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Real-world safety and effectiveness of insulin glargine 300 U/mL in participants with type 2 diabetes who fast during Ramadan: The observational ORION study

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ABSTRACT

Aims: ORION evaluated the safety and effectiveness of Gla-300 in insulin-treated people with T2DM before, during and after Ramadan, in a real-world setting.

Methods: This prospective, observational study across 11 countries included participants with T2DM treated with Gla-300 in pre-Ramadan, Ramadan and post-Ramadan periods. The primary endpoint was the percentage of participants experiencing ≥1 event of severe and/or symptomatic documented hypoglycaemia with self-monitored plasma glucose (SMPG) ≤70 mg/dL during Ramadan. Secondary endpoints included change in HbA_{1c} and insulin dose and adverse events (AEs).

Results: The mean ± SD number of fasting days was 30.1 ± 3.2. The percentage of participants experiencing ≥1 event of severe and/or symptomatic documented hypoglycaemia (SMPG ≤70 [<54] mg/dL) was low in the pre-Ramadan (2.2% [0.8%]), Ramadan (2.6% [0%]) and post-Ramadan (0.2% [0%]) periods. No participants reported severe hypoglycaemia during Ramadan or post-Ramadan; one participant reported severe hypoglycaemia in pre-Ramadan. HbA_{1c} fell pre- to post-Ramadan, and Gla-300 daily dose (mean ± SD) was reduced pre-Ramadan to Ramadan (from 25.6 ± 11.9 U/0.32 ± 0.14 U/kg to 24.4 ± 11.5 U/0.30 ± 0.13 U/kg). Incidence of AEs was 5.5%.

Conclusions: In ORION, people with T2DM treated with Gla-300 who fasted during Ramadan had a low risk of severe/symptomatic hypoglycaemia and improved glycaemic control.

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1. Introduction

The holy month of Ramadan poses various challenges for Muslims with type 2 diabetes (T2DM) who choose to fast. Despite many Muslim individuals receiving educational guidance from their treating physician/healthcare professional on the potential risks of fasting during Ramadan, or being advised on their eligibility for medical exemption, many still choose to fast [1,2]. Previous studies have shown that the majority of people with T2DM will fast for at least 2 weeks, if not the entire Ramadan period; in the DAR-MENA and CREED studies, 86–94% of participants with T2DM fasted for ≥ 15 days and over half of participants (57–64%) with T2DM fasted for the full duration of Ramadan [3,4].

People with T2DM are at greater risk of hypoglycaemia during Ramadan compared with the rest of the year [5,6]. Studies within this population have shown that rates of severe hypoglycaemia increase during the Ramadan period; the DAR-MENA study observed a 4.5-fold increase in severe hypoglycaemic events during Ramadan compared with the 4-weeks prior to Ramadan [7], while the EPIDIAR study observed a 7.5-fold increase in severe hypoglycaemic events during Ramadan compared with the preceding year [8]. In both studies, fewer than half of the participants changed their diabetes treatment dose during Ramadan (approximately one third of participants were treated with insulin, with or without oral anti-hyperglycaemic drugs) [7,8].

The International Diabetes Federation and the Diabetes and Ramadan International Alliance (IDF-DAR) have developed guidelines for the management of people with T2DM during the Ramadan period. These guidelines define three risk categories to identify an individual patient's risk of potential complications from fasting during Ramadan, including hypoglycaemia, hyperglycaemia and diabetic ketoacidosis, that are based on knowledge from clinical practice. The 'very high-risk' category includes patients with a history of recurrent hypoglycaemia, or severe hypoglycaemia and/or diabetic ketoacidosis in the 3 months prior to Ramadan, while the 'high risk' category includes people with T2DM who have sustained poor glycaemic control or controlled T2DM using multiple dose/mixed insulin; people with T2DM in these categories are advised not to fast during Ramadan. People with well-controlled T2DM who are receiving lifestyle therapy, oral anti-hyperglycaemic drugs and/or basal insulins are categorised as being at 'moderate–low risk' of complications when fasting; these people are advised to check their blood glucose regularly and adjust their dose of diabetes medication [9].

The use of basal insulin analogues is recommended during Ramadan, due to the lower risk of hypoglycaemia compared with regular human insulin [1,6]; for once-daily basal insulin analogues, IDF-DAR guidelines recommend a reduced (15–30%) dose, administered at iftar (meal at sunset, after fasting during the Ramadan period) [9].

