A randomized controlled, treat-to-target study evaluating the efficacy and safety of insulin glargine 300 U/mL (Gla-300) administered using either device-supported or routine titration in people with type 2 diabetes

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Abbreviations: ADA, American Diabetes Association; AE, adverse event; ANCOVA, analysis of covariance; BI, basal insulin; CMH, Cochran Mantel Haenszel; DTSQs, diabetes treatment satisfaction questionnaire status version; EUT, enhanced usual therapy; FPG, fasting plasma glucose; FSMPG, fasting self-monitored plasma glucose; GMS, glucose monitoring satisfaction survey; HCP, healthcare provider; HFS-II, hypoglycemia fear survey; MCID, minimum clinically-important difference; mITT, modified intent-to-treat; MMRM, mixed model for repeated measures; MRE, meter-related event; NPH, neutral protamine Hagedorn; OAD, oral antihyperglycemic drug; PRO, patient-reported outcome; SD, standard deviation; T1DM, type 1 diabetes; T2DM, type 2 diabetes; TEAE, treatment-emergent adverse event

Keywords: basal insulin, blood glucose meter, hypoglycemia, titration

Number of tables/figures: 2/3

Number of supplementary tables/figures: 4/2

Abstract

Background: The efficacy/safety of device-supported versus routine titration with Gla-300 in type 2 diabetes (T2DM) was evaluated.

Method: AUTOMATIX was a 16-week, randomized, open-label, parallel-group, multicenter, non-inferiority trial in insulin-treated or insulin-naïve people with T2DM. The fasting self-monitored plasma glucose (FSMPG) target was 90–130 mg/dL (5.0–7.2 mmol/L). Primary endpoint: proportion of participants achieving target FSMPG at week 16 without severe hypoglycemia. Secondary endpoints included: proportion reaching FSMPG target without confirmed (≤70 mg/dL [≤3.9 mmol/L]) or severe hypoglycemia; time to first achieve FSMPG target; mean FSMPG and HbA_{1c} change (baseline to week 16). Safety endpoints included hypoglycemia and adverse events. Patient-reported outcomes (PROs) were also assessed.

Results: Participants were randomized to device-supported (n=75) or routine titration (n=76); 17 participants in the device-supported group discontinued device use. Noninferiority was achieved for the primary endpoint (device-supported: 45.9%, routine: 36.8%; weighted difference: 9.04 [95%CI: -6.75, 24.83]), but not superiority (p=0.262). The proportion reaching FSMPG target range without confirmed (≤70 mg/dL [≤3.9 mmol/L]) or severe hypoglycemia was 34.3% versus 14.5%, respectively. The time at which 50% of the participants achieved the FSMPG target was less in the device-supported than routine titration arm (10- vs 13-weeks). Least squares mean HbA_{1c} reduction, safety profiles, and PROs were similar in both arms. Mean 'ease of use' score for the device, assessed by healthcare professionals and participants on a scale of 1–7, was ≥6.

Conclusions: Device-supported self-titration had a good safety/efficacy profile, and was non-inferior to routine titration and well accepted by diabetes specialists and patients.

Introduction

Type 2 diabetes (T2DM) is usually treated initially with oral antihyperglycemic drugs (OADs), but as the disease progresses many individuals need insulin to maintain glycemic control.[1] Despite recommendations that basal insulin (BI) therapy is initiated in those unable to achieve or maintain the recommended HbA_{1c} target (<7.0 %, 53 mmol/mol) after 3 months at maximum tolerated doses of OADs,[2] suboptimal glycemic control with OADs may continue for up to 7 years before insulin initiation.[3] Even after BI is initiated, approximately 70% of individuals are unable to titrate the dose appropriately and fail to reach recommended glycemic targets;[4] if targets are initially achieved, subsequently over 50% of these individuals fail to maintain long-term glycemic control.[5] The failure to achieve or maintain glycemic control can be attributed to a significant delay in the initiation and dose optimization of BI, often termed as 'clinical inertia', and defined as the 'failure of healthcare providers to initiate or intensify therapy when indicated'.[6] Addressing issues that contribute to clinical inertia (e.g. fear of undesirable side effects, lack of self-confidence in adhering to complex regimens, lack of trust in the efficacy of insulin etc.[7]), and achieving optimal BI-dose titration is key to ensuring individuals achieve and maintain optimal-glucose control.[3]

Healthcare providers (HCPs) should strike a balance between the need for tight glycemic control early in T2DM, with its associated benefits of reduced risk of macrovascular and microvascular complications, myocardial infractions and death,[8, 9] with the risk of hypoglycemia.[10] In the real-world setting BI dose is often titrated at the treating physician's discretion during routine-clinic visits. While such visits provide support for individuals and allow HCPs to provide consistent advice and

simple treatment algorithms, they may be infrequent (e.g. at 3-monthly intervals or longer), and delay insulin intensification. Empowering and supporting people with T2DM to self-titrate their BI dose could enable more individuals to achieve optimal glycemic control with fewer delays.[11] For example, better glycemic control with BI has been observed when dose titration was self-managed every 3 days rather than physician-led weekly-dose titration.[12] It has also been observed that when individuals with T2DM are involved in treatment decision-making, their understanding of diabetes care increases and positively impacts upon their self-management.[13] Device-supported self-titration may empower individuals with T2DM by allowing them to make informed treatment decisions without having to rely as much on HCPs and may also improve understanding of dose optimization to better self-manage their condition.

MyStar DoseCoach® is an integrated titration device/blood glucose meter designed to assist people with T2DM to self-titrate insulin glargine by providing automated dosing suggestions. The AUTOMATIX study aimed to compare the efficacy and safety of a device-supported treat-to target regimen versus diabetes knowledgeable investigator-recommended routine titration with Gla-300 in people with T2DM.

Methods

Study design and participants

AUTOMATIX (NCT02585674) was an open-label, randomized, controlled, parallel-group, multicenter, phase 3 study in people with T2DM conducted at 19 study centers (Supplementary Figure 1). The study was performed in accordance with the

Good Clinical Practice and the Declaration of Helsinki. All participants provided written informed consent.

Participants were aged ≥18 years, with T2DM for ≥1-year, either insulin-naïve or previously treated with BI, with HbA_{1c} between 7.5–11.0 % (58–97 mmol/mol inclusive) and fasting self-monitored plasma glucose (FSMPG) >130 mg/dL (7.2 mmol/L). Key exclusion criteria (Supplementary Materials) included diabetes other than T2DM, device-supported titration not being appropriate or use of device otherwise contraindicated (in the opinion of the investigator), and the use of mealtime insulin for more than 10 days in the last 3 months before screening.

