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Safety of lixisenatide versus sulfonylurea added to basal insulin treatment in people with type 2 diabetes mellitus who elect to fast during Ramadan (LixiRam): An international, randomized, open-label trial

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ABSTRACT

Aims: Adding lixisenatide to basal insulin (BI) instead of sulfonylurea (SU), versus continuing SU + BI was assessed in people with type 2 diabetes mellitus (T2DM) who intended to fast during Ramadan 2017.

Methods: LixiRam (NCT02941367) was a phase 4, randomized, open-label, 12–22-week study in people with T2DM insufficiently controlled with SU + BI ± 1 oral anti-diabetic. Endpoints included the percentage of participants with ≥1 documented symptomatic hypoglycemia event (plasma glucose ≤70 mg/dL; primary endpoint) and any hypoglycemia during Ramadan fasting.

Results: A numerically lower percentage of participants with lixisenatide + BI (3.3%, 3/91) versus SU + BI (8.9%, 8/90) had ≥1 documented symptomatic hypoglycemia event (intent-to-treat visit 4) during Ramadan fasting (OR: 0.34; 95% CI 0.09, 1.35; proportion difference −0.06, 95% CI −0.13, 0.01); the difference was statistically significant for the 'any hypoglycemia' category (lixisenatide + BI: 4.3%, 4/92; SU + BI: 17.4%, 16/92; OR: 0.22; 95% CI 0.07, 0.68; proportion difference −0.13, 95% CI −0.22, −0.04; intent-to-treat). No new treatment-emergent adverse events occurred.

Conclusions: Compared with SU + BI, lixisenatide + BI provided lower rates of any hypoglycemia in people with T2DM during Ramadan fasting. Lixisenatide + BI therapy may be a suitable treatment option during fasting.

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1. Introduction

Fasting during the holy month of Ramadan is common among people with type 2 diabetes mellitus (T2DM) [1,2], despite the potential risk of acute complications including severe hypoglycemia, hyperglycemia, dehydration, thrombosis, dyslipidemia, and deterioration of glycemic control [1,3–7]. However, fasting risks can be mitigated in patients with well-controlled diabetes who are compliant with their diet and medication regimen (taking medications that have a lower propensity to cause hypoglycemia), and follow suitable pre-Ramadan advice on managing diabetes during fasting [6,8–13].

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) may be an advantageous treatment strategy for T2DM during Ramadan due to their efficacy, safety, tolerability, and pleiotropic benefits according to recently published guidelines, which reviewed evidence supporting the use of GLP-1 RAs during Ramadan [13,14]. This class of anti-hyperglycemic agents are likely to aid patient adherence due to low frequency of injections versus basal bolus and premixed insulin, flexible timing of administration, and availability as fixed-ratio combinations in certain markets [14]. People with T2DM treated with basal insulin (BI) are considered at moderate/low risk of acute complications for fasting according to the International Diabetes Federation and the Diabetes and Ramadan International Alliance (IDF-DAR) guidelines [13]. In this group of people with suboptimal control, uptitration of the BI dose could increase the risk of hypoglycemia. GLP-1 RAs are a potential add-on therapeutic option, which could help minimize this risk due to their multiple impacts on the ominous octet of pathophysiologic disturbances present in T2DM and glucose-dependent mechanism of action [15]. However, there are no randomized controlled trials that have investigated the use of GLP-1 RAs as an add-on to BI during Ramadan fasting.

Lixisenatide is a once-daily, short-acting, prandial GLP-1 RA that may be effective and well tolerated during Ramadan fasting due to its effect on post-prandial glycemic excursion (prandial GLP-1 RA), and a relatively low risk of hypoglycemia [16]. This study investigated adding lixisenatide to BI instead of sulfonylurea (SU), versus continuing SU + BI in people with T2DM who elected to fast during Ramadan. The primary objective was to compare the safety of these therapeutic approaches in terms of hypoglycemia. Secondary objectives included the efficacy and general safety of this regimen before, during, and after Ramadan fasting.

2. Subjects, materials and methods

2.1. Study design

The LixiRam study was a phase 4, international, multi-center, randomized, open-label, parallel-group, clinical trial (ClinicalTrials.gov: NCT02941367). The study was conducted at 16 hospitals/clinic sites in five countries (India, Israel, Kuwait, Lebanon, and Turkey) around the 2017 Ramadan period (February 18 to August 4, 2017); the 2017 Ramadan fast occurred between May 27 and June 24/25.

The trial consisted of a ≤2-week screening period, followed by the 12–20-week whole treatment period (8–12 weeks pre-Ramadan, 29–30 days of Ramadan, and 0–4 weeks post-Ramadan) (Fig. 1). Post-Ramadan included '0 weeks' as some participants were assessed on the last day of Ramadan. The pre-Ramadan period included a medical assessment, pro-

