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Sponsor: Sanofi **Drug substance(s):** AVE0010	**Study Identifiers:** U1111-1172-3026, NCT02941367 **Study code:** LPS14410
Title of the study: International, randomized, open label study to compare the safety and efficacy of lixisenatide vs sulfonylurea on top of basal insulin treatment in Type 2 Diabetes Mellitus subjects who elect to fast during Ramadan	
Study center(s): Twelve sites in India, 2 sites in Israel, and 1 each in Kuwait and Turkey	
Study period: Date first patient enrolled: 23/Feb/2017 Date last patient completed: 04/Aug/2017	
Phase of development: Phase 4	

Objectives: The primary objective of this study was to compare the safety, in terms of percentage of patients with symptomatic documented hypoglycemia during Ramadan fast, of lixisenatide versus sulfonylurea (SU), both on top of basal insulin, in Type 2 Diabetes Mellitus patients fasting Ramadan.

The secondary efficacy objectives of this study were to assess the effect of lixisenatide versus SU on the following endpoints:

- Glycemic control (glycated hemoglobin A1c [HbA1c] and fasting plasma glucose [FPG], pre-prandial plasma glucose [2hPPG])
- Changes in body weight

The secondary safety objectives were to assess overall safety and tolerability of lixisenatide and SU in terms of:

- Hypoglycemia (All, confirmed symptomatic, and severe)
- Adverse events (AE), serious adverse events (SAE), adverse events of special interest (AESI), laboratory variables.

Other objectives were:

- Change in patient-reported outcome (PRO) results (Hypoglycemia Fear Survey II [HFS II])
- Patient qualitative assessment of Ramadan's impact on their diabetes at the end of the Ramadan
- Treatment changes (basal insulin, SU).

Methodology: This was an international, randomized, open label, parallel-group, 12 to 20 weeks treatment clinical trial.

The sample size was computed in order to ensure a sufficient precision for the assessment of the odds ratio (OR) of Lyxumia® versus SU for the incidence of patients with at least one documented symptomatic hypoglycemia event [plasma glucose ≤70 mg/dL (3.9 mmol/L)] during Ramadan period. Assuming that a total of 53% patients in the SU group were to experience one or more such events, and assuming an absolute risk reduction of 15% for Lyxumia (estimated OR of 0.54), a total sample size of 200 patients in the primary analysis population were to provide a precision of at least 0.41 for the OR estimate. Assuming that around 15% patients will withdraw from treatment between randomization and the pre-Ramadan visit, a total of 236 patients were needed to be randomized (118 in each treatment group) in 2 arms:

- Test: Lyxumia investigational medicinal product (IMP) + basal insulin +/- metformin
- Control: SU (IMP) + basal insulin +/- metformin

Number of patients**:**	Planned: 236
	Randomized: 184
	Treated: 184
Evaluated:	
	Efficacy: 181 for primary endpoint, 184 for other endpoints
	Safety: 184 for all variables except hypoglycemia (181)

Diagnosis and criteria for inclusion: The study population consisted of adult patients with type 2 diabetes mellitus diagnosed for at least 1 year, treated with basal insulin + SU (≤ 50% maximum allowed dose) ±1 oral antidiabetic (OAD). Patients were required to intend to fast during Ramadan and have HbA1c at screening between 7.5% and 10% inclusive.

Study treatments

Investigational medicinal product(s): Lyxumia (lixisenatide)

Formulation: 10 µg (initiation dose) and 20 µg (maintenance dose)

Route(s) of administration: Subcutaneous injection

Dose regimen: Once daily

Investigational medicinal product(s): Sulfonylurea

Formulation: according to local labeling

Route(s) of administration: Oral

Dose regimen: according to local labeling

Duration of treatment: 8 to 12 weeks

Duration of observation: Minimum 12 weeks and maximum 22 weeks (up to 2 weeks screening period; on treatment period consisting of 8 to 12 weeks pre-Ramadan period + 29 to 30 days Ramadan + 0 to 4 weeks post-Ramadan period).

Criteria for evaluation:

Efficacy: The primary endpoint was the percentage of patients with at least 1 documented symptomatic hypoglycemia event (plasma glucose ≤ 70 mg/dL; 3.9 mmol/L) during Ramadan fast (29-30 days; from start to end of Ramadan holy month) regardless of study treatment discontinuation and/or treatment intensification.

