efficacy, treatment satisfaction) of the DMSRQ. The original 55-item DMSRQ was validated in persons with type 2 diabetes.²⁹ Since no Dutch DMSRQ version was available at the start of the study, the selected items were translated by us using the back-translation procedure. Total scores ranging from 0 to 58 were computed by summing all the items, with higher scores indicating more favorable diabetes medication convenience.

Sleep quality and duration over the past month was assessed by a selection of three items of the validated PSQI³⁰: (1) mean number of hours slept per night; (2) how many times the person experienced trouble sleeping; and (3) global assessment of the sleep quality. The latter two items are scored on a 4-point Likert scale.

Treatment adherence was measured by the one item of the SDSCA on insulin injection adherence.³¹ This SDSCA item asks how many of the last 7 days the person took the recommended insulin injections as prescribed. Scores range from 0 to 7 days.

The physician collected the following data from the medical chart during the baseline visit: age, gender, education level, diabetes duration, height, previous and current diabetes medication, diabetes complications, and comorbidities. The data collected by the physician from the medical charts at all visits were the most recent HbA1c and weight/body mass index.

Data analyses

With the WHO-5 as the primary outcome, a sample size of 119 would achieve 90% power to detect an effect size of 0.3, indicating a moderate effect over 6 months, with an estimated SD of differences of 1.0 and a significance level (alpha) of 0.05. Taking into account a 25% dropout, we aimed to include at least 160 patients.

Both *reasons for switching to Gla-300* and the *evaluation of Gla-300* were analyzed using descriptive statistics, namely frequencies and valid percentages per category. Mixed model analyses were used to analyze the change over time in the primary outcome, *emotional well-being* (WHO-5), and the secondary outcomes: *hypoglycemia* (symptomatic, nocturnal, severe), *HbA1c*, *hypoglycemia worries* (HFS-W), *diabetes distress* (PAID-SF), *diabetes medication convenience* (DMSRQ), *sleep quality and duration* (PSQI), and *injection adherence* (SDSCA). Linear mixed model analyses were used for continuous outcomes and logistic mixed model analyses for dichotomous outcomes. Time was treated as categorical represented by dummy variables. For every model a random intercept for a patient was added in order to adjust for the dependency of the observations within the patient. Significance was set at a p value threshold of 0.05 for the relationship between time and the primary outcome. For the secondary outcomes, significance was set to a p value of 0.01 to correct for multiple testing and reduce the risk of type 1 error. Since no other variables than the outcomes were expected to be related to the independent variable time, we did not adjust for potential confounding.

Multiple imputation on item level was used only for missing values where the total scores were to be calculated (WHO-5, HFS-W, PAID-SF, DMSRQ), because this gives the most accurate regression model estimates for total scores.³² When all items of a questionnaire were missing on a certain visit, no imputation for this questionnaire was performed. For patients dropping out of the study, missing items were imputed until the moment of dropout.

Hypoglycemia (symptomatic, nocturnal, severe) was measured on a discrete scale, but as its distribution was skewed to the right analyzed as dichotomous ('0 episodes' vs '1 or more episodes'). All PSQI items were analyzed as continuous in the longitudinal analyses, but because PSQI items 2 and 3 were skewed to the right, they were log-transformed. The SDSCA score was dichotomized (' <7 days a week adherent' vs ' ≥ 7 days a week adherent').

RESULTS

Participants

In total 162 patients from 10 primary and 13 secondary diabetes care clinics spread over the Netherlands participated in the study. Seventeen dropouts were registered: 12 participants 3 months after baseline and 5 participants 6 months after baseline. The main reasons for dropout were changing healthcare professional, changing treatment regimen, difficulties completing the questionnaire, and adverse events.