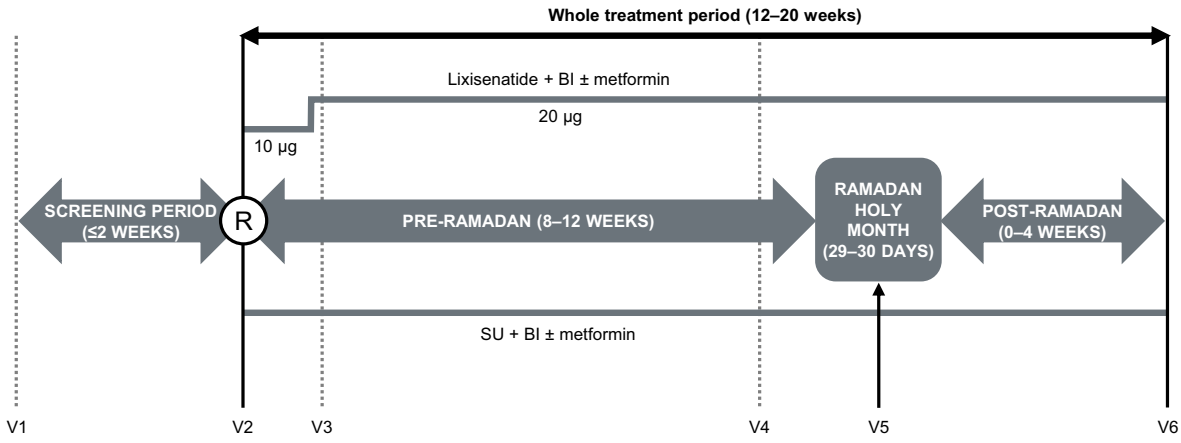

Fig. 1 – Study design. Ramadan started on May 27, 2017 (all countries) and ended on June 25, 2017 (India) and June 24, 2017 (all other countries). Visits: V1: Week −1 ± 1 week; V2: Day 1; V3: 4 weeks ± 3 days; V4: 2 weeks ± 2 weeks prior to the start of Ramadan and >8 weeks after V2; V5: 2 weeks ± 3 days after Ramadan start; V6: 2 weeks ± 2 weeks after end of Ramadan. BI: basal insulin, R: randomization, SU: sulfonylurea, V: visit.

vided diet and lifestyle advice, and refined treatment to maximize safe fasting in line with guideline recommendations [3].

Participants with T2DM (diagnosed for ≥1 year) insufficiently controlled with SU + BI (≤50% of the maximum allowed dose) ± one oral anti-diabetic drug (OAD) who expressed the intention to fast during Ramadan and provided written informed consent were included in the study. Exclusion criteria are listed in Supplementary Table 1.

Eligible participants were randomized 1:1 without stratification, according to a randomization scheme provided by the study biostatistician, to receive BI ± existing metformin plus either open-label subcutaneous lixisenatide (identified with treatment kit numbers generated by Sanofi) or oral open-label SU (provided according to local regulations). All other OADs were stopped at randomization. The investigator/designee contacted the Interactive Response Technology for the participant number at screening and to allocate the treatment arm at randomization. The inclusion of participants with suboptimal SU treatment (≤50% of the maximum allowed dose) enabled dose adjustment after randomization. The maximum dose for each SU was as follows: glibenclamide: 15 mg, gliclazide: 320 mg, glimepiride: 8 mg, glipizide: 20 mg, and diapride forte: 8 mg.

Participants documented fasting self-measured plasma glucose (SMPG) values and reported all events that they believed might have an impact on dose adjustment (such as hypoglycemia, an increase in routine exercise, a change in routine diet, intercurrent illness, etc.) in participant diaries. Treatment compliance was monitored by counting tablets/pens at each visit and monitoring recorded dosing information.

The manuscript was prepared in line with the Consolidated Standards of Reporting Trials (CONSORT) guidelines [18]. The study was designed and monitored in accordance with Good Clinical Practice and the Declaration of Helsinki (1964), and all applicable amendments. The study also complied with the laws and regulations, as well as any applicable guidelines, of the countries where the study was conducted. Each participant provided written informed consent.

2.2. *Interventions*

The IDF-DAR 'Diabetes and Ramadan: Practical Guidelines' were suggested as a resource for treatment during Ramadan fasting [18].

For the lixisenatide + BI arm, lixisenatide was to be administered once daily, within 1 h before a meal, starting at a dose of 10 μg at randomization and increased to 20 μg after 2 weeks. During the Ramadan fast, lixisenatide was administered within 1 h prior to iftar (meal after sunset). If participants did not tolerate the 20 μg lixisenatide dose, the guidance from the summary of product characteristics (SmPC) was followed [16].

For the SU + BI arm, SU was started at the same dose and timing/frequency of administration used previously, and could be adjusted based on glycemic control and hypoglycemia risk at the investigator's discretion. During the Ramadan fast, SU was to be administered at iftar, if taken once-daily, and at suhur (predawn meal) and iftar, if taken twice-daily. In participants with well-controlled blood glucose levels, the SU dose could be reduced at iftar for once-daily SU and should be reduced at suhur for twice-daily SU. Second-generation SUs should be used in preference and older SUs should be avoided due to higher risk of hypoglycemia, in line with the IDF-DAR guidelines [18].

Participants continued on the BI (not considered as an investigational medicinal product) taken prior to screening. For the lixisenatide + BI arm, the starting BI dose could be reduced by 20% if the patient's glycated hemoglobin (HbA1c) was ≤8.0% (64 mmol/mol), and was to be kept stable for the first 4 weeks and then adjusted weekly according to SMPG values, following the guidance from the SmPC [16]. For the SU + BI arm, BI was started at the same dose previously used and was to be adjusted weekly according to fasting SMPG values during the pre-Ramadan period. In both arms, BI was to be adjusted weekly according to the target fasting plasma glucose (FPG), which was 80–130 mg/dL outside the month of Ramadan and 90–130 mg/dL during Ramadan. BI doses could be reduced or modified at any time for hypoglycemia. Other details, such as the timing of the dose change and dosing timing, were left to the discretion of the investigators.

During Ramadan fasting, switching from twice-daily to once-daily BI administration (at randomization) by reducing total insulin dose (e.g., by 30%) was recommended for both treatment arms [3,18]. If used prior to the study, metformin (not considered as an investigational medicinal product) was to be continued at the same dose used prior to the study and kept stable (unless there was a specific safety issue related to this treatment requiring a dose descrease). Lifestyle and diet therapy were continued as previously established prior to the start of the trial.

2.3. *Endpoints*

The primary endpoint was the percentage of participants with ≥1 documented symptomatic hypoglycemia event (plasma glucose ≤70 mg/dL) during Ramadan fasting.