Insulin glargine 300 U/mL (Gla-300) is a second-generation basal insulin analogue that provides comparable glycaemic control and reduced hypoglycaemia compared with the first-generation analogue insulin glargine 100 U/mL (Gla-100), in adults with T2DM [10–13]. However, there are limited data on the clinical characteristics of newer basal insulin analogues on people with T2DM who fast during Ramadan. The ORION real-world study was undertaken to prospectively evaluate the safety and effectiveness of Gla-300 in participants with T2DM prior to, during and after Ramadan.

2. Materials and Methods

2.1. Study design

ORION (CTRI/2019/02/017636, World Health Organization International Clinical Trials Registry Platform) was a prospective, observational, international multicentre study including participants with T2DM treated with Gla-300, in pre-Ramadan, Ramadan and post-Ramadan periods.

Participants were selected at 64 centres across 11 countries (Kuwait, Qatar, Saudi Arabia, United Arab Emirates, Jordan, Lebanon, Turkey, Egypt, India, Pakistan and Canada). Written informed consent was obtained from each participant. The study was conducted in 2019, with the Ramadan fast occurring between 5 May and 4 June.

Participants visited the study centres and had Gla-300 treatment prescribed as per routine clinical practice; dose adjustments during Ramadan were made based on the advice of the treating physician, guided by IDF-DAR recommendations and individual patient characteristics [6]. Participants were expected to visit the centre as per routine practice, ideally at three timepoints including the recruitment period (in the 3-month period prior to Ramadan), the pre-Ramadan period and the post-Ramadan period (Supplementary Fig. 1). Therefore, the pre-Ramadan period was defined as 1–3 months, the Ramadan period was defined as 1 month and the post-Ramadan period was defined as 1 month (although hypoglycaemia and adverse events occurring ≥ 1 month after the end of Ramadan are also recorded if the patient visit was made more than one month after Ramadan). Participants completed diaries with information on glucose values, basal insulin doses, episodes of symptomatic hypoglycaemia and days with/without fasting.

Participants who discontinued Gla-300 treatment during the study were observed until the end of the study. The IDF-DAR definitions for very high-, high- and moderate/low-risk in patients with diabetes who fast during Ramadan were considered by the physicians and used to determine the risk level of the participants in this study [9].

2.2. Inclusion and exclusion criteria

Eligible participants were adults (aged ≥ 18 years or at legal age of adulthood) with T2DM who were treated with Gla-300 as basal insulin for ≥ 8 weeks prior to inclusion in the study, who were planning to continue Gla-300 treatment during the Ramadan period and intended to fast for ≥ 15 days during Ramadan. Exclusion criteria included pregnancy or current breastfeeding status, the use of basal bolus or premix insulin in the 6 months prior to starting Gla-300 treatment, use of any investigational drug within 1 month/5 half-lives prior to selection visit, and known hypersensitivity/intolerance to Gla-300 (or its excipients).

2.3. Outcomes

The primary objective was to assess the percentage of participants experiencing ≥ 1 event of severe and/or symptomatic documented hypoglycaemia with self-monitored plasma glucose (SMPG) ≤ 70 mg/dL in the pre-Ramadan, Ramadan and post-Ramadan periods, with the primary endpoint analysed in the Ramadan period.

The secondary endpoints for hypoglycaemia included incidence of ≥ 1 event of severe and/or symptomatic documented hypoglycaemia with SMPG < 54 mg/dL, and event rates of severe and/or symptomatic documented hypoglycaemia with SMPG ≤ 70 mg/dL and < 54 mg/dL across the three time periods and by time of day. Assessment by time of day included daytime (06:00 am to 11:59 pm) and nocturnal (12:00 am to 05:59 am) during the pre-Ramadan and post-Ramadan periods, and fasting hours of the day (i.e. between the pre-dawn meal and meal at sunset) and non-fasting hours during the Ramadan period. Secondary effectiveness endpoints were mean change in HbA_{1c}, fasting plasma glucose (FPG) and SMPG, from pre- to post-Ramadan periods, and mean fasting SMPG in the evening (just before iftar) during the Ramadan period. Other endpoints included change in Gla-300 dose from pre-Ramadan to Ramadan and to post-Ramadan periods, and mean change in body weight from pre- to post-Ramadan periods. Adverse events (AEs), including episodes of hyperglycaemia, and serious adverse events (SAEs) were also reported.

