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Safety and efficacy of a pragmatic self-titration 1 unit/day (INSIGHT) algorithm for insulin glargine 300 U/mL (Gla-300)

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INTRODUCTION

- Compared with insulin glargine 100 U/mL (Gla-100), insulin glargine 300 U/mL (Gla-300)[1] has a flatter pharmacokinetic profile resulting in a lower hypoglycemia risk.
- In the EDITION program, the clinical benefits of Gla-300 were compared with Gla-100 in multicenter, randomized, open-label, phase 3a, two-arm trials. All studies (EDITION 1, 2 and 3) used a similar healthcare professional (HCP)-driven titration algorithm (**Table 1**).[2–4]
- It remains unclear whether the use of a pragmatic patient-driven protocol (INSIGHT),[5] which involves increasing insulin dosages every day, i.e. without waiting for a steady state of insulin action to be reached after each adjustment, may cause more hypoglycemia with the longer-acting Gla-300 insulin.

OBJECTIVE

To compare efficacy and safety of two different titration algorithms, INSIGHT and EDITION, for Gla-300 in patients with type 2 diabetes mellitus, mainly in a primary care setting.

METHODS

- A Canadian, multicenter, open-label, randomized, phase 3b pilot descriptive study (NCT02401243).
- People with uncontrolled type 2 diabetes mellitus ≥18 years of age were included.
- In both groups, participants were initiated or switched from their previous basal insulin therapy to Gla-300 (once-daily injection in the evening).
- In the INSIGHT algorithm group, the dose was self-titrated by the patients by 1 U/day until reaching a fasting self-monitored plasma glucose (FSMPG) in the target range of 80–100 mg/dL (4.4–5.6 mmol/L).
- In the EDITION algorithm group, the dose was titrated by the participants following the directions of the site based on the median FSMPG values of the last 3 days at least weekly but no more than every 3 days (**Table 1**).

Table 1: Titration algorithm in EDITION 1, 2 and 3

Median FSMPG from last 3 days in the range of:	Dose adjustment for Gla-100 or Gla-300, U/day
≥140 mg/dL (≥7.8 mmol/L)	+6
>100–<140 mg/dL (>5.6–<7.8 mmol/L)	+3
80–100 mg/dL (4.4–5.6 mmol/L)	No change
≥60–<80 mg/dL (≥3.3–<4.4 mmol/L)	–3
<60 mg/dL (<3.3 mmol/L) or occurrence of ≥2 symptomatic or 1 severe hypoglycemia episode(s) in the preceding week	–3 or at investigator's discretion

FSMPG, fasting self-monitored plasma glucose

- The study consisted of 2 weeks of screening, 12 weeks of treatment, and 2 days of safety follow-up.
- Primary endpoint was the percentage of participants reaching FSMPG ≤100 mg/dL (≤5.6 mmol/L) without nocturnal (00:00–05:59 h) hypoglycemia (confirmed or symptomatic or severe) at 12 weeks.
- Further endpoints of the study included the percentage of patients at target HbA_{1c} (≤7 %) at week 12, as well as changes in HbA_{1c}, insulin dose, and body weight. Adverse events and hypoglycemia were evaluated for an overview of safety. Treatment satisfaction was assessed using the Diabetes Treatment Satisfaction Questionnaire (DTSQ) and HCP satisfaction questionnaire.
- Descriptive analyses were performed using the safety population, i.e. all randomized patients who received at least one dose of Gla-300.

RESULTS

- Baseline characteristics are shown in **Table 2**.

Table 2: Patient characteristics (safety population)

		INSIGHT algorithm N=108	EDITION algorithm N=104
Age	years	61.8 (10.4)	62.9 (11.4)
BMI	kg/m²	33.4 (7.0)	35.0 (8.0)
HbA_{1c}	%	8.4 (1.1)	8.4 (1.0)
	mmol/mol	68.2 (12.5)	68.1 (10.7)
Insulin naïve	n (%)	40 (37.0)	34 (32.7)
Prior insulin dose	U/day	54.0 (37.2)	60.3 (39.0)

Data are presented as mean (SD), unless otherwise indicated.
BMI, body mass index; SD, standard deviation