Randomization and treatment

All participants were given a titration device/blood glucose meter (MyStar DoseCoach®, Agamatrix Inc., Salem NH, US), and self-administered Gla-300 subcutaneously once-daily. Participants were randomized 1:1 to either device-recommended titration (the titration feature was activated by investigator at randomization visit 3) or routine titration (titration feature of the device turned off) as recommended by the investigator, who were diabetes specialists, stratified by previous use of insulin (insulin naïve vs insulin treated). For insulin-naïve participants, the starting daily dose of Gla-300 was 0.2 U/kg body weight. Participants on previous BI therapy were switched to the same daily dose if they had been receiving once-daily Gla-100/neutral protamine Hagedorn (NPH) insulin/insulin detemir and to 80% of the previous daily dose if they had been receiving more than once-daily NPH insulin/insulin detemir.

Dosing recommendations (Supplementary Table 1) for participants randomized to the device-supported titration were provided by the device titration meter after a minimum of 3 consecutive days of FSMPG and insulin dose data, based on a FSMPG target range of 90–130 mg/dL (5.0–7.2 mmol/L). Participants who discontinued device-supported titration recommendations, for whatever reason, continued until the study end and followed the titration recommendations provided by the investigator from the time of discontinuation.

Outcomes

The primary efficacy endpoint was the percentage of participants reaching a FSMPG target of 90–130 mg/dL (5.0–7.2 mmol/L) following 16 weeks of treatment without severe hypoglycemia. Reaching the FSMPG target range required the mean of the last five FSMPG readings recorded in the previous 2 weeks to be within the target range before the end of the 16-week on-treatment period.

Secondary efficacy endpoints included percentages of participants reaching target FSMPG range (90–130 [5.0–7.2 mmol/L]) following 16 weeks of treatment without confirmed (≤70 mg/dL [3.9 mmol/L] or <54 mg/dL [3.0 mmol/L]) or severe hypoglycemia events, time to first reach FSMPG target, change in mean FSMPG, change in HbA_{1c} and mean central laboratory measured fasting plasma glucose (FPG) from baseline to week 16, and percentage of participants with FPG in the target range of 90–130 mg/dL (5.0–7.2 mmol/L) without severe hypoglycemia at the week 16 time point.

Safety endpoints included hypoglycemia, categorized based upon American Diabetes Association (ADA) definitions (Supplementary Methods),[2] adverse events (AEs), and meter- and pen-related events as reported by the participant or noted by the investigator. Hypoglycemia endpoints included the percentage of participants reporting ≥1 events.

Patient reported outcomes (PROs) were assessed using PRO/questionnaires including the diabetes treatment satisfaction questionnaire (DTSQs),[14] the hypoglycemia fear survey (HFS-II),[15] the diabetes distress scale,[16] the glucose monitoring satisfaction survey (GMS)[17], with emotional well-being analyzed using the WHO-5 well-being index.[18] Ease of use of the device was assessed in HCPs and participants during week 16 using questionnaires consisting of a series of questions to which responses were rated from 1 (extremely difficult) to 7 (extremely easy).

Statistical analysis

A sample size of 148 participants (74 per titration arm) was estimated to demonstrate non-inferiority of the device-supported arm with a 0.15 margin for the difference versus routine titration, 80% power and 2.5% one sided alpha; assuming the proportion reaching the FSMPG target range without severe hypoglycemia during the on-treatment period was 0.42 (routine-titration) and 0.50 (device-supported titration). All efficacy endpoints were analyzed or summarized for the 16-week on-treatment period using the modified intent-to-treat (mITT) population (Supplementary Materials), unless otherwise specified.

The primary endpoint was analyzed using a multiple imputation approach (Supplementary Materials), using effect estimators of titration regimen, weighted by

the randomization stratum of previous use of insulin. A stepwise closed-testing approach was used to first assess non-inferiority followed by superiority of device-supported versus routine titration. Non-inferiority required the lower bound of the two-sided 95% CI for the difference in percentage of participants between titration arms to be greater than the predefined non-inferiority margin of -15%. If the non-inferiority was demonstrated, superiority required the lower bound of the two-sided 95% CI for the weighted difference in the % of participants between titration arms to be >0.

A similar multiple imputation approach was used to assess the secondary efficacy endpoints related to percentage of participants reaching FSMPG target range without a hypoglycemic event. Change in mean FSMPG from baseline to the end of the 16-week on-treatment period was analyzed using a mixed model for repeated measures (MMRM) approach (Supplementary Materials). Time to first FSMPG target range of 90–130 mg/dL (5.0–7.2 mmol/L) was defined by the first 2-week period in which the mean FSMPG of the last 5 values was within target (Supplementary Materials). Change in HbA_{1c} from baseline to week 16 was analyzed using an analysis of covariance (ANCOVA) model (Supplementary Materials). Change in mean FPG from baseline to week 16 was analyzed using a MMRM approach, while the pre-specified FPG target was analyzed using a Cochran Mantel Haenszel (CMH) method (Supplementary Materials). Safety analyses were descriptive and based on the safety population (Supplementary Materials).

The change in score from baseline to week 16 for each PRO/questionnaire was analyzed in the mITT population using ANCOVA. The percentage of PROs responders

based on the minimum clinically-important difference (MCID) was analyzed using a CMH method (Supplementary Materials).

Results

Study population

In total, 151 participants with T2DM were enrolled from 19 centers (device-supported titration, n=75; routine titration, n=76) (Supplementary Figure 2). All participants were exposed to Gla-300 and included in the safety and mITT populations. Five participants (6.7%) in the device-supported titration arm did not complete the study period and permanently discontinued Gla-300 treatment (Supplementary Figure 2). Overall, 17/75 (23%) of the participants randomized to the device-supported arm discontinued use of device, 9 (12%) due to misunderstanding the device titration function and 8 (11%) due to other reasons including withdrawal of consent (Supplementary Figure 2). Baseline characteristics (Table 1) were generally well balanced across the two arms with a slightly higher proportion of females in the device-supported titration versus routine titration arm (36.0% vs 26.3%). All enrolled participants were Caucasians.

Efficacy outcomes

The percentage of participants who achieved the primary endpoint, FSMPG in the target range of 90–130 mg/dL after 16-weeks of treatment without severe hypoglycemia, was 45.9% in the device-supported titration arm compared with 36.8% in the routine-titration arm (weighted difference: 9.04 [95% CI: −6.75 to 24.83], Figure 1). Non-inferiority of the device-supported versus the routine-titration arm was demonstrated as the lower bound of the 95% CI for the weighted

difference in percentage of patients between arms (9.04; 95 % CI [-6.748 to 24.829]) was greater than the predefined non-inferiority margin of -15%. Superiority of device-supported versus routine-titration was not statistically shown (p=0.262).

The percentage of participants who reached the FSMPG target range without confirmed (≤70 mg/dL [≤3.9 mmol/L]) or severe hypoglycemia was higher in the device-supported than the routine titration group (34.3% vs 14.5%; [weighted difference: 19.75 (95% CI: 6.28 to 33.21)], Figure 1). A comparable proportion of participants in the device-supported and routine-titration arm (40.0% vs 34.2%) reached the FSMPG target range without confirmed (<54 mg/dL [<3.0 mmol/L]) or severe hypoglycemia.