Table 1 Demographic and medical characteristics of the study population*

Demographics	Baseline	3 months	P values change from baseline to 3 months	6 months	P values change from baseline to 6 months
N	162				
Gender					
Men	87 (53.70%)				
Women	75 (46.30%)				
Age (years)	65.54 (9.05)				
Level of education					
Low	81 (57.10%)				
Average	39 (27.50%)				
High	22 (15.50%)				
Diabetes duration (years)	15.14 (6.65)				
BMI	33.58 (6.09)	33.87 (6.17)		33.74 (6.11)	
Total number of currently ongoing complications and/or comorbidities					
0	53 (34.20%)				
1	44 (28.40%)				
2	37 (23.90%)				
3 or more	21 (13.50%)				
HbA1c (%)	7.87 (1.15)	7.70 (1.03)	0.072	7.67 (1.11)	0.020
HbA1c (mmol/mol)	62.48 (12.61)	60.63 (11.29)	0.072	60.32 (12.09)	0.020
Self-reported symptomatic hypoglycemia, n (%)					
0 episode	111 (68.50)	118 (79.20)	0.026	109 (75.20)	0.176
1 or more episodes	51 (31.50)	31 (20.80)		36 (24.80)	
Self-reported nocturnal hypoglycemia, n (%)					
0 episode	151 (93.20)	144 (96.60)	0.351	139 (95.90)	0.472
1 or more episodes	11 (6.80)	5 (3.40)		6 (4.10)	
Self-reported severe hypoglycemia, n (%)					
0 episode	154 (95.10)	149 (100)	0.198	145 (100)	0.202
1 or more episodes	8 (4.90)	0 (0)		0 (0)	

*For dichotomous or categorical variables the absolute numbers by subgroups and the valid percentages relative to the study population without missing values for the regarding variables are displayed. For normally distributed variables the mean and standard deviation are shown. For skewed variables the median and the 25th and 75th percentile are shown
BMI, body mass index; HbA1c, hemoglobin A1c.

Patient characteristics are described in [table 1](#). Of the 162 patients included, 53.70% were men and the mean age was 65.54 years (9.05). The baseline (T0) mean HbA1c was 7.87% (1.15) (62.48 mmol/mol (12.61)), and the mean diabetes duration was 15.14 years (6.65).

Gla-100 was the most frequently used basal insulin prior to switching to Gla-300 (128 patients); all other patients (2 missing) had used insulin detemir (32 patients). Of the patients, 80.20% used a short-acting insulin at baseline. Basal insulin dose increased from 54.85 (23.71) units/day (0.55 (0.22) units/kg bodyweight) at baseline to 57.63 (25.94) units/day (0.57 (0.23) units/kg bodyweight) and 57.78 (26.73) units/day (0.57 (0.24) units/kg bodyweight) at 3 and 6 months, respectively.

[Table 2](#) shows the scores for PROs. Symptomatic hypoglycemia incidence decreased non-significantly from

31.50% at baseline (T0) to 24.80% at 6 months (T2) (T0–T2, p=0.176), from 6.80% at T0 to 4.10% at T2 (T0–T2, p=0.472) for nocturnal episodes, and from 4.90% at T0 to 0% at T2 (T0–T2, p=0.202) for severe episodes (see [table 1](#) and online supplementary appendix 1). The mean HbA1c decreased non-significantly to 7.67% (1.11) (60.32 mmol/mol (12.09)) at T2 (T0–T2, p=0.020) (see [table 1](#) and online supplementary appendix 1).

Reasons for switching and evaluation of Gla-300

[Table 3](#) shows *patients' top three reasons* for switching to Gla-300: (1) dose (less volume) (69.60%); (2) quality of life (48.60%); and (3) flexibility (33.30%). *Physicians' top three reasons* are (1) dose (less volume) (63%); (2) flexibility (24.70%); and (3) HbA1c (22.20%). According to 88.90% of physicians and 92.30% of patients, Gla-300