2.4. Data analysis and statistics

Data were collected at the recruitment visit, and for the pre-Ramadan, Ramadan and post-Ramadan periods. A sample size of 430 participants was recommended to ensure sufficient precision for the primary endpoint (number of participants experiencing ≥ 1 episode of severe and/or symptomatic documented hypoglycaemia with SMPG ≤ 70 mg/dL, based on the 2-sided 95% confidence interval [CI] for the percentage of participants), while taking into account study duration and participant loss to follow-up. The secondary endpoint (number of participants experiencing ≥ 1 event of severe and/or symptomatic documented hypoglycaemia with SMPG < 54 mg/dL across the three periods) was analysed as per the primary endpoint analysis. The event rates of severe and/or symptomatic hypoglycaemia with SMPG ≤ 70 mg/dL and < 54 mg/dL during the pre-Ramadan, Ramadan, and post-Ramadan periods were analysed across 1–3 months for the pre-Ramadan period, across one month for the Ramadan period and across 1–2 months for the post-Ramadan period. The secondary endpoints of effectiveness, safety, Gla-300 dose and body weight were summarised using descriptive statistics.

3. Results

3.1. Demographics and participant characteristics

Overall, 502 participants were included in the study, of whom 493 (98.2%) were eligible for assessment; the majority of participants completed the study (466 [94.5%]) and continued to be treated with Gla-300 until the end of the study (488 [99.0%] participants at final evaluation).

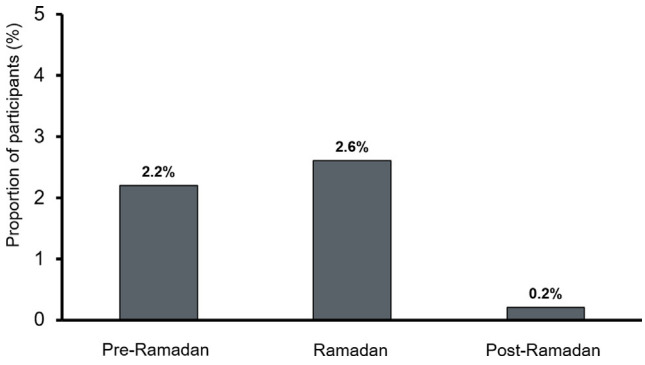

Fig. 1 – Proportion of participants with anytime severe and/or symptomatic documented hypoglycaemic events with SMPG ≤ 70 mg/dL. SMPG, self-monitored plasma glucose. No severe hypoglycaemic events occurred during the Ramadan or post-Ramadan periods.

At study initiation, the mean ± standard deviation (SD) participant age was 54.4 ± 11.0 years and 51.7% of participants were male (Table 1). The mean ± SD body mass index (BMI) was 29.7 ± 5.3 kg/m^2 and 77.5% of participants had a BMI of 25–40 kg/m^2. The median (Q1:Q3) duration of diabetes was 9.1 (5.0:15.0) years and almost half (230 [46.7%]) of the participants had a T2DM duration of ≥ 10 years; most of the participants were recent insulin users (median [Q1:Q3] 1.0 [0.3:3.0] year), with a median (Q1:Q3) Gla-300 treatment duration of 4.1 (3.0:9.0) months. Prior to study initiation (i.e. before the Ramadan period), Gla-300 dose adjustments were recommended every week for 134 (28.4%) participants and every 1–6 days for 206 (43.6%) participants, with an increment of two units per adjustment recommended for the majority of participants (398 [84.3%]). The mean ± SD individualised HbA_{1c} target was 6.9 ± 0.4% (52 ± 4 mmol/mol) and only 66 (15.3%) participants were at target during the pre-Ramadan period. The majority (404 [82.8%]) of the participants were considered to have moderate/low risk of complications when fasting, as determined by their physician. Three quarters (371 [75.3%]) of participants were treated with ≥ 2 non-insulin anti-hyperglycaemic treatments, and 222 (45.0%) participants were treated with sulfonylureas (Table 2).

In the pre-Ramadan period, the number of participants treated with ≥ 2 non-insulin anti-hyperglycaemic treatments was similar to the number at study initiation (391 [79.3%]; Table 2). Similar numbers of participants taking other classes of non-insulin treatments at study entry continued these treatments in the pre-Ramadan (Table 2) and Ramadan periods (data not shown).

The majority of participants (402 [85.0%]) fasted for the entire Ramadan period (mean duration of fasting [SD]: 30.1 days [3.2]). Of the 71 (15%) patients who broke their fast at least once, 65 (13.8%) fasted for ≥ 15 days. The recommended timing for Gla-300 dose injection was in the evening (at iftar) for 441 (93.2%) participants; all participants complied with this recommendation. Most participants (446 [94.1%])

reported full adherence to daily treatment (i.e. Gla-300 was administered every day of the Ramadan period).