- A comparable number of participants in each group reached the primary endpoint of FSMPG ≤100 mg/dL (≤5.6 mmol/L) without nocturnal (00:00–05:59 h) hypoglycemia (confirmed SMPG ≤70 mg/dL (≤3.9 mmol/L) or symptomatic or severe) at week 12 (**Table 3**).
- The incidence and rate of hypoglycemia was similar in both groups (**Table 3**).
- The percentages of patients achieving HbA_{1c} ≤7 % were comparable, with a mean HbA_{1c} of 7.6 % in both groups (**Table 3**).
- FSMPG at week 12 was 118 mg/dL (6.6 mmol/L) and 123 mg/dL (6.8 mmol/L) with the INSIGHT and the EDITION algorithm, respectively.
- Mean insulin dose at week 12 was comparable between algorithms (**Table 3**).
- Change in weight was also similar (**Table 3**).
- Treatment satisfaction (DTSQ) increased in both groups to a comparable extent.
- Both groups had similar reductions in perceived hyper- and hypoglycemia.
- 86% (30/35) of HCPs preferred the INSIGHT algorithm vs EDITION, as demonstrated via the HCP questionnaire.
- No differences between groups were observed for adverse events.

Table 3: Efficacy and Safety outcomes (safety population)

		INSIGHT algorithm	EDITION algorithm
Number of patients	n	108	104
FSMPG ≤100 mg/dL (≤5.6 mmol/L) without nocturnal hypoglycemia	n (%)	23 (21.3)	21 (20.2)
Confirmed or severe hypoglycemia	n (%)	60 (55.6)	51 (49.0)
	rate‡ (SE)	6.9 (1.3)	7.0 (1.3)
Symptomatic hypoglycemia	n (%)	43 (39.8)	39 (37.5)
	rate‡ (SE)	3.3 (0.7)	3.6 (0.8)
Confirmed hypoglycemia*	n (%)	60 (55.6)	50 (48.1)
	rate‡ (SE)	6.9 (1.3)	7.0 (1.3)
Nocturnal hypoglycemia before 06:00 h	n (%)	36 (33.3)	35 (33.7)
	rate‡ (SE)	2.3 (0.5)	3.1 (0.7)
Nocturnal hypoglycemia before 08:00 h	n (%)	53 (49.1)	44 (42.3)
	rate‡ (SE)	4.5 (0.9)	5.1 (1.0)
Severe hypoglycemia†	n (%)	1 (0.9)	3 (2.9)
	rate‡ (SE)	0.0 (0.0)	0.1 (0.1)
HbA_{1c} at week 12	%	7.6 (0.9)	7.6 (1.0)
	mmol/mol	59.7 (9.6)	59.3 (10.8)
HbA_{1c} ≤7 % at week 12	n (%)	29 (26.9)	30 (28.8)
FSMPG at week 12	mmol/L	6.6 (1.9)	6.8 (2.2)
Weight change from baseline	kg	0.4 (3.2)	0.1 (2.4)
Insulin dose at week 12	U/day	67.0 (37.8)	70.0 (43.1)

*Confirmed hypoglycemia: SMPG ≤70 mg/dL (≤3.9 mmol/L). †Individual requires assistance, unconsciousness may occur, plasma glucose is typically <50 mg/dL (<2.8 mmol/L). ‡Semi-annualized rate
Data are presented as mean (SD), unless otherwise indicated. FSMPG, fasting self-monitored plasma glucose; SD, standard deviation; SE, standard error

LIMITATIONS: Descriptive analysis, open-label design, short (12-week) duration.

Table 4: HCP satisfaction questionnaire scores (all completed questionnaires, N=35)

	Score	
	INSIGHT algorithm	EDITION algorithm
Algorithm is simple	2.5 (0.7)	1.0 (1.6)
Algorithm is effective	2.3 (0.9)	1.3 (1.5)
Algorithm is safe	2.5 (0.8)	1.4 (1.4)

Scores are presented as mean (SD). Possible scores ranged from 3 ("totally agree") to –3 ("totally disagree"). HCP, healthcare professional; SD, standard deviation

CONCLUSION

Application of a self-titration of 1 U/day algorithm with Gla-300 resulted in a good safety profile, was effective and comparable to the previously tested EDITION algorithm, and was preferred by HCPs.

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