Table 2 Changes in patient-reported outcomes over time*

	Baseline	3 months	P values change from baseline to 3 months	6 months	P values change from baseline to 6 months
WHO-5					
Mean (SD)	61.94 (19.52)	62.59 (22.01)	0.429	63.83 (19.67)	0.135
HFS-W					
Median (IQR)	11 (3–20)	7 (2–16)	0.086	8 (2–18)	0.024
PAID-SF					
Median (IQR)	20 (10–35)	15 (5–30)	0.286	15 (5–30)	0.039
DMSRQ					
Mean (SD)	32.96 (9.02)	36.62 (7.89)	<0.001	36.70 (8.85)	<0.001
PSQI item 1 (hours sleep per night)	6.75 (1.49)	6.67 (1.39)	0.318	6.66 (1.39)	0.292
PSQI item 2 (trouble sleeping)					
Not at all	65 (41.90%)	46 (31.30%)	0.139	59 (41.80%)	0.382
Less than once a week	28 (18.10%)	39 (26.50%)		35 (24.80%)	
Once or twice a week	29 (18.70%)	32 (21.80%)		23 (16.30%)	
Three times or more a week	33 (21.30%)	30 (20.40%)		24 (17%)	
PSQI item 3 (global sleep quality)					
Very good	35 (22.30%)	36 (24.50%)	0.202	39 (27.50%)	0.091
Fairly good	90 (57.30%)	86 (58.50%)		78 (54.90%)	
Pretty bad	24 (15.30%)	20 (13.60%)		21 (14.80%)	
Very bad	8 (4.90%)	5 (3.40%)		4 (2.80%)	
SDSCA					
6 days or less	28 (18.70%)	20 (13.50%)	0.224	22 (15.60%)	0.531
7 days	122 (81.30%)	128 (86.50%)		119 (84.40%)	

*Scores based on the original (non-imputed) data. P values based on imputed data for WHO-5, HFS-W, PAID-SF, and DMSRQ. For dichotomous or categorical variables, the absolute numbers by subgroups and the valid percentages relative to the study population without missing values for the regarding variables are displayed. For normally distributed variables, the mean and SD are shown. For skewed variables (PAID-SF and HFS-W), the median and the 25th and 75th percentiles are shown. DMSRQ, Diabetes Medication System Rating Questionnaire; HFS-W, worry subscale of the Hypoglycemia Fear Survey; PAID-SF, short form of the Dutch version of the Problem Areas In Diabetes Scale; PSQI, Pittsburgh Sleep Quality Index; SDSCA, Summary of Diabetes Self-Care Activities; WHO-5, WHO-5 Well-Being Index.

fulfilled their *expectations* (or better than expected) (see [table 3](#)).

Primary analyses

The mean WHO-5 scores improved non-significantly from 61.94 (19.52) at baseline (T0) to 62.59 (22.01) at 3 months (T1) and 63.83 (19.67) at 6 months (T2) (see [table 2](#)). The estimated change from T0 to T1 was 1.283 (p=0.429; 95% CI –1.895 to 4.462), for T1–T2 was 1.150 (p=0.485; 95% CI –2.079 to 4.379) and for T0–T2 was 2.433 (p=0.135; 95% CI –0.756 to 5.622) (see [table 2](#) and online supplementary appendix 1).

Based on imputed data, in total 41 patients (25.50%) reported suboptimal well-being at baseline: 27 patients (16.70%) scored between 29 and 50 at baseline (indicative of low mood), and 14 patients (8.60%) scored 28 or lower (indicative of clinical depression).

Secondary analyses

The mean DMSRQ scores improved from 32.96 (9.02) at baseline (T0) to 36.62 (7.89) at 3 months (T1) (estimated change T0–T1=3.280; p<0.001; 95% CI 1.670 to 4.890) and 36.70 (8.85) at 6 months (T2) (estimated change T0–T2=4.396; p<0.001; 95% CI 2.774 to 6.019) (see [table 2](#) and online supplementary appendix 1).