The following were the main secondary efficacy endpoints:

- Mean change in HbA1c from baseline to pre-Ramadan visit and from baseline to post-Ramadan visit.
- Mean change in body weight from baseline to pre-Ramadan visit and from baseline to post-Ramadan visit.
- Percentage of patients with 2hPPG <189 mg/dL (10 mmol/L) (mean self-measured plasma glucose [SMPG] levels 2 hours after IFTAR) during the last 14 days of Ramadan.
- Percentage of patients with HbA1c <7% at pre-Ramadan and post-Ramadan visits.
- Percentage of patients with FPG <130 mg/dL (7.22 mmol/L) at pre-Ramadan visit.

Safety:

- Hypoglycemia: assessment of the hypoglycemia risk for Lyxumia and SU in terms of: percentages of patients and annualized event rates for the hypoglycemia categories defined by the American Diabetes Association (ADA) Workgroup of Hypoglycemia and using 2 different thresholds of plasma glucose: ≤70 mg/dL (≤3.9 mmol/L) and <54 mg/dL (<3.0 mmo/L) for confirmation of hypoglycemia.
- Change in cholesterol, triglycerides, high density lipoproteins (HDL) and low density lipoproteins (LDL) from baseline to pre-Ramadan and post-Ramadan visits.
- Reported SAEs/AEs/AESIs.

Statistical methods:

Primary analysis:

Percentages of patients with at least 1 documented symptomatic hypoglycemia event during Ramadan fast were analyzed in both arms (Lyxumia versus SU) by using a logistic regression model.

Comparison of Lyxumia versus SU on the incidence of symptomatic documented hypoglycemia during Ramadan fast was assessed by the odds-ratio estimate and its 95% confidence interval (CI).

For the primary objective, the population was the ITT V4, defined as patients included in the intent-to-treat (ITT) population who are still on study treatment (Lyxumia or SU) and assessed at the pre-Ramadan visit V4.

Analysis of secondary endpoints:

Change in HbA1c during the study was analyzed using a mixed model for repeated measures (MMRM) with treatment (Lyxumia or SU) as fixed effects and using the baseline HbA1c value as a covariate. The baseline value was defined as the latest available value prior to the randomization. Difference between treatment groups and 2-sided 95% CI were estimated using the above mentioned mixed-effect model with repeated measures (MMRM).

The same model was used for change in secondary continuous endpoints: body weight. One analysis by parameter was performed. It included the 3 study time points and enabled both to compare treatments on change from baseline and to assess effect of Ramadan on parameters (Least Squares means change between baseline and pre-Ramadan visit, and between baseline and post-Ramadan visit in each treatment group).

Categorical parameters were analyzed using a logistic regression model. The baseline HbA1c value was included in each model as covariate as an indicator of the severity of diabetes.

Safety endpoints:

Safety analyses (adverse events [AEs], serious adverse events [SAEs], adverse events of special interest [AESIs]) were descriptive, based on the safety population.

Hypoglycemia events in each treatment group were described in terms of percentages of patients during each period according to categories defined by the American Diabetes Association [ADA] Workgroup of Hypoglycemia and using 2 different thresholds of plasma glucose: ≤70 mg/dL (≤3.9 mmol/L) and <54 mg/dL (<3.0 mmol/L) for confirmation of hypoglycemia.

Percentage of patients with hypoglycemia were analyzed using a logistic regression model for defined study periods (main-on-treatment, pre-Ramadan and during Ramadan fast).

Summary:

Population characteristics:

- A total of 184 patients were randomized across all participating countries, 92 in the LYXUMIA® treatment group and 92 in the SU treatment group. Among them 150 patients were randomized in India.
- Patients' demographics and characteristics at baseline were similar in the 2 treatment arms.
    - Mean age of the population was 53.4 years, 26 of 184 patients (14.1%) were ≥65 years,
    - Mean body mass index (BMI) was 29.3 kg/m2,
    - Mean duration of diabetes prior to study start was 7.3 years (median 6.0),
    - 173 patients (94.0%) received >1 OAD at screening,
    - Mean HbA1c at screening was 8.72% in the LYXUMIA® group, and 8.51% in the SU group.
- 5 patients permanently discontinued from treatment prematurely (3 in LYXUMIA® arm and 2 in SU arm) due to adverse event, withdrawal of consent or other reasons.