The Kaplan-Meier cumulative incidence curves of participants reaching the FSMPG target of 90–130 mg/dL showed an overall shorter time to reach the FSMPG target in the device-supported titration arm than the routine arm, but this trend was driven by participants who did not reach the target within the first 8 weeks (p=0.171). The time at which 50% of the participants achieved the FSMPG target was less in the device-supported than in the routine-titration arm (10 weeks [95% CI: 8–10] vs 13-weeks [95% CI: 6–16], respectively). Mean FSMPG (mean of the last 5 readings recorded over the last 2 weeks) reduced from baseline to the week 16 time-point in both titration arms, (least squares [LS] mean change −41.7 mg/dL vs –43.3 mg/dL; Table 2 and Figure 2).

The LS mean reduction in HbA_{1c} from baseline to week 16 was similar in the device-supported (−1.12 %) and the routine-titration (−1.07 %) arms (Table 2).

For laboratory measured FPG, both titration groups showed reductions from baseline to week 16, although the reductions were slightly lower in the device-supported than the routine-titration arm (−44.05 mg/dL vs −49.46 mg/dL). The percentage of participants with laboratory measured FPG in the target range of 90–130 mg/dL (5.0–7.2 mmol/L) without severe hypoglycemia at week 16 was also higher in the routine-titration arm (29.3% vs 43.4%; Table 2)**, which may be due to a higher mean (standard deviation [SD]) FPG value at baseline in the device-supported arm (192.30 [39.83] mg/dL vs 186.78 [47.15] mg/dL)**.

Basal insulin dose

During the study, BI dose rose steadily in both treatment arms and the change in average BI dose from baseline to week 16 was 0.213 (SD: 0.185) U/kg and 0.157 (SD: 0.153) U/kg in the device-supported and routine-titration arms, respectively.

Safety

The percentage of participants with at least one hypoglycemic event in any category including nocturnal (00:00–05:59 h) hypoglycemia during the on-treatment period was generally comparable between both the titration arms (Figure 3). A slightly higher proportion of participants in the routine-titration arm reported at least one asymptomatic hypoglycemic event (27.6%), and at least one confirmed (≤70 mg/dL [3.9 mmol/L]) or severe hypoglycemic event (35.5%) during the on-treatment period compared with that in the device-supported arm (20.0% and 29.3%, respectively). One case of severe hypoglycemia was reported in the routine-titration arm.

The safety profile was comparable between the titration arms (Supplementary Table 2). For participants in the device-supported arm, the proportion of treatment-emergent adverse events (TEAEs) during on-treatment period and device-support period were similar. The proportion of TEAEs was slightly higher in the device-supported versus routine titration arm (45.3% vs 38.2%). However, the proportion of serious TEAEs was slightly lower in the device-supported versus routine-titration arm (2.7% vs 3.9%). No TEAE resulted in treatment discontinuation or death.

The percentage of participants with at least one meter-related event (MRE) was higher in the device-supported arm compared with the routine-titration arm (70.7% vs 9.2%) and mainly related to the functionality of the device (not activated in the routine-titration arm as per protocol) (Supplementary Table 2). The percentage of participants with at least one pen-related event(s) was low and comparable between the device-supported and routine-titration arms (4.0% vs 3.9%).

Patient reported outcomes

Overall, there were no major differences in PROs between the device-supported and routine-titration arms (Supplementary Table 3). For DTSQ total treatment satisfaction score, the LS mean change from baseline to week 16 was 4.46 using routine-titration versus 2.90 using device-supported titration (Supplementary Table 3). The LS mean change in HFS-II scores were similar for both titration arms at week 16 (Supplementary Table 3). There was little change in Diabetes Distress Scale scores from baseline to week 16 for both titration arms with no clinically-relevant differences between arms in the proportion of participants reaching the MCID (Supplementary Table 3). Improvements in GMS from baseline to week 16 was seen

in both titration arms (Supplementary Table 3). LS mean change in WHO-5 well-being index scores from baseline to week 16 were −0.03 and 6.20 for device-supported group and routine group, respectively (Supplementary Table 3).

Participants were asked to rate how easy or difficult it was to use the device on a scale of 1–7 with 1=very difficult and 7=very easy. The mean scores for how easy it was "to decide what insulin dose to take", "to do the dose calculations correctly" and "to adjust their insulin dose" were 6.11, 6.07 and 6.24 indicating that individuals found the device easy to use.

Discussion

AUTOMATIX indicates that device-supported titration with Gla-300 was statistically non-inferior to diabetes knowledgeable, investigator-led routine titration in achieving the FSMPG target of 90–130 mg/dL (5.0–7.2 mmol/L) without experiencing severe hypoglycemia. Most people with T2DM and HCPs found the device easy to use. As discussed below, however, the higher number of MRE, and the finding that 23% of individuals in the device-supported arm discontinued using the device indicates that further improvements to the training/support provided to users, or changes to improve device ease of use, may be required.

Previously it has been suggested that based on their knowledge, expertise or interest in the use of technology, some individuals may need additional guidance and support as they may not like technical language while others may need more extensive details.[19] Participants had a mean age >60 years, with **44**% being aged 65

years **or over**, a group at higher risk of cognitive impairment compared with younger-age groups,[2] which may impact on their ability to correctly understand instructions and use the device. In total, 17 participants (23%, mean age: 60.6 years; range: 42–74 years) discontinued device-supported titration, of whom 9 (12%) discontinued due to a misunderstanding of the device function. This limited number of participants does not allow an assessment of whether older age and cognitive ability may have been a contributing factor. However, as approximately 70% of individuals in the device-supported group experienced MREs, which included user error in operating the device (e.g. not tagging the FSMPG reading or the incorrect inputting of the insulin dose used), misunderstanding device instructions, and device malfunctions, it appears that increasing participant age is unlikely to underpin these errors. There were also some minor differences in patient-reported treatment satisfaction and well-being that favored routine titration that did not reflect any disparities in HCP contact between the groups. Overall, these findings suggest that discontinuations could be a potential challenge in managing compliance with device use in a minority of individuals, and that this device may not be suitable for all individuals with T2DM who **wish** to use device-supported titration. **These outcomes highlight the need for careful selection of patients in whom use of the device is most appropriate and the need to provide appropriate training in its use. To facilitate this, b**ased on AUTOMATIX, the device user interface has subsequently been optimized and the training materials reworked, for example, to simplify tagging of the FSMPG reading (Supplementary Table 4).