All other secondary longitudinal analyses showed non-significant changes at a p value threshold of 0.01, although a trend toward improvement in HbA1c (T0–T2), HFS-W (T0–T2), PAID-SF (T0–T2), and PSQI item 2 (trouble sleeping; T1–T2) was found using a significance level of 0.05 (see [tables 1 and 2](#) and online supplementary appendix 1).

Based on imputed data, 33 patients (20.40%) had more than one elevated HFS-W items (indicative of clinically relevant fear of hypoglycemia) at baseline and 36

Table 3 Reasons for and evaluation of switching to glargine 300 (Gla-300)

	Patients*	Physicians†
Reasons for switching to Gla-300		
Quality of life	67 (48.60%)	35 (21.60%)
(Fear of) hypoglycemia	14 (10.10%)	26 (16%)
Treatment satisfaction	15 (10.90%)	7 (4.30%)
Dose (less volume)	96 (69.60%)	102 (63%)
Flexibility	46 (33.30%)	40 (24.70%)
Adherence	3 (2.20%)	0 (0%)
Hemoglobin A1c	19 (13.80%)	36 (22.20%)
Evaluation of switching to Gla-300		
Worse than expected	4 (2.80%)	3 (2.10%)
Slightly worse than expected	7 (4.90%)	13 (9%)
As expected	48 (33.60%)	58 (40%)
Slightly better than expected	28 (19.60%)	24 (16.50%)
Better than expected	56 (39.10%)	47 (32.40%)

*The n regarding reasons for switching to Gla-300 is 138; the n regarding evaluation of Gla-300 is 143.

†The n regarding reasons for switching to Gla-300 is 162; the n regarding evaluation of Gla-300 is 145.

patients (22.20%) had a PAID score of ≥ 40 (indicating severe diabetes-specific emotional problems) at baseline.

Post-hoc analyses

Based on imputed data, the mean WHO-5 and DMSRQ scores were calculated to assess differences between the original and imputed WHO-5 and DMSRQ scores. No remarkable differences were observed (see online supplementary appendix 2).

We also performed linear mixed model analyses to check for changes over time *per DMSRQ item*. A p value threshold of 0.01 was used. The DMSRQ total score improved significantly between T0 and T1, as well as between T0 and T2 ($p < 0.01$). This pattern is seen in all items of the *convenience* and *treatment satisfaction* subscale, as well as multiple, but not all, *efficacy* scale items. Only one *interference* subscale item improved significantly over 6 months (see online supplementary appendices 3 and 4).

CONCLUSIONS

This is to the best of our knowledge the first observational study looking at PROs following switching to Gla-300 in patients with type 2 diabetes treated in primary and secondary care, and adds to previous literature.¹¹ Patients with type 2 diabetes who changed to Gla-300 experienced more convenience with respect to their diabetes medication over 6 months. No changes were seen in emotional well-being and other PROs. This finding should not surprise given the relatively favorable profile of the

patients in this study. Compared with other studies, the level of well-being at baseline was relatively high (mean WHO-5 score > 60), and the proportion of patients reporting low well-being or depressed mood (about a quarter) was relatively low.^{33–35} The same is true for fear of hypoglycemia and diabetes-related distress, suggesting little room for improvement. The EDITION 1 study in people with type 2 diabetes using mealtime insulin and basal insulin (Gla-100 or Gla-300)³⁶ found a higher symptomatic, nocturnal, and severe hypoglycemia incidence based on confirmation by plasma glucose compared with the current study in which 80% of patients at baseline used mealtime insulin in addition to basal insulin. Possibly, this difference in hypoglycemia incidence is due to the difference in measurement methods and/or case-mix. Future studies are warranted to explore the potential benefits of switching to Gla-300 in patients more frequently experiencing hypoglycemia and related (sleep) problems.

Post-hoc analyses regarding the changes *per DMSRQ item* showed that overall the improvements over time were seen in the *convenience*, *efficacy*, and *treatment satisfaction* domains, and barely in the *interference* domain. This may be explained by the fact that low interference was experienced already at the outset of the study, leaving again little room for improvement.