3.2. Severe and/or symptomatic documented hypoglycaemia

The number of participants experiencing ≥ 1 event of severe and/or symptomatic documented hypoglycaemia with SMPG ≤ 70 mg/dL was low and similar in the pre-Ramadan (11 [2.2%], 95% CI; 1.1 to 4.0) and Ramadan (13 [2.6%], 95% CI; 1.4 to 4.5) periods, and was even lower in the post-Ramadan period (1 [0.2%], 95% CI; 0.0 to 1.1) (Fig. 1 and Supplementary Table 1). No participants reported severe hypoglycaemia in the Ramadan and post-Ramadan periods; a single participant (0.2%) reported severe hypoglycaemia during the pre-Ramadan period. In the Ramadan period, of the 13 participants who reported symptomatic documented hypoglycaemia (SMPG ≤ 70 mg/dL), 11 participants experienced this during fasting hours. The proportion of participants experiencing a daytime vs nocturnal severe and/or symptomatic hypoglycaemia event (SMPG ≤ 70 mg/dL) in pre-Ramadan was 1.6% vs 0.8% of participants respectively, while in post-Ramadan the proportion of participants experiencing either a daytime or nocturnal symptomatic event was 0.2% vs 0%. The event rates (per participant-month of follow up [PPM]) for severe and/or symptomatic documented hypoglycaemia with SMPG ≤ 70 mg/dL were 0.021 pre-Ramadan, 0.039 during Ramadan and 0.003 post-Ramadan. The single severe hypoglycaemic event in the pre-Ramadan period occurred during the daytime (event rate 0.001 PPM).

Of the 13 participants who reported those hypoglycaemic events during Ramadan, six participants (46%) were from Canada. Overall, 4 (0.8%, 95% CI; 0.2 to 2.1) participants experienced ≥ 1 event of severe and/or symptomatic documented hypoglycaemia at the lower SMPG threshold of < 54 mg/dL, all of which occurred within the pre-Ramadan period; of these, two participants (50%) were from Canada.

Table 1 – Participant demographics and disease characteristics at study initiation (eligible population).

	Gla-300 (N = 493)
Age, years, mean ± SD	54.4 ± 11.0
<65 years, n (%)	410 (83.2)
65–75 years, n (%)	67 (13.6)
≥75 years, n (%)	16 (3.2)
Gender, n (%)	
Male	255 (51.7)
Female	238 (48.3)
BMI, kg/m^2, mean ± SD	29.7 ± 5.3
<25, n (%)	93 (19.1)
25–30, n (%)	181 (37.2)
30–40, n (%)	196 (40.3)
≥40, n (%)	16 (3.3)
Duration of T2DM, years (median [Q1:Q3])	9.1 (5:15)
<10 years, n (%)	263 (53.3)
≥10 years, n (%)	230 (46.7)
HbA$_{1c}$, mean ± SD	
%	8.1 ± 1.3
mmol/mol	65 ± 14
Target HbA$_{1c}$, mean ± SD	
%	6.9 ± 0.4
mmol/mol	52 ± 4
Proportion at target HbA$_{1c}$ in pre-Ramadan period, n (%)	66 (15.3)
FPG, mg/dL, mean ± SD	144.3 ± 45.8
Presence of any complication or comorbidity (investigator-assessed), n (%)	192 (38.9)
Diabetic neuropathy	128 (26.0)
Diabetic retinopathy	65 (13.2)
Impaired renal function	71 (14.4)
Coronary heart disease	40 (8.1)
Risk level associated with fasting, determined by physician, n (%)	
Moderate/low risk	404 (82.8)
High risk	70 (14.3)
Very high risk	14 (2.9)
Time since first insulin treatment, years (median [Q1:Q3])	1.0 (0.3:3.0)
Duration of Gla-300 treatment, months (median [Q1:Q3])	4.1 (3.0:9.0)
Gla-300 dose, mean ± SD	
U	24.9 ± 12.2
U/kg	0.3 ± 0.14

BMI, body mass index; T2DM, type 2 diabetes.

Table 2 – Non-insulin anti-hyperglycaemic treatments taken prior to and during the Pre-Ramadan period.