Technological advances to aid insulin titration have demonstrated improved outcomes and safety in both type 1 diabetes (T1DM) and T2DM **in several studies**. [20]

[21, 22 23 24 25] The INNOVATE study examined titration with insulin glargine 100 U/mL (Gla-100) using the long-acting insulin glargine titration web tool (LTHome) in T2DM,[26] using the same rules and engine-based algorithm for titration as that for MyStar DoseCoach®. Of note, a similar percentage of participants reached FPG targets without experiencing hypoglycemia with LTHome as with device-supported titration observed in AUTOMATIX (47% vs 45.9%, respectively). There were similar HbA_{1c} reductions in the LTHome versus the enhanced usual therapy (EUT) arm, but with the EUT arm receiving more HCP resources. While cost-effectiveness data were not collected in AUTOMATIX, the potential for device-supported titration to cut healthcare costs by enabling people with T2DM to achieve glycemic targets while reducing the involvement of physicians and other ancillary healthcare services is of interest.

In AUTOMATIX, outcomes reported for the routine-titration arm were probably better than that observed in the real world. Participants in AUTOMATIX were instructed by investigators (all diabetes specialists with extensive experience working with T2DM) on the recommended method for titration of Gla-300 at each scheduled visit, whereas in real life, routine BI titration in many people with T2DM is not as well managed and follow-up visits are generally less frequent than the clinical-trial setting. Therefore, the numerical difference seen in AUTOMATIX might be predictive of more clinically-meaningful differences in real-life clinical practice, and it is possible that differences in outcomes between device-titration and routine-titration could be better demonstrated using a real-world study. While the performance of device-supported titration is less likely to be affected by infrequent

clinic visits in clinical practice, outcomes in the routine-titration group may be poorer.

The limitations of AUTOMATIX are those inherently associated with the use of devices and device-titration. The open-label trial design and the use of block randomization instead of cluster randomization could have been a potential source of bias. Dosing recommendations were not standardized for the routine-titration arm, and were at the discretion of each investigator, which may have contributed to dosing variability and influenced target achievement**; although, this may also be considered a strength of the study as it ensures that the control is more representative of real-life practice despite the caveats mentioned above**. Several variables may have influenced target achievement in the routine-titration arm that were not able to be controlled (e.g. participant behavior, potential investigator bias, and participant education on how to titrate). Lastly, the short trial duration may have been insufficient to allow observations on long-term challenges in adherence to titration device, and longer term, real-world studies would be of interest.

Conclusions

Device-supported titration with Gla-300 demonstrated a good safety profile and was non-inferior to routine titration (led by diabetes specialists), with a trend towards shorter times being needed to reach FSMPG target. While further work to support people with T2DM in terms of making the device easier to use and providing suitable training materials is required, this study provides additional support for device-supported insulin titration. By helping individuals to make timely and sensible dosing choices, devices such as MyStar DoseCoach® and other innovative technologies may

help to address the clinical inertia in optimizing insulin dosing.

Funding source

AUTOMATIX study was sponsored by Sanofi

Acknowledgments

Editorial and writing assistance was provided by Sharon Eastwood (DPhil) of Fishawack Communications and was funded by Sanofi.

Disclosures

Melanie Davies — Advisory board: AstraZeneca, Boehringer Ingelheim, Eli Lilly, Janssen, Novo Nordisk, Sanofi, Servier; Consultant: AstraZeneca, Boehringer Ingelheim, Eli Lilly, Janssen, Merck, Novo Nordisk, Sanofi; Speaker's bureau: AstraZeneca, Boehringer Ingelheim, Eli Lilly, Janssen, Merck, Novo Nordisk, Sanofi, Takeda, Tanabe; Research support: Boehringer Ingelheim, Janssen, Novo Nordisk.

Steve Bain — Advisory panel: Sanofi, Novo Nordisk, Eli Lilly, Boehringer Ingelheim, Merck, Johnson & Johnson; Research support: Novo Nordisk, Merck.

Guillaume Charpentier — Advisory panel: Eli Lilly; Board member: Sanofi, Eli Lilly, Novo Nordisk, Boehringer Ingelheim; Consultant: AstraZeneca.

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Christoph Hasslacher — No conflicts of interest to declare.

Giacomo Vespasiani — Advisory panel: Sanofi; Consultant: Meteda.

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Tables

Table 1. Baseline demographics and patient characteristics (randomized population)

	Device-supported titration n=75	**Routine titration n=76**	**All N=151**
Age, years, mean (SD)	61.2 (9.5)	62.9 (9.4)	62.1 (9.5)
Age group, years, n (%)			
<65	43 (57.3)	42 (55.3)	85 (56.3)
65–75	29 (38.7)	24 (31.6)	53 (35.1)
≥75	3 (4.0)	10 (13.2)	13 (8.6)
Sex, n (%)			
Male	48 (64.0)	56 (73.7)	104 (68.9)
Female	27 (36.0)	20 (26.3)	47 (31.1)
Race, Caucasian, n (%)	75 (100)	76 (100)	151 (100)
Body Weight, kg, mean (SD)	96.9 (24.0)	100.0 (23.8)	98.5 (23.8)
BMI, kg/m^2, mean (SD)	33.2 (6.9)	33.3 (7.0)	33.2 (6.9)
BMI categories, kg/m^2, n (%)			
<25	5 (6.7)	5 (6.6)	10 (6.6)
25–30	24 (32.0)	20 (26.3)	44 (29.1)
30–40	35 (46.7)	37 (48.7)	72 (47.7)
≥40	11 (14.7)	14 (18.4)	25 (16.6)
Estimated GFR, L/min/1.73m^2, mean (SD)	82.02 (27.60)	84.04 (24.02)	83.04 (25.80)
Estimated GFR categories, n (%)			
≥90	22 (29.3)	33 (43.4)	55 (36.4)
60–90	40 (53.3)	30 (39.5)	70 (46.4)
30–60	13 (17.3)	13 (17.1)	26 (17.2)
Randomization stratum[a] (previous insulin use)			
Insulin-naïve	30 (40.0)	30 (39.5)	60 (39.7)
Insulin-pretreated	45 (60.0)	46 (60.5)	91 (60.3)

[a]Due to stratification errors, 4 insulin pre-treated participants were randomized as insulin-naïve and 1 insulin-naïve participant was randomized as insulin pre-treated.

