Device-supported versus routine titration of insulin glargine 300 U/ml (Gla-300) in T2DM: efficacy and safety

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INTRODUCTION

- Good glycaemic control in people with type 2 diabetes (T2DM) is associated with a reduced risk of microvascular complications.[1] Basal insulin therapy is recommended in people with T2DM unable to achieve target HbA_{1c} levels after 3 months of maximum oral antihyperglycaemic drug therapy.[2]
- However, there is often a long delay in both initiating insulin therapy and insulin intensification in people with inadequately controlled T2DM.[3,4]
- Typically, basal insulin is titrated at the treating physician's discretion; however, better glycaemic control has been observed when people with T2DM self-managed dose titration.[5]
- MyStar DoseCoach™ is an integrated titration device/blood glucose meter (BGM) designed to assist people with T2DM to self-titrate insulin glargine 300 U/ml (Gla-300) by providing automated dosing suggestions.

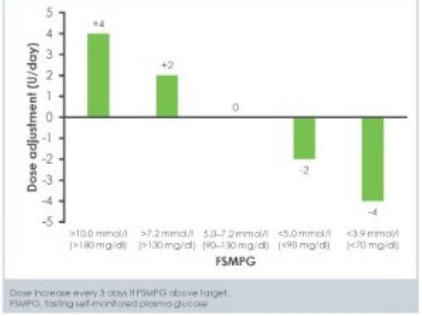
OBJECTIVE

To evaluate the efficacy and safety of device-supported versus routine (investigator-recommended) Gla-300 titration regimens.

METHODS

- **Design:** AUTOMATIX (NCT02585674) was an open-label, randomised, controlled, parallel-group, multicentre study with a 16-week treatment period.
- **Participants:** People with T2DM ≥18 years of age initiating or switching to Gla-300 with HbA_{1c} 7.5–11.0% at screening and fasting self-monitored plasma glucose (FSMPG) >7.2 mmol/l (>130 mg/dl) at screening and randomisation.
- **Treatments:** Participants were randomised 1:1 to self-administer Gla-300 using only the BGM function of the MyStar DoseCoach™ (routine titration arm), or the BGM feature combined with the titration algorithm to provide dose suggestions (device-supported titration arm) (**Figure 1**).

Figure 1: Dosing recommendations for device-supported titration



Dose increase every 3 days if FSMPG above target.
FSMPG, fasting self-monitored plasma glucose

- **Outcomes:**
  - Percentage of participants reaching target FSMPG (5.0–7.2 mmol/l [90–130 mg/dl]) at week 16 without severe hypoglycaemia (primary endpoint).
  - Percentage of participants achieving target FSMPG at week 16 without confirmed or severe hypoglycaemia.
  - Change in HbA_{1c}, basal insulin dose, fasting plasma glucose (FPG) and FSMPG from baseline to week 16.
  - Time to first reach FSMPG target.
  - Safety endpoints included incidence and rates of hypoglycaemia (ADA-based classifications),[2] adverse events and meter- and pen-related events.
- **Data analysis and statistics:** Unless otherwise stated, all efficacy analyses were performed on the modified intention-to-treat (mITT) population (all randomised participants allocated to a titration arm and treated with Gla-300) using post-baseline data from the on-treatment period. The primary endpoint was tested using a multiple imputation approach, followed by estimation of the difference between arms using titration regimen effect estimators, weighted by randomisation strata of previous insulin use (naïve vs pre-treated). A mixed model repeated measures approach was used for change in FSMPG and FPG. HbA_{1c} change was assessed using analysis of covariance. Time to first reach the FSMPG target was defined as the first 2-week period in which the mean of the last five FSMPG values was in the target range. Safety analyses were descriptive and based on the safety population (all randomised participants who received at least one dose of Gla-300).

RESULTS

- A total of 151 participants with T2DM (60 [39.7%] of whom were insulin-naïve) were enrolled from 19 centres (**Table 1**).
- Non-inferiority was achieved for the primary endpoint, the proportion of participants achieving target FSMPG without severe hypoglycaemia (**Table 2**).