	Prior to study initiation	Pre-Ramadan
	Gla-300 (N = 493)	
Number of non-insulin anti-hyperglycaemic treatments*, n (%)		
0	56 (11.4)	38 (7.7)
1	66 (13.4)	64 (13.0)
2	202 (41.0)	200 (40.6)
>2	169 (34.3)	191 (38.7)
Type of non-insulin anti-hyperglycaemic treatments, n (%)		
Any	437 (88.6)	455 (92.3)
Biguanides	366 (74.2)	382 (77.5)
DDP-4 inhibitors	232 (47.1)	245 (49.7)
Sulfonylureas	222 (45.0)	234 (47.5)
SGLT-2 inhibitors	118 (23.9)	131 (26.6)
GLP-1 receptor agonists	28 (5.7)	30 (6.1)
Thiazolidinediones	27 (5.5)	30 (6.1)
Alpha-glucosidase inhibitors	16 (3.2)	28 (5.7)
Glinides	5 (1.0)	6 (1.2)
Sulfonylurea treatment, n (%)	222 (45.0)	234 (47.5)
Glimepiride	99 (20.1)	106 (21.5)
Gliclazide	95 (19.3)	95 (19.3)
Glimepiride + metformin	7 (1.4)	7 (1.4)
Glimepiride + metformin + voglibose	7 (1.4)	7 (1.4)
Glimepiride + metformin hydrochloride	5 (1.0)	6 (1.2)
Glibenclamide + metformin hydrochloride	4 (0.8)	4 (0.8)
Glibenclamide	2 (0.4)	2 (0.4)
Gliclazide + metformin hydrochloride	1 (0.2)	1 (0.2)
Glimepiride + metformin hydrochloride + voglibose	1 (0.2)	4 (0.8)
Glimepiride + pioglitazone hydrochloride	1 (0.2)	1 (0.2)
Glipizide	0	1 (0.2)

*One month prior to Ramadan for the pre-Ramadan period.

3.3. *Change in glycaemic control parameters (HbA_{1c}, FPG and SMPG)*

Mean ± SD HbA_{1c} values were 8.1 ± 1.3% [65 ± 14 mmol/mol]) in the pre-Ramadan period. A reduction in HbA_{1c} was observed from the pre- to the post-Ramadan period (7.6 ± 1.1% [60 ± 12 mmol/mol]); the mean ± SD change was −0.4 ± 1.0% (−5 ± 11 mmol/mol, Fig. 2A). FPG (mean ± SD) was also reduced from the pre-Ramadan period (144.3 ± 45.8 mg/dL) to the post-Ramadan period (128.5 ± 37. 8 mg/dL); the mean ± SD change was −13.5 ± 44.1 mg/dL. Finally, a reduction in fasting SMPG (mean ± SD) was observed from the pre-Ramadan period (130.7 ± 32.9 mg/dL) to the post-Ramadan period (126.8 ± 28.5 mg/dL); the mean ± SD change was −3.3 ± 26.6 mg/dL. During Ramadan, mean ± SD fasting SMPG in the evening before iftar was 119.7 ± 27.1 mg/dL.

3.4. *Change in insulin dose*

The Gla-300 daily dose (mean ± SD) was 25.6 ± 11.9 U (0.32 ± 0.14 U/kg) in the pre-Ramadan period, and marginally decreased to 24.4 ± 11.5 U (0.30 ± 0.13 U/kg) in the Ramadan period; (mean ± SD change −1.2 ± 6.4 U/−0.015 ± 0.08 U/kg) (Fig. 2B). A relative reduction in Gla-300 dose of ≥ 15% in the Ramadan period was observed in 114 (24.1%) participants. In the post-Ramadan period, the mean ± SD daily Gla-300 dose was 26.0 ± 12.2 U (0.32 ± 0.14 U/kg), with a mean ± SD change of 0.36 ± 5.8 U/0.005 ± 0.07 U/kg from the pre- to post-Ramadan periods. Relative change was −0.020 ± 0.28 U or U/kg from pre-Ramadan to Ramadan and 0.035 ± 0.24 U or U/kg from pre-Ramadan to post-Ramadan.

3.5. *Change in body weight*

There was minimal change in body weight (mean ± SD) from the pre-Ramadan period (81.8 ± 14.9 kg) to the post-Ramadan period (81.4 ± 14.7 kg); the mean ± SD change was −0.5 ± 2.3 kg (Fig. 2C).

3.6. *Adverse events*

At least one AE was reported in 27 (5.5%) participants throughout the study period, including 15 (3.0%) participants during Ramadan (Table 3). Five participants had an SAE, including two (0.4%) participants who had an SAE during Ramadan; echinococciasis and ovarian adenoma (the latter led to discontinuation of Gla-300). One non-serious AE was considered related to Gla-300 (accidental overdose that did not occur during Ramadan). There were no deaths during the study period.

During the study, three (0.6%) participants had at least one AE of hyperglycaemia (Table 3); no events were considered serious, related to Gla-300 or resulted in discontinuation of Gla-300. Of these, 2 (0.4%) participants had hyperglycaemia AEs during Ramadan.