Secondary safety endpoints included the percentage of participants with ≥1 any hypoglycemia event from baseline to pre-Ramadan fasting, during Ramadan fasting, and during the whole treatment period. A post hoc analysis included the incidence of any hypoglycemia. The American Diabetes Association and the Endocrine Society classification was used to define hypoglycemia categories [19]. The 'any hypoglycemia' category included severe hypoglycemia, documented symptomatic hypoglycemia (≤70 mg/dL and <54 mg/dL), relative hypoglycemia (>70 mg/dL), asymptomatic hypoglycemia (≤70 mg/dL and <54 mg/dL), and probable symptomatic hypoglycemia. The whole treatment period included pre-Ramadan, Ramadan, and post-Ramadan, and was defined from first day of study drug administration to last day of study drug administration + 3 days. Pre-Ramadan period was defined as the period between baseline (visit 2) to pre-Ramadan visit (visit 4). Ramadan fast was defined from the start to end of Ramadan.

Secondary efficacy endpoints included mean change in HbA1c, body weight, and treatment dose (BI, lixisenatide, and SU) from baseline (visit 2) to the pre-Ramadan visit (visit 4) and post-Ramadan visit (visit 6). Post hoc analyses included the number of participants using the maximum treatment dose, the type of SU used, the number of days fasted, hypo-

glycemia events for Ramadan fasting over 24 hours, and the distribution of the number of hypoglycemic events by participant.

Adverse events were reported by the participant or noted by the investigator. Treatment-emergent adverse events (TEAEs) were reported for the Pre-Ramadan period, Ramadan on-treatment period, and whole treatment period. Ramadan on-treatment period was defined from pre-Ramadan visit (visit 4) to post-Ramadan visit (visit 6) or last day of study drug administration + 3 days, whichever came first.

2.4. Statistical analysis

The intent-to-treat (ITT) population (efficacy endpoints) was defined as all randomized participants treated at least once with the study treatment and grouped according to randomization assignment. The primary endpoint used the ITT visit 4 (ITT-V4) population, defined as participants included in the ITT population who were on study treatment and assessed at the pre-Ramadan visit 4. Secondary endpoints used the ITT population. The safety population (safety endpoints) included all randomized participants treated at least once with the study treatment grouped according to treatment actually received.

Percentage of participants with ≥1 documented symptomatic hypoglycemia event and any hypoglycemia event was analyzed using a logistic regression model with estimated odds ratio (OR) and 95% confidence interval (CI). Proportion difference (95% CI) was evaluated during post hoc analysis. Change in HbA1c and body weight was analyzed using a mixed-model for repeated measures and assessed with least squares (LS) mean change. The estimated difference between treatment groups and two-sided 95% CIs were calculated for HbA1c. Safety analyses were descriptive.

The sample size was computed to ensure a sufficient precision for the assessment of the OR of lixisenatide versus SU for the primary endpoint, assuming 53% of people receiving SU and 15% receiving lixisenatide had at least one documented symptomatic hypoglycemia event during the Ramadan fast (OR: 0.54). Assuming a dropout rate of 15%, the estimated required sample size was 236 participants, with 118 in each of the two treatment groups. No imputation was made for participants with missing or incomplete data.

3. Results

3.1. Population demographics and clinical characteristics

A total of 184 participants was randomized (lixisenatide + BI: n = 92; SU + BI: n = 92; Supplementary Fig. 1) and five participants discontinued the study prematurely, three in the lixisenatide arm and two in the SU arm.

Patient demographics and characteristics at baseline were comparable between treatments (Table 1). Participant mean age was 53.4 years (14.1% were ≥65 years), mean body mass index was 29.4 kg/m^2, and mean disease duration was 7.3 years. A total of 173 participants (94.0%) were receiving >1 OAD, and 159 participants (86.4%) were receiving long-acting BI at screening. HbA1c at baseline was slightly higher in the lixisenatide + BI arm (8.7% [72 mmol/mol]) versus the SU + BI arm (8.5% [69 mmol/mol]). For people receiving SU, the most common were glimepiride (76.1%), gliclazide (10.9%), and glibenclamide (4.3%).

3.2. Number of fasted days

The mean ± standard deviation (SD) number of days fasted during Ramadan was 26.9 ± 5.9 days for lixisenatide + BI (n = 85) and 27.7 ± 3.4 days for SU (n = 86). The median number of days was 29.0 for both treatment arms.

3.3. Hypoglycemia events

3.3.1. Participants with at least one documented symptomatic hypoglycemia event

During the pre-Ramadan period, the percentage of participants experiencing ≥1 documented symptomatic hypoglycemia event (≤70 mg/dL) was 2.2% (2/91) for lixisenatide + BI and 8.9% (8/90) for SU + BI (OR: 0.20; 95% CI 0.04, 0.99; proportion difference −0.07 [95% CI −0.13, −0.00]; ITT-V4 population). During Ramadan fasting, a numerically lower percentage of participants receiving lixisenatide + BI (3.3%, 3/91) compared with those receiving SU + BI (8.9%, 8/90) had ≥1 documented symptomatic hypoglycemia event (OR: 0.34; 95% CI 0.09, 1.35; proportion difference −0.06 [95% CI −0.13, 0.01]; ITT-V4 population). During the whole treatment period, the percentage of participants experiencing ≥1 documented symptomatic hypoglycemia event (≤70 mg/dL) was 4.4% (4/91) with lixisenatide + BI and 16.7% (15/90) with SU + BI (OR: 0.22; 95% CI 0.07, 0.70; proportion difference −0.12 [95% CI −0.21, −0.04]; ITT-V4 population). See Supplementary Table 2 for documented symptomatic hypoglycemia event (≤70 mg/dL) results using the ITT population.