We asked both patients and physicians to indicate the most important reasons for switching (predominantly from Gla-100) to Gla-300. The two most common reasons for both patients and physicians were *dose (less volume)* and *flexibility*, which may underlie the observed improvement in *diabetes medication convenience*. As patients changed their basal insulin and their pen device as well, this may have played a role in the improved medication convenience. Therefore, future studies may capture additional information about the (change of) injection device.

Gla-300 does allow for more *flexibility* in injection timing and therefore an indication to consider. It is possible that the advantage of *flexibility* and greater *diabetes medication convenience* is less pronounced in patients with a basal-bolus insulin regimen. Nonetheless, our results regarding *diabetes medication convenience* are in line with previous studies^{36,37} that reported increased treatment satisfaction. However, these studies also observed improved treatment satisfaction in patients treated with Gla-100, and most patients in these randomized controlled trials were using Gla-100 as previous basal insulin.^{36,37} Although not likely, we cannot rule out the possibility that medication convenience would also have improved if patients had stayed on Gla-100 due to a study effect. A controlled study design is needed to draw firm conclusions regarding a causal relationship between initiating Gla-300 and improved patient-reported medication convenience.

In this observational study, we included patients from a mix of regions in the Netherlands and settings, adding to the external validity. The observational single-arm character of the study is a limitation, as we have no control group to compare with and therefore cannot ascertain

a causal relationship between the observed changes and the switch to Gla-300. Attentional bias may be introduced by physicians expecting greater flexibility and reduction of the volume to be injected, and mentioning these expectations to their patients, but we have not documented this. It would seem interesting to record what physicians actually say to patients as a way of capturing a possible placebo-by-proxy effect.³⁸ In contrast to our expectations, we did not find a significant improvement in well-being scores (WHO-5) following Gla-300 initiation. This may be explained by larger SD than previously observed, indicating large heterogeneity. The study may have been underpowered to detect changes in the secondary outcomes as well, where changes in the expected direction were found but failed to reach statistical significance. Overall, our population sample was generally a well-functioning group of persons in terms of PROs, glycemic control, and hypoglycemia. This has likely limited the possibility to show significant improvements. Further research therefore is needed to examine the impact of Gla-300 in persons with type 2 diabetes with a less favorable psychomedical profile.

After switching to Gla-300, the most prominent change observed was an improvement in medication convenience. This matches the finding that the vast majority of patients (and physicians) found Gla-300 to meet their expectations, with most patients wishing for a volume reduction. Insulin Gla-300 is experienced as a convenient glucose-lowering medicine by persons with type 2 diabetes wishing their current treatment to increase flexibility of injection time, as well as to decrease the volume to be injected and the risk of hypoglycemia. These data provide a basis for future research to identify which patients may benefit most from this new long-acting insulin analog.

Contributors THW performed the data analyses and wrote the manuscript. MdW and FJS designed the study and reviewed the manuscript. JWRT supported THW in analyzing the data and reviewed the manuscript. All authors read and approved the final manuscript.

Funding This study was financially supported by Sanofi Netherlands. THW is the guarantor of this work and, as such, has full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analyses.

Competing interests Sanofi contributed to the study design. Physicians' initial interest to participate in the study was given via an information leaflet, after which a Sanofi employee of the Clinical Study Unit performed an initiation visit for eligibility. Physicians (or their organization) received a monetary reward from Sanofi for participation. Data were collected by physicians and sent to a clinical research organization, which was responsible for data entering. The contract research organization created the database and sent it to Amsterdam UMC. Data analyses were under the responsibility of THW, MdW, and FJS, and were performed without participation of Sanofi.

Patient consent Not required.

Ethics approval In view of its observational and non-invasive nature, this study was deemed not subject to the Dutch Medical Research Involving Human Subjects Act.

Provenance and peer review Not commissioned; externally peer reviewed.

Data statement The dataset analysed during the current study is available from the corresponding author on reasonable request.

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