BMI, body mass index; GFR, glomerular filtration rate; SD, standard deviation

Table 2. Secondary efficacy outcomes during the 16 week on-treatment period (modified intent-to-treat po

	Device-supported titration n=75	**Routine titration n=76**	**LS Mean differen (SE) vs. routi titration, 95% CI**
Change in mean FSMPG from baseline to week 16 time-point, LS mean (SE) mg/dL	−41.70 (3.32)	−43.26 (3.18)	1.56 (4.60), −7.55 10.66
Change in HbA_{1c} from baseline to week 16, LS mean (SE) %	−1.12 (0.09)	−1.07 (0.08)	−0.05 (0.12), −0. to 0.19
Change in FPG from baseline to week 16, LS mean (SE) mg/dL	−44.05 (4.26)	−49.46 (4.08)	5.40 (5.91), −6.28 17.09
	Device-supported titration n=75	**Routine titration n=76**	**RR (95% CI) v routine titration[a]**
Laboratory measured FPG at target (90–130 mg/dL [5.0–7.2 mmol/L]) at week 16 without severe hypoglycemia, n (%)	22 (29.3)	33 (43.4)	0.67 (0.438 1.039)

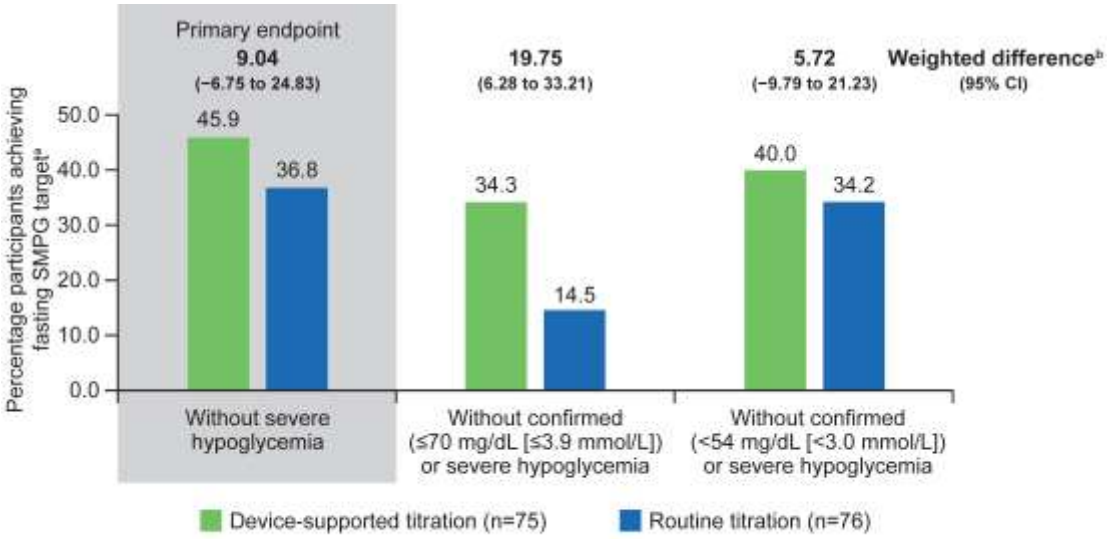
[a]Based on RR stratified by randomization stratum of previous use of insulin (insulin naïve, insulin pre-treated), using a CMH (Cochran

CI, confidence interval; FPG, fasting plasma glucose; LS, least squares; RR, relative risk, SD, standard deviation; SE, standard error; F

glucose

Figures

Figure 1. Estimated percentage of participants achieving target FSMPG without hypoglycemia during the 16-week on-treatment period (modified intent-to-treat population)

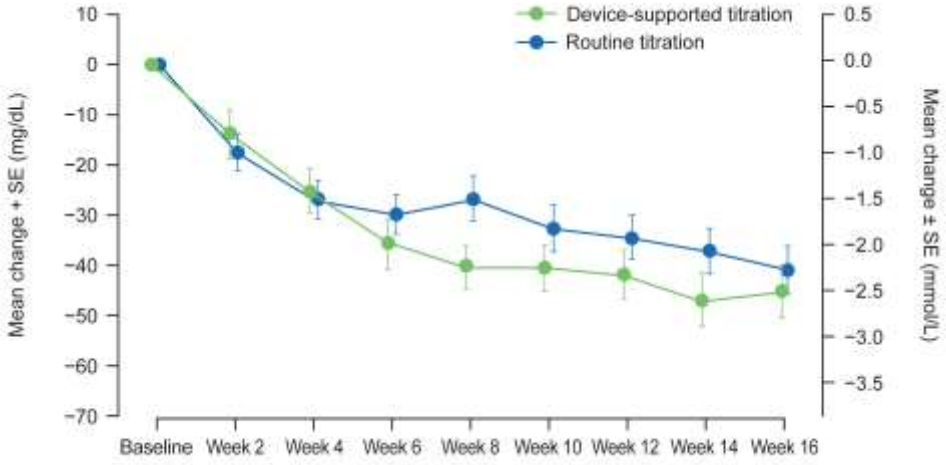


[a]Estimated proportion of participants was obtained using a multiple imputation method was to address missing values in the mITT population

[b]Estimated weighted difference of proportions obtained by combining the difference in percentage, weighted by the randomization stratum of previous use of insulin (insulin naive, insulin pre-treated), between titration groups of all different imputed data sets

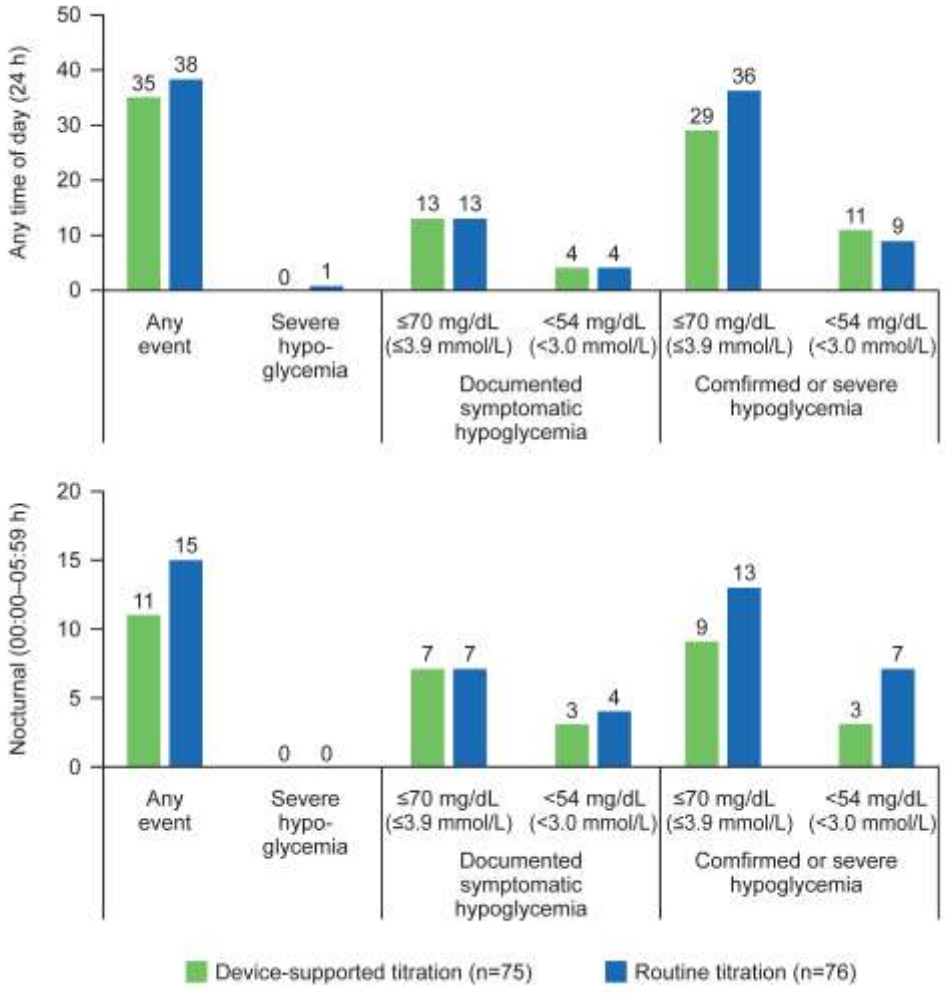
CI, confidence interval; FSMPG, fasting self-monitored plasma glucose