3.3.2. Any hypoglycemia

During the whole treatment period, and for both the pre-Ramadan period and during Ramadan fasting, the percentage of participants experiencing any hypoglycemia event was significantly lower with lixisenatide + BI versus SU + BI (ITT population; Fig. 2A). The percentage of participants experiencing any hypoglycemia events was 3.3%, 4.3%, and 5.4% with lixisenatide + BI versus 15.2%, 17.4%, and 26.1% with SU + BI during the pre-Ramadan period (OR: 0.17; 95% CI 0.05, 0.61; proportion difference −0.12 [95% CI −0.20, −0.04]), Ramadan fasting period (OR: 0.22; 95% CI 0.07, 0.68; proportion difference −0.13 [95% CI −0.22, −0.04]), and whole treatment period (OR lixisenatide + BI versus SU + BI: 0.16; 95% CI 0.06, 0.44; proportion difference −0.21 [95% CI −0.31, −0.11]), respectively. The number of any hypoglycemia events was numerically lower with lixisenatide + BI versus SU + BI for all periods (Fig. 2B); the number of any hypoglycemia events was 7, 8, and 16 for lixisenatide + BI and 45, 30, and 77 for SU + BI for the pre-Ramadan, Ramadan fasting, and whole treatment period (including the post-Ramadan period), respectively.

The proportion of participants experiencing any hypoglycemia during Ramadan fasting according to type of SU was as follows: diapride forte: 1/3 (33.3%); gliclazide: 3/10

Table 1 – Patient demographics and clinical characteristics at baseline (ITT population).

	Lixisenatide + BI (n = 92)	SU + BI (n = 92)	All (n = 184)
Age (years)	52.6 ± 9.5	54.1 ± 10.6	53.4 ± 10.1
Age category, n (%)			
<65 years	81 (88.0)	77 (83.7)	158 (85.9)
≥65 years	11 (12.0)	15 (16.3)	26 (14.1)
Female, n (%)	52 (56.5)	49 (53.3)	101 (54.9)
Weight (kg)	76.0 ± 14.6	75.0 ± 11.6	75.5 ± 13.2
BMI (kg/m^2)	29.7 ± 5.3	29.0 ± 4.3	29.4 ± 4.8
Diabetes duration (years)	7.1 ± 4.8	7.4 ± 5.4	7.3 ± 5.1
HbA1c, % (mmol/mol)[a]	8.7 ± 0.7 (72 ± 8)	8.5 ± 0.7 (69 ± 8)	8.6 ± 0.7 (70 ± 8)
HbA1c, n (%)[a]			
<7.5	0	0	0
7.5–8.0	17 (18.7)	29 (32.2)	46 (25.4)
8.0–10.0	71 (78.0)	60 (66.7)	131 (72.4)
≥10.0	3 (3.3)	1 (1.1)	4 (2.2)
FPG (mg/dL)[a]	174.8 ± 57.7	167.6 ± 63.1	171.2 ± 59.5
Pre-breakfast SMPG (mg/dL)[a]	165.8 ± 48.6	144.1 ± 37.8	155.0 ± 45.0
OADs, n (%)			
1	5 (5.4)	6 (6.5)	11 (6.0)
2	76 (82.6)	79 (85.9)	155 (84.2)
>2	11 (12.0)	7 (7.6)	18 (9.8)
Biguanides (metformin), n (%)	85 (92.4)	85 (92.4)	170 (92.4)
SU, n (%) / mg[b]			
Glibenclamide	–	4 (4.3) / 7.8 ± 2.6	–
Gliclazide	–	10 (10.9) / 76.7 ± 33.9	–
Glimepiride	–	70 (76.1) / 3.5 ± 1.0	–
Glipizide	–	3 (3.3) / 8.3 ± 2.9	–
Diapride forte[c]	–	3 (3.3) / 4.0 ± 0.0	–
BI therapy, n (%)			
Intermediate acting	12 (13.0)	12 (13.0)	24 (13.0)
Long acting	80 (87.0)	79 (85.9)	159 (86.4)
Intermediate or long acting combined with RAI	0	1 (1.1)	1 (0.5)
BI dose (U)	23.8 ± 15.9	22.4 ± 17.1	23.1 ± 16.5

Data are expressed as mean ± standard deviation unless stated otherwise.

BI: basal insulin, BMI: body mass index, FPG: fasting plasma glucose, HbA1c: glycated hemoglobin, ITT: intent-to-treat, OAD: oral anti-diabetic drug, RAI: rapid-acting insulin, SMPG: self-measured plasma glucose, SU: sulfonylurea.

[a] HbA1c data were missing for one participant in the lixisenatide + BI arm and two participants in the SU + BI arm, FPG data were missing for one participant in the lixisenatide + BI arm and four participants in the SU + BI arm, pre-breakfast SMPG data were missing for seventeen participants in the lixisenatide + BI and eighteen participants in the SU + BI arm.

[b] Type of SU was missing for two participants; one participant used glibenclamide at baseline and glimepiride post-baseline.

[c] Combination of glimepiride and metformin.

(30.0%); glimepiride: 12/71 (16.9%); glibenclamide: 0/3 (0%); glipizide: 0/3 (0%); and unspecified SU: 0/2 (0%).

During the whole treatment period, the proportion of participants who experienced more than one 'any hypoglycemia' event was numerically lower with lixisenatide + BI (4 participants) versus SU + BI (14 participants) (Supplementary Table 3).

The incidence of any hypoglycemia over 24 hours was measured during the Ramadan fasting period. The incidence of any hypoglycemia was lower with lixisenatide + BI versus SU + BI in almost all 2-hour time periods over 24 hours during the Ramadan fast (Fig. 3). During the fasting period of the day, no participants experienced any hypoglycemia events in the lixisenatide + BI arm whereas in the SU + BI arm, people experienced hypoglycemia events during the estimated fasting hours of 04:00–20:00 (11/92 [12.0%] experiencing events; 15 events) with the highest rates of hypoglycemia occurring during the last 3–4 hours of the fast.

Severe hypoglycemia was rare; one episode of severe hypoglycemia was reported in the SU + BI arm by one participant (SMPG value of 70 mg/dL) during the Ramadan fast, which required assistance for oral carbohydrate administration (Supplementary Table 2).

