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

Type of TEAE, n (%)	Device-supported titration (n=75)		Routine titration (n=76)
	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 instructions or user error, which led or may have led to a AEs was reported as a meter-related event.

PTC, product technical complaint; TEAE, treatment-emergent adverse event

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)

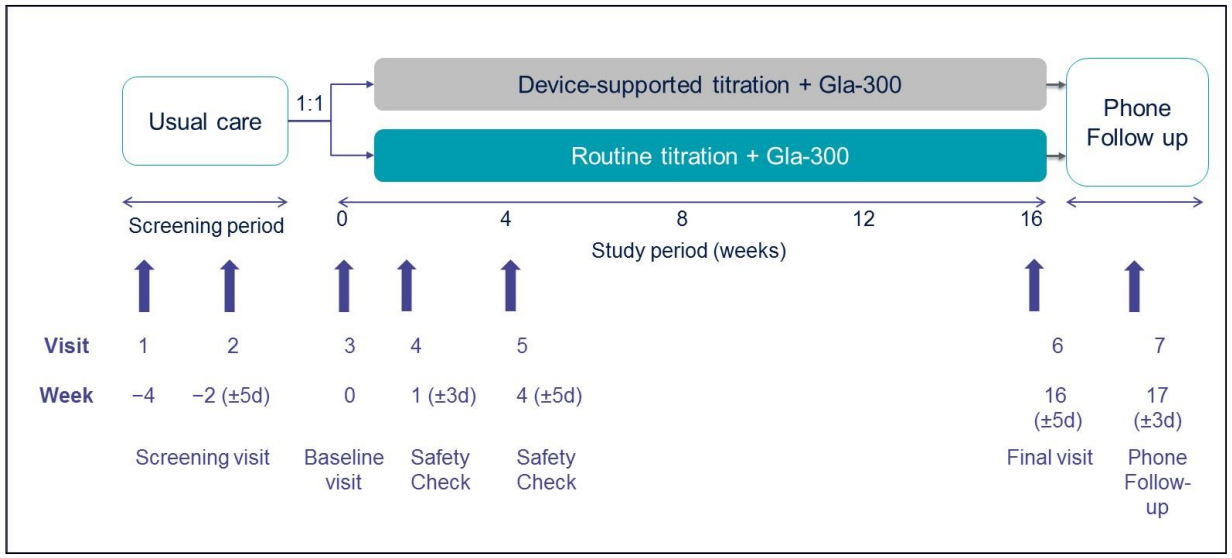
The Diabetes Treatment Satisfaction Questionnaire (DTSQs) consists of 8 items scored on a 7-point scale with a higher score indicating greater satisfaction. HFS-II consists of 33 items in 2 subscales HFS-B (behavior to avoid hypoglycemia) and HFS-W (worry about hypoglycemia). It is rated on a 5-point 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

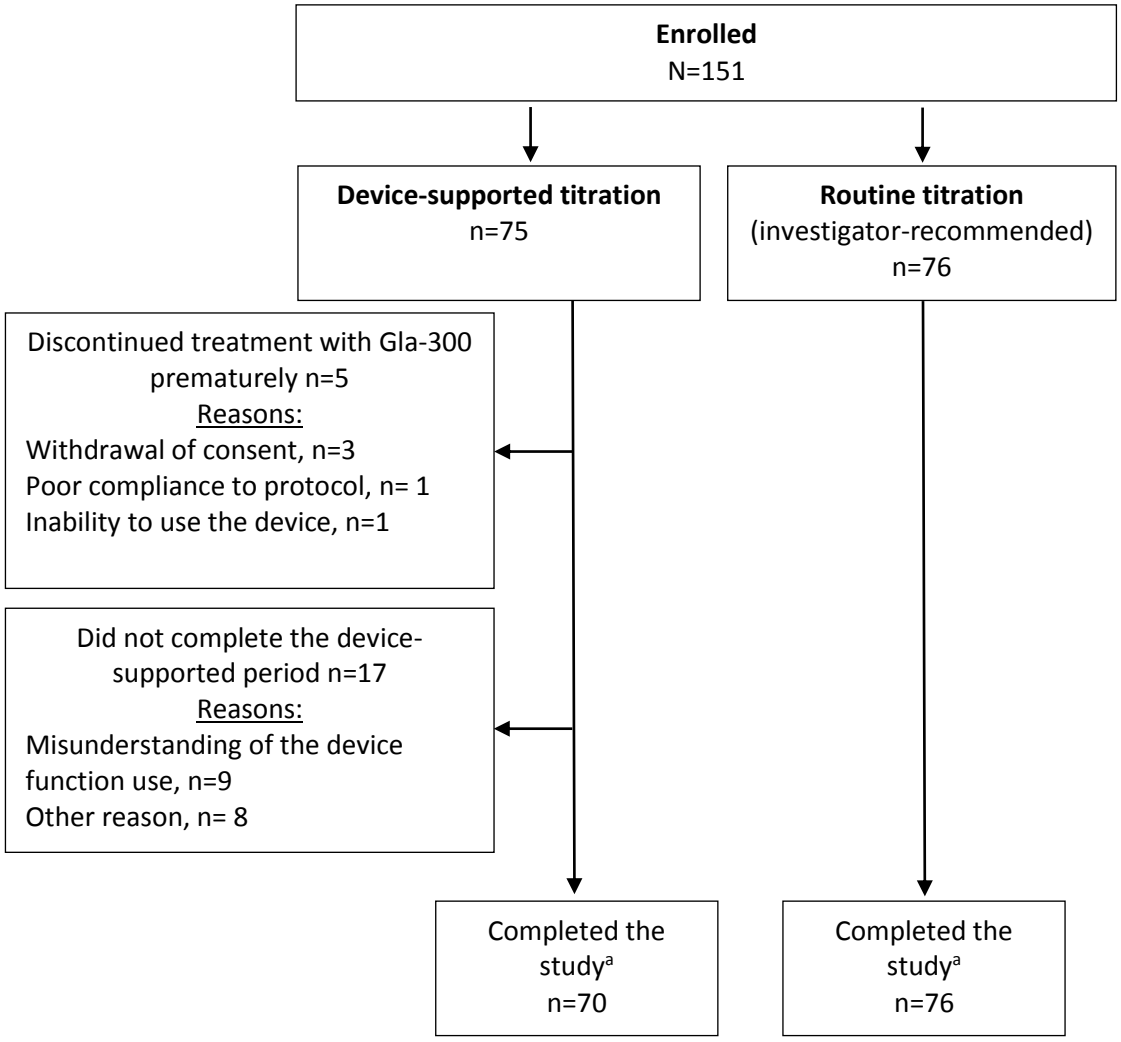
Issue identified	Solution
• Users not understanding tagging and the importance of applying a fasting tag	• New screens added to improve accuracy of tagging: o "Is this a fasting reading?" if blood glucose test performed within the usual fasting window o New "fasting readings are used by dose-helper to determine dose suggestions" has been added o 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.