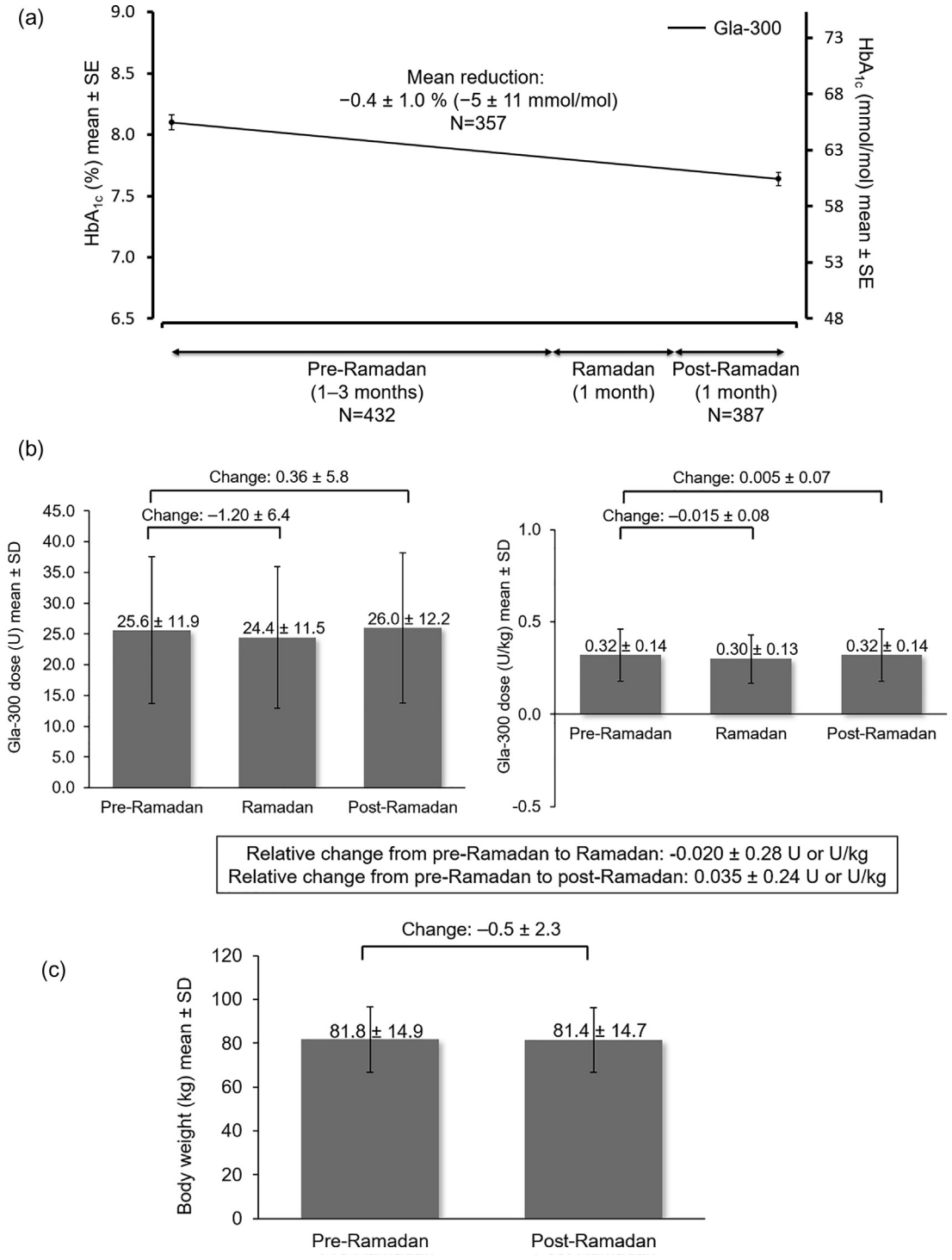

Fig. 2 – A) Mean HbA_{1c}, B) mean Gla-300 dose (U and U/Kg) and C) mean body weight pre-to post-Ramadan. SD, standard deviation; SE, standard error.

4. Discussion

The ORION study included over 490 Muslim participants with T2DM treated with Gla-300, the majority of whom fasted for the entire Ramadan period; mean diabetes duration was 10.7 years, and few participants (15.3%) were at their HbA_{1c} target in the pre-Ramadan period. The reported incidence and event rates of severe/and or symptomatic hypoglycaemia were low, HbA_{1c}, FPG and fasting SMPG levels were improved, and there was minimal Gla-300 dose adjustment and no weight change.