3.4. *Treatment dose*

There was no clinically relevant change in insulin dose during the study period. The mean ± SD BI dose at baseline was 23.7 ± 16.0 U for lixisenatide + BI (n = 91) and 22.5 ± 17.3 U for the SU + BI (n = 88). The LS mean change ± standard error (SE) in BI dose from baseline to the pre-Ramadan visit and from baseline to the post-Ramadan visit was 2.0 ± 0.4 U (95% CI 1.3, 2.7; n = 91) and 2.4 ± 0.6 U (95% CI 1.2, 3.7; n = 89) for lixisenatide + BI, and 2.1 ± 0.4 U (95% CI 1.4, 2.8; n = 88) and 3.2 ± 0.6 U (95% CI 2.0, 4.5; n = 87) for SU + BI, respectively. Similarly, there was no clinically significant change in SU dose, by SU type, during the study period (Supplementary Table 4).

The percentage of participants who had reached the maximum dose with lixisenatide (20 μg) during the whole treat-

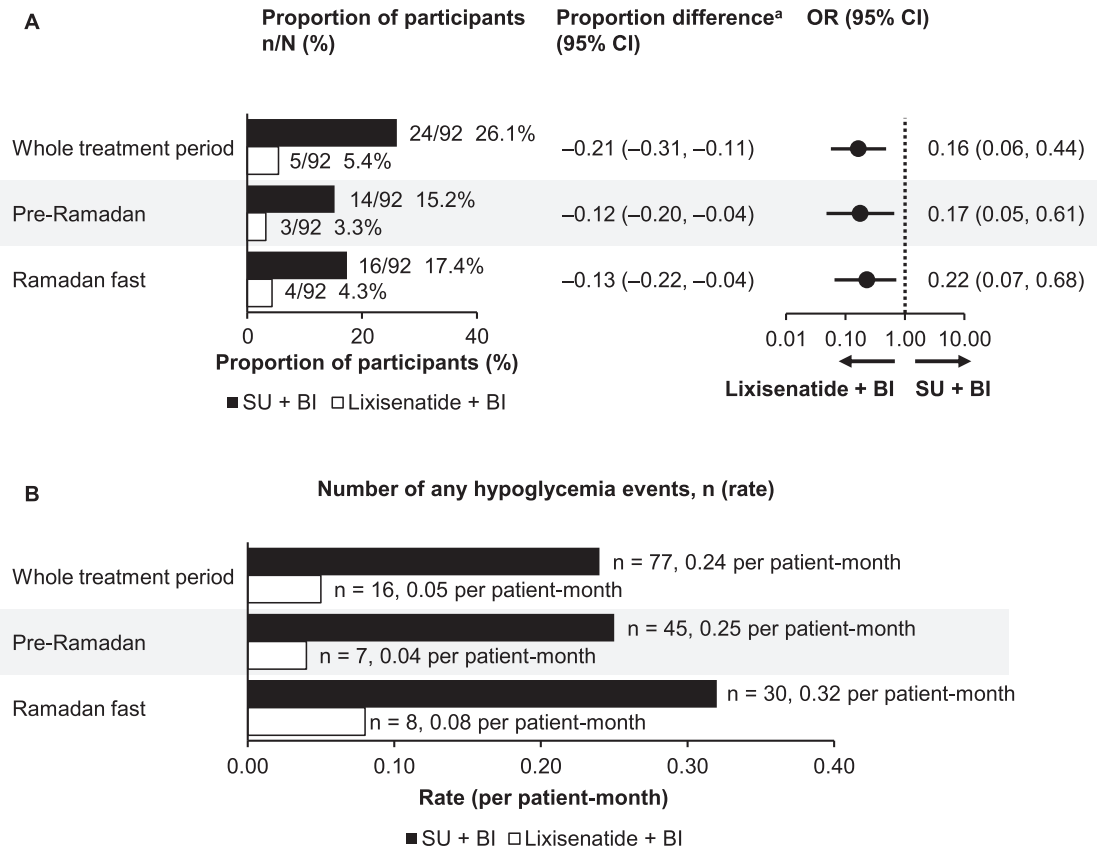

Fig. 2 – Any hypoglycemia event. (A) Proportion of participants with ≥1 hypoglycemia event; (B) Number of hypoglycemia events (ITT population). [a] Lixisenatide versus SU. BI: basal insulin, CI: confidence interval, ITT: intent-to-treat, OR: odds ratio, SU: sulfonylurea.

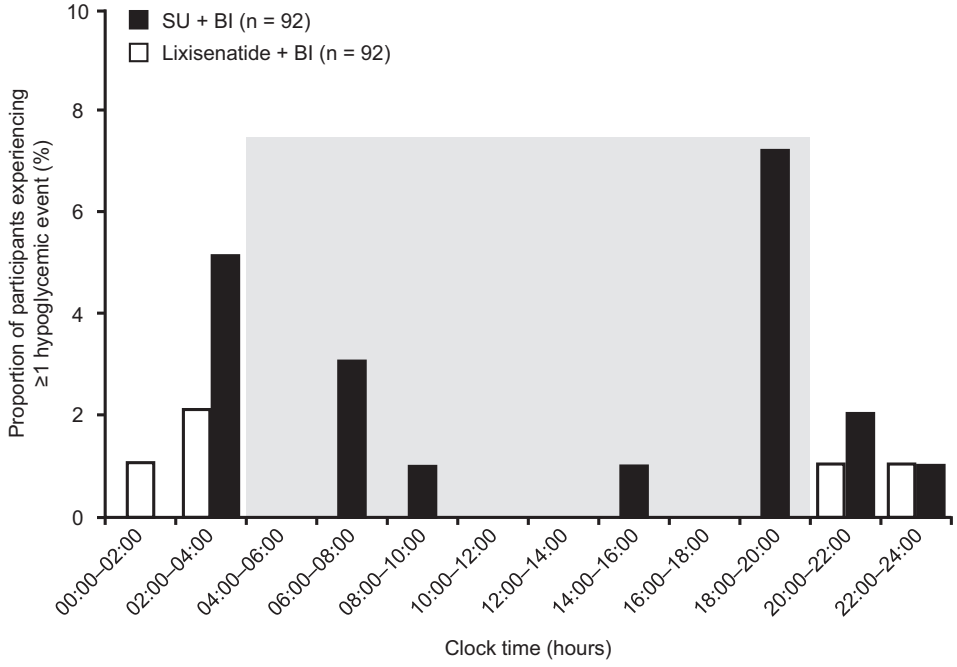

Fig. 3 – Incidence of any hypoglycemia event by time of day during the Ramadan fast (safety population). BI: basal insulin, SU: sulfonylurea. The shaded area displays the approximate daily fasting period during Ramadan.