Table 1: Baseline characteristics (randomised 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)
Sex, male, n (%)	48 (64.0)	56 (73.7)	104 (68.9)
BMI, kg/m², mean (SD)	33.2 (6.9)	33.3 (7.0)	33.2 (6.9)
Estimated GFR, ml/min/1.73 m², mean (SD)	82.02 (27.6)	84.0 (24.0)	83.0 (25.8)
Randomisation strata (previous insulin use[a])			
Insulin-naïve	30 (40.0)	30 (39.5)	60 (39.7)
Insulin pre-treated	45 (60.0)	46 (60.5)	91 (60.3)

[a]Owing to stratification errors, four insulin pre-treated participants were randomised as insulin-naïve and one insulin-naïve participant was randomised as insulin pre-treated.
BMI, body mass index; GFR, glomerular filtration rate; SD, standard deviation

- Although a numerically higher proportion of patients reached the primary endpoint in the device-supported vs routine titration arm, superiority was not demonstrated (p=0.262).
- A greater proportion of participants in the device-supported titration arm achieved FSMPG without confirmed or severe (≤3.9 mmol/l [≤70 mg/dl]) hypoglycaemia (**Table 2**).

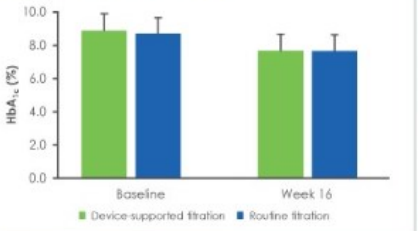
Table 2: Percentage of participants achieving target FSMPG without hypoglycaemia during the on-treatment period (mITT population)

Participants reaching mean FSMPG target range (5.0–7.2 mmol/l) at week 16, estimated %[a]	Device-supported titration (n=75)	Routine titration (n=76)
Without severe hypoglycaemia[b,c]	45.9	36.8
Weighted difference[d] (95% CI)	9.04 (−6.75 to 24.83)[e]	
Without confirmed (≤3.9 mmol/l [≤70 mg/dl]) or severe hypoglycaemia	34.3	14.5
Weighted difference[d] (95% CI)	19.75 (6.28 to 33.21)	
Without confirmed (<3.0 mmol/l [<54 mg/dl]) or severe hypoglycaemia	40.0	34.2
Weighted difference[d] (95% CI)	5.72 (−9.79 to 21.23)	

[a]Estimated percentage of participants obtained by averaging all imputed data for percentage of participants reaching the endpoint. [b]Primary endpoint. [c]Non-inferiority demonstrated (non-inferiority margin: −15%). [d]Estimated weighted difference of percentages obtained by combining the difference in percentage, weighted by the randomisation stratum of previous use of insulin (insulin-naïve vs pre-treated), between titration groups of all different imputed data sets, using Rubin's formula. [e]Superiority not demonstrated (p=0.262).
CI, confidence interval; FSMPG, fasting self-monitored plasma glucose; mITT, modified intention-to-treat

- Mean change in HbA_{1c} from baseline to week 16 was similar between titration regimen arms (least squares [LS] mean −1.12 [SE: 0.086] vs −1.07 [SE: 0.084] % for device-supported vs routine titration, respectively) (**Figure 2**).

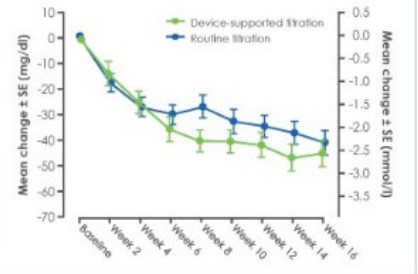
Figure 2: Mean (+SE) HbA_{1c} at baseline and week 16 during the on-treatment period (mITT population)