The ITTV4 population (primary endpoint population) included 181 patients.

Efficacy results:

The proportion of patients experiencing primary endpoint of at least 1 documented symptomatic hypoglycemia event (plasma glucose ≤70 mg/dL [3.9 mmol/L]) during Ramadan was numerically lower in the Lyxumia arm versus the SU arm. This difference was not statistically significant, which may be at least partly due to a lower than initially expected percentage of patients experiencing such events and the fact that planned patient number was not reached (184 patients randomized instead of 236).

Change of HbA1c from baseline to pre-Ramadan visit and to post-Ramadan visit was modest with a similar reduction in both groups. This is certainly related to the lack of basal insulin up-titration due to the real life nature of the trial. Indeed, from baseline to pre-Ramadan visit and to post-Ramadan visit, only a very small increase of basal insulin dose was observed in both study arms. No intensive basal insulin up-titration was performed (minimum increase in basal insulin dose and few patients reaching the targeted FPG) in perspective of a safe Ramadan fast as recommended by guidelines. Moreover, the period given to investigators to achieve glycemic target of 80 to 130 mg was relatively short (8 weeks).

Accordingly, many patients did not achieve glycemic targets:

- A small percentage of patients achieved HbA1c target of 7% at the pre-Ramadan visit (Lyxumia: 9%; SU: 17%) and at the post-Ramadan visit (Lyxumia: 14%; SU: 17%).
- The percentage of patients achieving the target of FPG <130 mg/dL at pre-Ramadan visit was low in both treatment groups: 41% in the Lyxumia group and 36% in the SU groups.
- The percentage of patients achieving 2hPPG <180 mg/dL (<10 mmol/L) during the 14 days of Ramadan was also low in both treatment groups: 46% in the Lyxumia group and 49% in the SU group.

Suboptimal glycemic control has probably greatly contributed to the lower incidence of hypoglycemic events during the study period.

No statistically significant differences were found between treatment groups for any secondary efficacy endpoint. However, the percentage of patients with HbA1c <7% at both the pre-Ramadan and the post-Ramadan visit was numerically lower in Lyxumia group versus SU treatment group, which may be partly due to a slightly higher baseline HbA1c in Lyxumia. On the other hand, the percentage of patients achieving the 2hPPG <180 mg/dL during the 14 days of Ramadan was numerically lower in Lyxumia group.

Regarding the HFS-II questionnaire, both treatment groups had lower total, worry and behavior scores from baseline and progressively during the Ramadan period, meaning lower fear of hypoglycemia, lower tendency to avoid hypoglycemia and/or its negative consequences, and lower worry of hypoglycemia and its consequences. However, no differences were found between treatment groups.

Safety results:

The overall proportion of patients experiencing at least one hypoglycemia event was lower than expected (ie, in the trial sample size calculation 53% of patients with documented symptomatic hypoglycemia were expected in the SU arm). An advantage in favor of Lyxumia was observed for all categories of hypoglycemia and during all study periods including during Ramadan fast. For any hypoglycemia event, during the entire on-treatment period and also during each of the individual observation periods except post-Ramadan fast, the incidence was approximately 4 times lower with Lyxumia compared with SU.

Incidence of hypoglycemia was usually higher during Ramadan fast compared with post-Ramadan fast in both treatment groups, but the residual risk of hypoglycemia associated with fasting appears to be lower with Lyxumia than with SU.

During the pre-Ramadan on-treatment period, the proportion of patients with at least one TEAE was higher in the Lyxumia group compared with the SU group (31.5% versus 7.6%), due to higher incidence of gastrointestinal events during initiation of Lyxumia.

During the Ramadan on-treatment period, the number of patients with any TEAE was similar in both treatment groups (Lyxumia: 17.4%, SU: 16.3%).

No deaths, SAEs or AESI were reported during the study.

Only one patient (in the Lyxumia group), reported a TEAE that led to the permanent IMP discontinuation.

Other than a small increase in Triglycerides (TG) with Lyxumia, lipids showed no significant change at pre-Ramadan and post-Ramadan compared with baseline.
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