Figure 2. Mean change in FSMPG over the 16-week on treatment period (modified intent-to-treat population)



FSMPG, fasting self-monitored plasma glucose

Figure 3. Incidence (%) of participants experiencing ≥1 hypoglycemic event during the on-treatment period (safety population)



Supplementary methods

Exclusion Criteria

- Age <18 years
- Diabetes other than type 2 diabetes mellitus
- MyStar DoseCoach™ device was not appropriate for the patient or use of device was otherwise contraindicated (in the opinion of the investigator)
- Conditions/situations that were contraindications or off-label use according to Summary of
  Product Characteristics (SmPCs) of oral antihyperglycemic drugs (OADs) and/or glucagon-like peptide-1 (GLP-1) receptor agonists when applicable (prescribed), or insulin glargine and as defined in the national product label
- Patients not on stable doses of glucose lowering therapy including OADs, GLP-1 receptor agonists, or basal insulin therapy, for the 3 months prior to screening (stable basal insulin therapy defined as maximum change in insulin dose of +/- 20%)
- Patients using mealtime insulin (short acting analogue, human regular insulin, or premix insulin) for more than 10 days in the last 3 months before screening visit
- Patients with hypoglycemia unawareness
- Patients with severe hypoglycemia in the past 90 days
- Hospitalization in the past 30 days
- Use of systemic glucocorticoids (excluding topical application or inhaled forms) for one week or more within 90 days prior to screening
- Unable to meet specific protocol requirements (e.g., inability to perform blood glucose measurements, manage their own insulin glargine administration, or deemed unlikely to safely manage titration based on guidance by their physician, etc.), because of a medical condition or because the patient was under legal guardianship
- Patients with cognitive disorders, dementia, or any neurologic disorder that would affect a patient's ability to participate in the study, including the inability to understand study requirements or to give complete information about adverse symptoms
- Conditions/situations such as:
  - Patients with conditions/concomitant diseases precluding their safe participation in this study (e.g., active malignant tumor, major systemic diseases, presence of clinically significant diabetic retinopathy or presence of macular edema likely to require treatment within the study period, etc.)
  - Patients unable to fully understand study documents and to complete them. Patients who have a caregiver together with whom they can fulfill all study requirements are eligible
  - Patient is the Investigator or any Sub-Investigator, research assistant, pharmacist, study coordinator, other staff or relative thereof directly involved in the conduct of the protocol
- Within the last 3 months prior to screening: history of myocardial infarction, unstable angina, acute coronary syndrome, revascularization procedure or stroke requiring hospitalization
- Severe or uncontrolled Congestive Heart Failure (New York Heart Association [NYHA] functional classification III and IV); or inadequately controlled

hypertension at the time of screening with a resting systolic or diastolic blood pressure >180 mmHg or >95 mmHg, respectively

- Pregnant or breast-feeding women or women who intend to become pregnant during the study period as glycemic control may be unstable and insulin doses may be variable during this period
- Women of childbearing potential (premenopausal, not surgically sterile for at least 3 months prior to the time of screening) must use an effective contraceptive method throughout the study. Effective methods of contraception include barrier methods (in conjunction with spermicide), hormonal contraception, or use of an intrauterine device (IUD) or intrauterine hormone-releasing system (IUS)

Hypoglycemia categories

Hypoglycemia endpoints included the percentage of participants reporting ≥1 event. Events were categorized based on American Diabetes Association (ADA) definitions: severe symptomatic hypoglycemia was defined as an event requiring third party assistance by another person to actively administer carbohydrate, glucagon, or other resuscitative actions; documented symptomatic hypoglycemia was defined as events during which typical symptoms of hypoglycemia were accompanied by a measured plasma glucose concentration of ≤70 mg/dL (≤3.9 mmol/L) or <54 mg/dL (<3.0 mmol/L); asymptomatic hypoglycemia included events that were not accompanied by typical symptoms of hypoglycemia but with a measured plasma glucose concentration ≤70 mg/dL (≤3.9 mmol/L) or <54 mg/dL (<3.0 mmol/L); confirmed or severe hypoglycemia included events with a plasma glucose ≤70 mg/dL (≤3.9 mmol/L) or <54 mg/dL (<3.0 mmol/L) or categorized as severe.

Statistical analysis

A total of 151 patients were randomized: 75 to the device-supported titration arm and 76 to the routine titration arm. The safety and modified intent-to-treat (mITT) populations included all 151 participants.

The on-treatment period for efficacy endpoints was defined as the time from the first injection of investigational medicinal product (IMP) until 7 days for HbA_{1c}, 2 days for hypoglycemia, or 1 day for FPG and FSMPG, after the last injection of IMP. For endpoints related to mean FSMPG (except time to first mean FSMPG), only assessments recorded during the on-treatment period and within 112 days (16 weeks) after the first injection of IMP were considered in the analyzes. The on-treatment period for safety endpoints was defined as the time from the first

injection of IMP until 2 days after the last injection of IMP. The device-support period was defined as the time from the date of device-supported activation or from the 1st IMP dose, whichever was later for the participant, up to 2 days after the date of the end use of the device functionality or 2 days after the last injection of the IMP, whichever was earlier for the participant.

The primary efficacy population was the mITT population, which included all randomized participants who were treated with Gla-300, analyzed according to the titration regimen group allocated by randomization. The safety population was defined as all randomized participants who received at least one dose of Gla-300, regardless of the amount of treatment administered and analyzed according to the titration regimen group actually followed.

The primary endpoint was analyzed using a multiple imputation approach for handling missing mean FSMPG continuous values at any time point, and missing status regarding severe hypoglycemic events during the 16-week on-treatment period.

Change in FSMPG from baseline to the end of the 16-week on-treatment period was analyzed using an mixed model for repeated measures (MMRM) approach on post-baseline data available during the 16-week on-treatment period; the model included fixed categorical effects of regimen group, 2-week periods, regimen-by-2-week period interaction, randomization stratum of previous use of insulin (insulin-naïve vs non-insulin-naïve) as well as the continuous fixed covariates of baseline FSMPG value and baseline FSMPG value-by-2-week period interaction.