The reported incidence of severe and/or symptomatic documented hypoglycaemia at the $\leq$ 70 mg/dL SMPG threshold was low before, during and after Ramadan, and no severe and/or symptomatic hypoglycaemia with an SMPG < 54 mg/dL was reported during the Ramadan or post-Ramadan peri-

Table 3 – Adverse events (eligible population).

	Gla-300 (N = 493)	
	Throughout study	During Ramadan
Any AE	27 (5.5)	15 (3.0)
Any SAE	5 (1.0)	2 (0.4)
Any AE considered related to Gla-300	1 (0.2)	0
Any AE leading to discontinuation of Gla-300	1 (0.2)	1 (0.2)
Death	0	0
AEs		
Headache	4 (0.8)	2 (0.4)
Hyperglycaemia	3 (0.6)	2 (0.4)
Influenza	3 (0.6)	2 (0.4)
Diarrhoea	2 (0.4)	1 (0.2)

AE, adverse event; SAE, serious adverse event. AEs reported in > 1 participant are listed (except for AEs considered related to Gla-300 or leading to discontinuation of Gla-300).

ods. These findings are encouraging, given that at study initiation, approximately 75.3% of participants were treated with ≥ 2 concomitant non-insulin medications, and 45.0% of participants were treated with sulfonylureas. Event rates for severe and/or symptomatic documented hypoglycaemia at the ≤ 70 mg/dL SMPG threshold were generally low in all study periods. Events of severe and/or symptomatic documented hypoglycaemia at the ≤ 70 mg/dL SMPG threshold were recorded in 13 participants during the Ramadan period, with most events occurring during fasting hours of the day. Around half of the participants reporting those events were from Canada; the disproportionately large number of events recorded in Canada is likely due to the extended day length, in which fasting hours can last 18 h or more, potentially increasing the risk of hypoglycaemia [14]. For example, fasting hours in 2019 were approximately 02:59 am to 09:43 pm (18 h, 44 min) in Edmonton, Canada [15], compared with 03:38 am to 06:35 pm (14 h 57 min) in Riyadh, Saudi Arabia [16]. It should be noted that HbA_{1c} target achievement was higher at baseline in Canada than in the overall population (data not presented), which may have had an influence on hypoglycaemic risk.

HbA_{1c}, FPG and fasting SMPG levels improved from the pre-Ramadan to post-Ramadan period. However, fasting *per se* may have contributed to the reduction in HbA_{1c} [4,17,18]; significant reductions in HbA_{1c}, FPG and SMPG were observed in a recent epidemiological study of people with T2DM who fasted during Ramadan and were receiving various different treatment approaches [4].

The IDF-DAR guidelines recommend that people with T2DM who are at 'very high-' or 'high-risk' should not fast during Ramadan [6]; regional advice on this topic from Diabetes Canada is in line with IDF-DAR recommendations [14]. This recommendation was not strictly adhered to, as 14.3% of participants in ORION (which specifically recruited participants who intended to fast during Ramadan) were at high risk and 2.9% at very high risk; however the majority were at moderate/low-risk (82.8%). During Ramadan, Gla-300 injections were recommended at iftar, as per DAR recommendations for basal insulins [6]. In this study, all participants were advised to time their injection at iftar, and 93.2% of participants complied with this recommendation. A reduced (15–30%) insulin dose is also advised during Ramadan [6]; however, in this study, approximately one quarter of participants reduced their Gla-300 dose by ≥ 15%. The low percentage of participants implementing a Gla-300 dose change may be due to the fact that Gla-300 dose was generally already low in the pre-Ramadan period, and a large proportion of the participants (85.0%) were not at HbA_{1c} target (mean 6.9%). High HbA_{1c} levels (≥ 8%) in the pre-Ramadan period are common in participants in studies investigating the effects of fasting during Ramadan [7,19].

The ORION study adds to the current body of evidence on the management of T2DM in Muslim individuals who choose to fast during Ramadan. This evidence base includes a number of other studies, including the randomised controlled trial LixiRam (in which lixisenatide plus basal insulin was associated with lower rates of any hypoglycaemia compared with sulfonylurea plus basal insulin in participants with T2DM who fasted during Ramadan [20]) and the epidemiological studies CREED and DAR-MENA [3,7]. CREED was a large retrospective worldwide study in 13 countries [3] and DAR-MENA was a prospective, observational study in countries in the Middle East/North Africa region [7]. In CREED, the treatment regimen was modified before Ramadan for 39% of patients, and over 50% of participants fasted for the entire Ramadan period [3]. The majority of patients in CREED were treated with oral anti-hyperglycaemic drugs, with around 20% of participants treated with both oral anti-hyperglycaemic and injectable drugs and only 5% of participants receiving injectable medications alone. In DAR-MENA, 57.3% of participants fasted for the duration of Ramadan; only one third were treated with insulin, 62% of whom changed their dose [7]. In contrast, in the ORION study a higher percentage of participants (85.0%) fasted for the duration of Ramadan, all received insulin and the majority (88.6%) received non-insulin anti-hyperglycaemic treatments alongside insulin. It is interesting to note that, despite the lower proportion of participants receiving insulin in CREED and DAR-MENA compared with ORION, both studies reported a higher incidence of hypoglycaemia compared with ORION. In CREED, 8.8% of participants experienced hypoglycaemia over the whole study period