ment period was 98.9% (91/92). No participants reached the maximum dose with SU during treatment, and SU was used at a suboptimal dose (<50%) during the entire study period in most instances; there were six participants with SU doses >50% (glimepiride: n = 3; glibenclamide: n = 3). However, it should be noted that this study enrolled participants with suboptimal SU treatment defined as ≤50% of the maximum allowed dose, and SU treatment was started at the same dose and timing/frequency of administration used previously. It was advised to reduce SU dose if the participant was well controlled according to blood glucose values.

All participants were 80–100% treatment compliant, defined as the actual number of days with at least one administration of the study drug compared to the planned number of days with the administration during the treatment period up to discontinuation, for both treatment arms.

3.5. *Secondary efficacy endpoints*

3.5.1. *HbA1c*

Changes in HbA1c from baseline during the study period were similar between treatment arms (baseline HbA1c mean ± SD: lixisenatide + BI: 8.7 ± 0.7% [72 ± 8 mmol/mol], n = 90; SU + BI: 8.5 ± 0.7% [69 ± 8 mmol/mol], n = 88). The LS mean ± SE HbA1c change from baseline to the pre-Ramadan visit was −0.4 ± 0.1% (95% CI −0.6, −0.2; −4 ± 1 mmol/mol [95% CI −7, −2]; n = 90) for lixisenatide + BI and −0.5 ± 0.1% (95% CI −0.7, −0.3; −6 ± 1 mmol/mol [95% CI −8, −3]; n = 88) for SU + BI. The LS ± SE mean difference between groups was 0.1 ± 0.1% (95% CI −0.2, 0.3; 1 ± 1 mmol/mol [95% CI −2, 3]; p = 0.7222). The LS mean ± SE HbA1c change from baseline to the post-Ramadan visit was −0.4 ± 0.1% (95% CI −0.7, −0.2; −4 ± 1 mmol/mol [95% CI −8, −2]; n = 89) for lixisenatide + BI and −0.5 ± 0.1% (95% CI −0.7, −0.3; −6 ± 1 mmol/mol [95% CI −8, −3]; n = 88) for SU + BI. The LS ± SE mean difference between groups was 0.1 ± 0.2% (95% CI −0.3, 0.4; 1 ± 2 mmol/mol [95% CI −3, 4]; p = 0.7387).

3.5.2. *Body weight*

The LS mean ± SE change from baseline to the pre-Ramadan visit was −1.2 ± 0.2 kg for lixisenatide + BI and −0.7 ± 0.2 kg for SU + BI. The LS mean difference between groups was −0.5 (95% CI −1.1, 0.2). The LS mean ± SE change from baseline to the post-Ramadan visit was −2.1 ± 0.3 for lixisenatide + BI and −1.4 ± 0.3 kg for SU + BI. The LS mean difference between groups was −0.6 (95% CI −1.4, 0.1).

3.6. *Treatment-emergent adverse events*

TEAEs during the Ramadan on-treatment period were similar between lixisenatide + BI (17.4%) and SU + BI (16.3%; Table 2). The incidence of TEAEs occurring during the whole treatment period was 45.7% with lixisenatide + BI and 22.8% with SU + BI; TEAEs with lixisenatide + BI were largely due to increased gastrointestinal disorders, which predominantly occurred during the pre-Ramadan period (Table 2). For lixisenatide + BI, gastrointestinal TEAEs were lower during the Ramadan on-treatment period (4.3%) compared to the pre-Ramadan period (23.9%). Gastrointestinal TEAEs for SU + BI were low for both periods. No new TEAEs were reported; there were no new safety concerns for lixisenatide + BI during the Ramadan on-treatment period.

4. Discussion

This clinical trial assessed the safety of switching from SU to lixisenatide in combination with BI compared with continuing SU + BI in people with T2DM who elected to fast during Ramadan. Participants were randomized to parallel treatment groups before switching to lixisenatide or continuing with SU. The study provides evidence that reflects Ramadan fasting in a real-life scenario.

The proportion of participants experiencing ≥1 documented symptomatic hypoglycemia event during Ramadan fasting (the primary endpoint) was numerically lower with lixisenatide + BI (3.3%) compared with SU + BI (8.9%). While not significantly different, these findings nevertheless indicate a trend towards a reduction in hypoglycemia incidence during Ramadan fasting for lixisenatide + BI versus SU + BI (OR: 0.34). This trend was confirmed by a significantly lower percentage for any hypoglycemia with lixisenatide + BI versus SU + BI during pre-Ramadan (3.3% versus 15.2%, respectively; OR: 0.17), Ramadan fasting (4.3% versus 17.4%, respectively; OR: 0.22) and during the whole treatment period (5.4% versus 26.1%, respectively; OR 0.16). This reduction was not due to changes in BI or SU dosing as there were no clinically significant increases in insulin or SU dose, and the SU dose remained below maximum levels throughout the study (<50% in most instances). The difference between participants experiencing documented symptomatic hypoglycemia events and 'any hypoglycemia' events with lixisenatide + BI arm was minimal for the pre-Ramadan (two versus three participants) and Ramadan fasting periods (three versus four participants). For the SU + BI arm, the difference in participants experiencing documented symptomatic hypoglycemia events and 'any hypoglycemia' events was much greater for both the pre-Ramadan (8 versus 14 participants) and Ramadan fasting periods (8 versus 16 participants; ITT population). The use of a BI + GLP-1 RA-intensified treatment regimen during Ramadan fasting has not been directly assessed in previous trials. In an observational study investigating liraglutide (a GLP-1 RA) as an add-on to existing anti-diabetic agents, in which 94.6% of participants were on insulin, SU, or both, adding liraglutide did not increase the risk of hypoglycemia [20]. In a study investigating BI (insulin glargine) + SU (glimepiride), the proportion of participants experiencing any hypoglycemia during Ramadan fasting was 18.9–24.4% [21], which is similar to but numerically higher than the percentage of any hypoglycemia experienced in the SU + BI arm in this study. The glimepiride dose used throughout the BI + glimepiride study (4.3 ± 1.0 mg) [21] was similar to the mean (SD) glimepiride dose used in the current study (post-Ramadan: 3.5 ± 1.1 mg) and within the percentage of maximum dose range when considering all SU types used in the current study.