Time to first FSMPG target range of 90–130 mg/dL (5.0–7.2 mmol/L) was defined by the first 2-week period in which the mean FSMPG of the last five values was in the target range and compared between the two titration regimen groups using the log-rank-test procedure stratified by randomization stratum of previous use of insulin. The cumulative incidence curve of patients reaching FSMPG target range was estimated using Kaplan-Meier method. Change in HbA_{1c} from baseline to week 16 was examined using an analysis of covariance (ANCOVA) model that included fixed

categorical effects of titration regimen group and stratum of randomization of previous use of insulin (insulin-naïve vs non-insulin-naïve) as well as the continuous fixed covariate of baseline HbA_{1c} value. The change in FPG from baseline to Week 16 was analyzed using a similar MMRM model as performed for the change in mean FSMPG. The adjusted LS means estimates at week 16 for both titration groups, as well as the differences of these estimates, with their corresponding SEs and 95% CIs were provided. The pre-specified FPG target was analyzed using Cochran Mantel Haenszel (CMH) method with titration group as factor and stratified on the randomization stratum of previous use of insulin, providing relative risk estimates and corresponding 95% confidence intervals.

Safety analyses were descriptive and based on the safety population. For participants in the device-supported arm, AEs were reported for the on-treatment period and device-supported period (device-emergent). Any suspected problem with the device such as meter performance failure, participant (or caregiver) having difficulty understanding the instructions or user error, which led or may have led to a AEs was reported as a meter-related event (MRE).

Patient-reported outcomes (PRO)/questionnaire ANCOVA model: included fixed categorical effects of titration group, randomization stratum of previous use of insulin (insulin-naïve, non-insulin-naïve), as well as the continuous fixed covariate of baseline PRO value. Percentage of PROs responders, defined by the number of patients with a change from baseline of PRO total scores equal or superior (for diabetes treatment satisfaction questionnaire [DTSQ], glucose monitoring satisfaction survey [GMS] and WHO-5 well-being index) or equal or less (for hypoglycemia fear survey [HFS-II] and diabetes distress scale) to the minimum clinically important difference (MCID), was analyzed using a CMH method. For each PRO score, the MCID value was defined as the half of the standard deviation of the PRO score at baseline within the whole mITT population.

Supplementary Table 1. Dosing recommendations for device-supported titration

FSMPG	**Gla-300 dose (U/day) adjustment**
>180 mg/dL (>10.0 mmol/L)	+4U[a]
>130 mg/dL (>7.2 mmol/L)	+2U
90-130 mg/dL (5.0 to 7.2 mmol/L) or within target range	No change
<90 mg/dL (5.0 mmol/L) and >70 mg/dL (3.9 mmol/L)	−2U
<70 mg/dL (<3.9 mmol/L)	−4U

[a]Dose increase every 3 days if FSMPG above target. Gla-300, insulin glargine 300 U/mL; FSMPG, fasting self-monitored plasma glucose

Supplementary materials

Supplementary Table 2. Overview of treatment-emergent adverse events (safety population)

	Device-supported titration (n=75)		**Routine titration (n=76)**
Type of TEAE, n (%)	**On-treatment period**	**Device-support period**	**On-treatment period**
Any	34 (45.3)	32 (42.7)	29 (38.2)
Serious	2 (2.7)	2 (2.7)	3 (3.9)
TEAE leading to treatment discontinuation	0	0	0
TEAE leading to death	0	0	0
Meter-related event[a]	53 (70.7)	52 (69.3)	7 (9.2)
Pen-related event	3 (4.0)	3 (4.0)	3 (3.9)
PTC for the meter	15 (20.0)	15 (20.0)	0
PTC for the pen	1 (1.3)	1 (1.3)	1 (1.3)

n (%) = number and percentage of participants with at least one TEAE.

[a]Any suspected problem with the device such as meter performance failure, participant (or caregiver) having difficulty understanding the instru

to a AEs was reported as a meter-related event.

PTC, product technical complaint; TEAE, treatment-emergent

Supplementary Table 3. Patient reported outcomes during the 16 week on-treatment period (modified intent-to-treat population)

Change from baseline to week 16, LS mean (SE)	**Device-supported titration (n=75)**	**Routine titration (n=76)**
Total treatment satisfaction score	2.90 (0.612)	4.46 (0.596)
Total HFS-II score	0.00 (0.050)	0.03 (0.048)
Total Diabetes Distress Scale score	0.08 (0.060)	-0.04 (0.058)
Total GMS score	0.10 (0.071)	0.30 (0.069)
WHO-5 well-being index score	−0.03 (1.788)	6.20 (1.750)

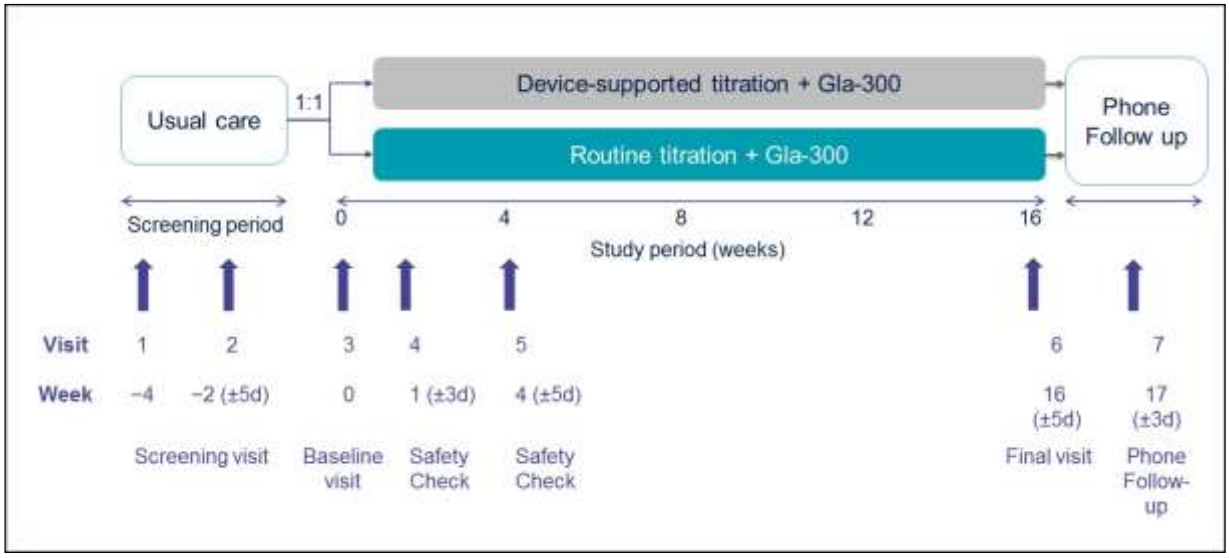
The Diabetes Treatment Satisfaction Questionnaire (DTSQs) consists of 8 items scored on a 7-point scale with a higher score indicating greater satisfaction. HFS-II consists of 33 items in 2 subscales HFS-B (behavior to avoid hypoglycemia) and HFS-W (worry about hypoglycemia). It is rated on a 5-point Likert scale ranging from 0 (never) to 4 (always). The Diabetes Distress Scale consists of 17 items scored on a 7-point scale rated from 1 (not a problem) to 6 (a very serious problem). The GMS consists of 15 items scored on a 5-point scale ranging from 1 (strongly disagree) to 5 (strongly agree). The WHO-5 well-being index includes five items rated on a 6-point scale with 0 (at no time) to 5 (all the time). The total raw score, ranging from 0 to 25, is multiplied by 4 to give the final score, with 0 representing the worst imaginable well-being and 100 representing the best imaginable well-being. GMS, glucose monitoring satisfaction survey; HFS-II, hypoglycemia fear scale; LS, least squares; SE, standard error; WHO, World Health Organization.