(event rate data not available), while incidence was 4.4% pre-Ramadan (event rate 0.11 events/month/participant) and 10.4% in Ramadan (event rate 0.22 events/month/participant) in DAR-MENA [3,7]. Incidence of hypoglycaemia in ORION, in contrast, was 2.2% pre-Ramadan (event rate 0.021 per participant-month), 2.6% in Ramadan (event rate 0.039 per participant-month) and 0.2% post-Ramadan (event rate 0.003 per participant-month). The lower risk of hypoglycaemia observed in ORION may have empowered more participants to fast for the entire duration of Ramadan. One possible explanation for the lower risk of hypoglycaemia in ORION could be that all participants received the second-generation basal insulin analogue, Gla-300. In a meta-analysis of participants with T2DM receiving Gla-300 vs Gla-100, Gla-300 provided comparable glycaemic control, with less hypoglycaemia, compared with Gla-100 [21]. In contrast, in CREED and DAR-MENA the insulin type was not specified [3,7] and would likely have included first-generation and intermediate-acting insulins.

Regarding study limitations, it should be noted that the number of participants varied by region, and that geographical and cultural diversity between Canada and the other countries (e.g. length of the fasting day and working hours) may have impacted the results. The population in ORION may be representative of people with T2DM treated with Gla-300 who consider themselves well enough to fast, as we only included those who intended to fast for $\geq$ 15 days; the majority of participants were ranked as moderate/low-risk according to IDF-MENA guidelines. Consequently, these data may not fully reflect the safety of Gla-300 in a very high/high-risk population according to the IDF-DAR guidelines.

5. Conclusion

In the present study, we report that in a real-life clinical practice setting, the use of Gla-300 as basal insulin was associated with positive outcomes in Muslim individuals with T2DM who chose to fast during Ramadan. Overall, the incidence of severe and/or symptomatic hypoglycaemia was low, with no severe hypoglycaemic events reported during Ramadan, while HbA_{1c} levels were reduced, corresponding to a clinical improvement. These data support the use of Gla-300 as basal insulin for people with T2DM and who intend to fast during the Ramadan period.

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Conflicts of interest

Baptiste Berthou: employee of Sanofi.

Mohamed Hassanein: attended advisory board for Sanofi, Boehringer Ingelheim and Novo Nordisk; speaker for Eli Lilly, Janssen, LifeScan, Merck Sharp and Dohme, Novo Nordisk, and Sanofi; received lecture/other fees from Sanofi, Novo Nordisk, Eli Lilly, Merck Sharp and Dohme, Janssen and LifeScan.

Mehmet Akif Buyukbese: has received speaker fees from Eli Lilly and speaker/other fees from Novartis and Sanofi pharmaceutical companies.

Rachid Malek: has received speaker fees and advisory board honoraria from Novo Nordisk.

Mubarak Naqvi: employee of Sanofi.

Valérie Pilorget: employee of Sanofi.

Rakesh Kumar Sahay: advisory board member for Boehringer Ingelheim, Dr Reddys Laboratories, Eli Lilly, and Sanofi; speaker for Boehringer Ingelheim, Eli Lilly, Novo Nordisk, and Sanofi.

Inass Shaltout: speaker and advisory board member for Sanofi, Novartis, MSD, AstraZeneca, Novo Nordisk, Lilly, Servier and Abbott.

Author contributions

MH, VP and MN were involved in the conception and design of the study, and MH, IS and RKS were involved in the conduct of the study and in data acquisition. All authors contributed to the data analysis or interpretation of the results and critically revised, provided final approvals of, and are accountable for the accuracy and integrity of the manuscript.

Data sharing

Qualified researchers may request access to patient-level data and related study documents including the study report, study protocol with any amendments, blank case report form, statistical analysis plan and dataset specifications. Patient-level data will be anonymised and study documents will be redacted to protect the privacy of the study participants. Further details on Sanofi's data sharing criteria, eligible studies, and process for requesting access can be found at: https://www.clinicalstudydatarequest.com.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2020.108189.

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