The fact that hypoglycemia incidence was generally low for lixisenatide + BI is reassuring given that these participants were receiving BI. This finding provides confidence in the combination of lixisenatide + BI, and increases the confidence relating to the potential for conducting a similar study with

Table 2 – TEAEs (safety population).

TEAEs, n (%)	Pre-Ramadan period		Ramadan on-treatment period[a]		Whole treatment period	
	Lixisenatide + BI (n = 92)	SU + BI (n = 92)	Lixisenatide + BI (n = 92)	SU + BI (n = 92)	Lixisenatide + BI (n = 92)	SU + BI (n = 92)
Participants with any TEAE	29 (31.5)	7 (7.6)	16 (17.4)	15 (16.3)	42 (45.7)	21 (22.8)
Infections and infestations	1 (1.1)[b]	0	1 (1.1)[c]	1 (1.1)[c]	2 (2.2)[b,c]	1 (1.1)[c]
Metabolism and nutrition disorders	3 (3.3)	5 (5.4)	5 (5.4)	10 (10.9)	9 (9.8)	14 (15.2)
Hyperglycemia	2 (2.2)	0	0	2 (2.2)	2 (2.2)	2 (2.2)
Hypertriglyceridemia	1 (1.1)	1 (1.1)	1 (1.1)	1 (1.1)	2 (2.2)	2 (2.2)
Dyslipidemia	0	1 (1.1)	3 (3.3)	5 (5.4)	4 (4.3)	7 (7.6)
Hypoglycemia	0	3 (3.3)	1 (1.1)	2 (2.2)	1 (1.1)	4 (4.3)
Cardiac disorders	0	0	1 (1.1)[d]	0	1 (1.1)[d]	0
Gastrointestinal disorders	22 (23.9)	0	4 (4.3)	1 (1.1)	25 (27.2)	1 (1.1)
Nausea	11 (12.0)	0	0	0	11 (12.0)	0
Gastritis	7 (7.6)	0	1 (1.1)	1 (1.1)	8 (8.7)	1 (1.1)
Vomiting	4 (4.3)	0	1 (1.1)	0	4 (4.3)	0
Abdominal distension	3 (3.3)	0	0	0	3 (3.3)	0
Abdominal pain	2 (2.2)	0	1 (1.1)	0	3 (3.3)	0
Abdominal discomfort	1 (1.1)	0	0	0	1 (1.1)	0
Abdominal pain upper	1 (1.1)	0	0	0	1 (1.1)	0
Diarrhea	1 (1.1)	0	1 (1.1)	0	2 (2.2)	0
Musculoskeletal and connective tissue disorders	0	1 (1.1)	1 (1.1)	2 (2.2)	1 (1.1)	3 (3.3)
Arthralgia	0	0	1 (1.1)	1 (1.1)	1 (1.1)	1 (1.1)
Pain in extremity	0	1 (1.1)	0	1 (1.1)	0	2 (2.2)
General disorders and administration-site conditions	3 (3.3)	1 (1.1)	2 (2.2)	0	5 (5.4)	1 (1.1)
Pyrexia	2 (2.2)	1 (1.1)	2 (2.2)	0	4 (4.3)	1 (1.1)
Fatigue	1 (1.1)	0	0	0	1 (1.1)	0
Investigations	3 (3.3)	0	2 (2.2)	1 (1.1)	6 (6.5)	1 (1.1)
Weight decreased	3 (3.3)	0	2 (2.2)	1 (1.1)	6 (6.5)	1 (1.1)
Participants with any TEAE possibly related to study drug	16 (17.4)	0	3 (3.3)	0	19 (20.7)	0
Participants with any treatment-emergent SAE	0	0	0	0	0	0
Participants with any treatment-emergent AESI[e]	0	0	0	0	0	0
Participants with any TEAE leading to treatment discontinuation	0	0	1 (1.1)[f]	0	1 (1.1)[f]	0

AE: adverse event, AESI: adverse event of special interest, BI: basal insulin, IMP/NIMP: investigational medicinal product/noninvestigational medicinal product, SAE: serious adverse event, SU: sulfonylurea, TEAE: treatment-emergent adverse event.

[a] Ramadan on-treatment period was defined from pre-Ramadan visit (visit 4) to post-Ramadan visit (visit 6) or last day of study drug administration + 3 days, whichever came first.

[b] Viral gastroenteritis.

[c] Viral upper respiratory tract infection for lixisenatide and tooth abscess for SU.

[d] Atrial fibrillation.

[e] AESI was an AE (serious or nonserious) of scientific and medical concern specific to the study drug or study, for which ongoing monitoring and rapid communication by the investigator/sponsor might be appropriate. Predefined AESIs included: pregnancy of a female patient entered in a study as well as pregnancy occurring in a female partner of a male patient entered in a study with IMP/NIMP, symptomatic overdose (serious or nonserious) with investigational or noninvestigational study drugs, and increase in alanine aminotransferase.