Supplementary Table 4. Improvements that have been made to the dose-helper device (MyStar DoseCoach™, Agamatrix Inc., Salem NH, US) following the AUTOMATIX study

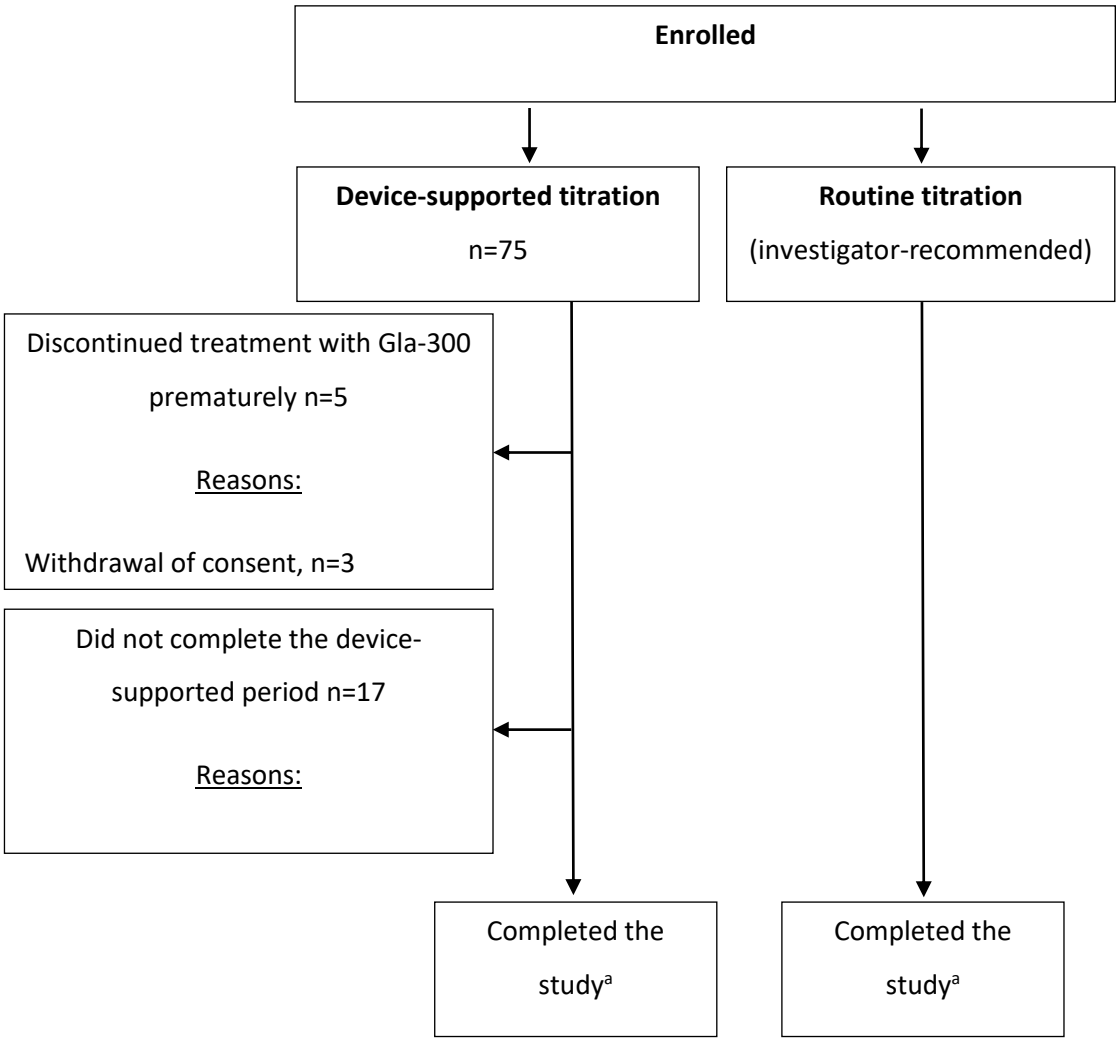
Issue identified	Solution
• Users not understanding tagging and the importance of applying a fasting tag	• New screens added to improve accuracy of tagging: ○ "Is this a fasting reading?" if blood glucose test performed within the usual fasting window ○ New "fasting readings are used by dose-helper to determine dose suggestions" has been added ○ The "fasting tag" selection has been greyed out when outside usual fasting time
• Users getting stuck in the dose-helper function not being able to get out	• Exit path provided from the dose-helper flow. Added "exit" button to "back button unavailable" screen and the wording has been clarified
• Previous dose prompt found to be confusing when the dose-helper is used for the first time	• New screen has been added to show if dose-helper is being run for the first time
• Users pressing the dose-helper button when they wanted to change the dose time.	• New "Welcome to dose-helper" menu screen and dose-helper settings screens have been added. The dose-helper icon has also been changed to a wrench for settings selection.
• Users misunderstanding the previous dose question	• The "previous dose question" and "additional dose question" screen has been broken into two screens so that the day picker is one screen and the time picker is on second screen. Time picker has been

	restricted to valid choices
• Twice-daily screen prompt was confusing for some users	• The wording on two screens has been changed to clarify if twice daily dosing has been prescribed
• Hypoglycemia questions were found to be confusing	• The possible number of answers to the hypoglycemia questions have been reduced from six to three; three screens have been reworded and one screen split into two for clarification
• Use of the left soft key for back navigation was found to be confusing	• Added six new screens at initial start-up to explain navigation (how buttons work)
• Improved feedback for the chosen time values required	• The sequence of time/date screens has been changed by moving the last three screens to be the first three screens. New screen has been added to confirm the time/date, and text added to time screens
• Users not understanding that they need to scroll down to read the full “User Agreement Screen”	• Wording and button icon has been added to two screens
• Improved differentiation of the activation key artwork required for healthcare providers	• One new screen has been added to inform healthcare providers that each key unlocks a different treatment plan

Supplementary Figure 1. Study Design



Supplementary Figure 2. Study participant disposition (randomized population)



[a]A patient was considered to have completed the study period if they attended the week 16 visit, irrespective of treatment and device compliance.