mITT, modified intention-to-treat; SE, standard error

- For device-supported titration, the mean change in average daily basal insulin dose from baseline to week 16 was 0.213 (SD: 0.185) U/kg (total dose: 22.0, SD: 19.9 U), while for routine titration it was 0.157 (SD: 0.153) U/kg (total dose: 15.9, SD: 16.7 U).
- From baseline to week 16, the mean change in FPG was similar for device-supported vs routine titration regimens (LS mean −44.05 [SE: 4.26] vs −49.46 [SE: 4.08] mg/dl, respectively).
- Mean change in FSMPG from baseline to week 16 was similar for the device-supported vs routine titration regimens (LS mean −41.70 [SE: 3.32] vs −43.26 [SE: 3.18] mg/dl, respectively) (**Figure 3**).
- The median time to first achieve target FSMPG was slightly less for device-supported titration (10 [95% CI: 8–10] weeks) compared with routine titration (13 [95% CI: 6–16] weeks), but this difference was not significant (p=0.171).

Figure 3: Mean change in FSMPG over the 16-week treatment period (mITT population)



FSMPG, fasting self-monitored plasma glucose; mITT, modified intention-to-treat; SE, standard error

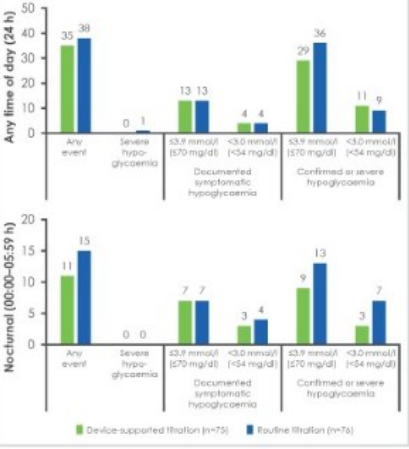
- **Safety:**
  - The risk of experiencing ≥1 hypoglycaemic event of any category was similar between groups (**Figure 4**).
  - Both titration regimens demonstrated comparable safety profiles, with 45.3% and 38.2% of participants in the device-supported vs routine titration arms, respectively, experiencing a treatment-emergent adverse event (TEAE); serious TEAEs were also rare (**Table 3**).
  - A higher incidence of participants with meter-related events (MREs) was reported in the device-supported (70.7%) than the routine titration arm (9.2%), mostly related to the device functionality that was not activated/used in the routine titration arm (as per the study protocol).

Table 3: Overview of treatment-emergent adverse events (safety population)

Type of TEAE, n (%)[a]	Device-supported titration (n=75)	Routine titration (n=76)
Any TEAE	34 (45.3)	29 (38.2)
Serious TEAE	2 (2.7)	3 (3.9)
TEAE leading to treatment discontinuation	0 (0.0)	0 (0.0)
TEAE leading to death	0 (0.0)	0 (0.0)
Meter-related event[b]	53 (70.7)	7 (9.2)
Pen-related event	3 (4.0)	3 (3.9)
PTC for the meter	15 (20.0)	0 (0.0)
PTC for the pen	1 (1.3)	1 (1.3)

[a]Data are for treatment period. [b]Any suspected problem with the device which has or may lead to an adverse event (e.g. meter performance failure, difficulty with understanding the meter instructions).
PTC, product technical complaint; TEAE, treatment-emergent adverse event

Figure 4: Proportion (%) of participants experiencing ≥1 hypoglycaemic event during the on-treatment period (safety population)



SUMMARY

- The AUTOMATIX study demonstrated that device-supported titration was non-inferior to investigator-led routine titration and resulted in a slightly greater proportion of participants achieving target FSMPG without severe hypoglycaemia (46% vs 37%, respectively, p=0.262).
- Mean change in FSMPG from baseline to week 16 was similar for device-supported vs routine titration but target FSMPG was achieved slightly faster (p=0.171).
- MREs (mostly related to device functionality) were more common in the device-supported than routine titration arms. However, this was likely due to more frequent and complex use of the devices in the device-supported group, and had no effect on the safety profile; comparable proportions of participants with hypoglycaemia were observed for both titration regimens.

CONCLUSIONS

- **Device-supported titration with Gla-300 was non-inferior to routine titration for achieving FSMPG target without severe hypoglycaemia.**
- **The results show that device-supported titration with Gla-300 had a good safety and efficacy profile and may help people with T2DM to achieve glycaemic targets.**

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