[f] Abdominal pain led to treatment discontinuation.

the fixed-ratio combination of insulin glargine and lixisenatide (iGlarLixi) in the future. The absence of hypoglycemia during fasting hours while on lixisenatide + BI would certainly be welcomed by many Muslim patients who fast during Ramadan. The low number of hypoglycemia events with SU + BI was likely due to a combination of factors including most participants taking a modern SU, which have less hypoglycemia risk compared to the first-generation options [22]; 4.3% of participants used glibenclamide at baseline, which has been shown to have higher rates of hypoglycemia in other Ramadan studies [4,23,24]. However, 0% (0/3) of participants on glibenclamide during Ramadan fasting experienced 'any hypoglycemia' events during the fast. Additionally, participants started on 50% of the maximum SU dose, as specified in the inclusion criteria to allow for uptitration, but no increase in SU dose occurred; SU doses remained at $\leq$50% of the maximum dose during the entire study period in most cases; only six participants had SU doses >50%.

Hypoglycemia events during Ramadan usually occur during fasting hours with the highest rates of hypoglycemia occurring during the last 3–4 hours of the fast. This trend was seen with SU + BI when observing the proportion of participants with a hypoglycemia event by time of day with 12.0% percentage of participants experiencing 'any hypoglycemia' events during the fasting hours. The proportion of participants experiencing hypoglycemia events with lixisenatide + BI was very low, with no people experiencing events during the fasting period of the day. We also note that there was no severe hypoglycemia for lixisenatide + BI during Ramadan.

The high treatment compliance rates and low dropout rate during this study demonstrate that people with T2DM can fast for Ramadan and aim for glycemic control with no additional risk of hypoglycemia while compliant with their BI + GLP-1 RA regimen. The tolerability and low rates of hypoglycemia were demonstrated with the free combination of lixisenatide + BI, which allows for the two injections to be administered once a day at the same time, at iftar. However, the fixed-ratio combination of insulin glargine + lixisenatide (iGlarLixi), allows for a single injection, and has been suggested as a convenient treatment option during Ramadan [14].

Reduction in HbA1c from baseline to the pre-Ramadan and post-Ramadan visit was similar between treatment arms. However, as mentioned, the trial was not designed as treat-to-target, and the treatment duration with lixisenatide following the switch from SU was very short; thus, it is not unexpected to see modest effects on efficacy. Body weight decreased with lixisenatide + BI during the whole treatment period as expected [14]. Interestingly, body weight also fell for SU + BI, which was unexpected, although a greater reduction was observed with lixisenatide + BI [25]. This might reflect the effects of fasting and the fact that neither the BI nor SU dose changed significantly from baseline. The incidence of TEAEs was numerically higher with lixisenatide + BI than with SU + BI due to a higher incidence of gastrointestinal events during the pre-Ramadan period corresponding to lixisenatide initiation. During the Ramadan on-treatment period, TEAEs were similar between treatment arms. No treatment-emergent serious adverse events were observed throughout the overall study period. Severe hypoglycemic events were rare, with no events recorded with lixisenatide + BI over the whole treatment period and one event reported for SU + BI, which occurred during the Ramadan fast.

In line with guidelines [3,26], the trial design included an 8- to 12-week period before Ramadan that enabled participants to undergo a medical assessment, receive diet and lifestyle advice, and optimize treatment to maximize safe fasting. Ramadan-focused education can empower participants to change their lifestyle during Ramadan, minimize the risk of hypoglycemic events, and prevent weight gain [26,27].

Limitations of the study include the lack of a washout period when switching from SU to lixisenatide, which may have resulted in participants having residue SU when taking lixisenatide at some point in the study. Any SU residue could have potentially affected the hypoglycemia incidence. Furthermore, as a result of the switch design, any benefit from lixisenatide had to counter SU removal. Additionally, the trial only included those participants who tolerated SU with low rates of hypoglycemia. There is a possibility that some participants did not report all hypoglycemic events while fasting. The specified sample size (236 participants) to provide sufficient precision for the comparison of lixisenatide versus SU for the primary endpoint was not met (ITT: n = 184; ITT-V4: n = 181). This can largely be attributed to the very short time period for participant selection and randomization in Ramadan trials, which prevented some investigation centers from participating.

In conclusion, lixisenatide + BI was beneficial for the treatment of people with T2DM before and during Ramadan fasting. The total number of days fasted (29.0 median days) suggesting that fasting can be achieved with lixisenatide and an intensified BI treatment regimen. The proportion of participants experiencing $\geq$1 symptomatic hypoglycemia event during Ramadan was numerically lower for lixisenatide + BI compared to SU + BI and was significantly lower for the any hypoglycemia category. The low percentage of participants experiencing severe hypoglycemia events provides robust efficacy and safety data for fasting during Ramadan while on BI and lixisenatide. Incidence of TEAEs during Ramadan was similar between treatment arms, and there were no new TEAEs reported. Thus, the data from this study demonstrate that people with T2DM can fast for Ramadan and aim for glycemic control with no additional risk of hypoglycemia while being on the lixisenatide + BI regimen, and that this is a valuable treatment option in this patient population.

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Data availability statement

The study overview is available at ClinicalTrials.gov. Qualified researchers may request access to patient-level data and related study documents, including the clinical study report,

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

Authors' contributions

M.H. developed the study concept and design. 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.

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Declaration of interest

M.H.: advisory board member for Boehringer Ingelheim, Novo Nordisk, and Sanofi; and speaker for Eli Lilly, Janssen, LifeScan BI, MSD, Novo Nordisk, and Sanofi.

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

K.H.: advisory board member for AstraZeneca, Boehringer Ingelheim, Janssen, Novo Nordisk, and Sanofi; research grant from Sanofi; and speaker for AstraZeneca, Boehringer Ingelheim, Eli Lilly, MSD, and Novo Nordisk.

K.D.: employee of Sanofi.

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S.A.: researcher and advisor for Amgen, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Merck & Co, MSD, Novo Nordisk, and Sanofi.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2019.01.035.

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