These results are supplied for informational purposes only.
Prescribing decisions should be made based on the approved package insert in the country of prescription.

Sponsor: Sanofi **Drug substance(s):** insulin glargine/lixisenatide	**Study Identifiers:** NCT03767543, U1111-1215-0238 **Study code:** LPS15544

Title of the study:

A randomized, 26-week, open-label, 2-treatment arm, parallel group multicenter study comparing the efficacy and safety of insulin glargine/lixisenatide fixed-ratio combination (Soliqua™) titrated using a simple titration algorithm (one unit daily adjustment) compared with insulin glargine/lixisenatide fixed-ratio combination (Soliqua™) titrated by weekly adjustment in patients with Type 2 diabetes mellitus (T2DM)

Study center(s):

A total of 32 study centers initiated in Canada to participate in the study, 31 study centers enrolled at least 1 patient and 30 study centers randomized patients

Study period:

Date first participant enrolled: 11/Mar/2019

Date last participant completed: 23/Oct/2020

Study Status: Completed

Phase of development: IIIb

Objectives:

Main Study Objectives

- **Primary objective**: To demonstrate that the simple daily titration algorithm is non-inferior to the weekly titration algorithm as described in Canadian product monograph
- **Secondary objective**: To gain additional information on the efficacy and safety of using a simple patient-titration protocol for administration of iGlarLixi

Sub-studies objectives

Abbott Freestyle Libre Pro sub-study objective: to evaluate the mean glucose level and glycemic variability before randomization and after 12 weeks of treatment.

Pen sub-study objective: to assess the ease of use of the SoloStar® pen injector after 4 weeks of use (patient). Additionally, the sub-study also assessed the ease of instruction on the use of the SoloStar pen injector after 4 weeks (HCP).

Methodology:

This was a Phase IIIb, open-label, randomized, 2-treatment arm, parallel-group, 26-week duration, multicenter study in outpatients with T2DM.

The study was comprised 3 periods:

- A screening period of up to 2 weeks
- A 26-week open-label randomized treatment period
- A 3-day post-treatment safety follow-up period (phone contact)

The maximum study duration per patient was 29 weeks. This was an outpatient study that consisted of Screening Visit, 4 on-site visits and 6 telephone contacts. Patients were assessed at baseline, 4, 12, and 26 weeks, with additional phone contacts scheduled at Weeks 1, 2, 6, 8, 10, and 20.

At screening, the Investigator installed an Abbott Freestyle Libre Pro. The patient wore the device, which contained a sensor for monitoring glucose levels, for 2 weeks in a continuous fashion. The patient returned the sensor (or detached the sensor) at Visit 0 (randomization). At screening, the patients completed Diabetes Treatment Satisfaction Questionnaire (status) (DTSQs).

At the end of screening period, eligible patients on basal insulin ± OADs (metformin, sodium glucose co-transporter 2 [SGLT2] inhibitor, dipeptidyl-peptidase-4 inhibitors [DPP4], or insulin secretagogues) were randomized (1:1) to 1 of 2 treatment groups:

- **Group 1 (DAILY TITRATION):** basal insulin was replaced by the iGlarLixi fixed-ratio combination injected once a day within 1 hour prior to the first meal of the day. iGlarLixi was titrated using a simple titration algorithm of 1 unit per day until a fasting plasma glucose (FPG) value of 4.4 to 5.6 mmol/L was reached.
- **Group 2 (WEEKLY TITRATION):** basal insulin was replaced by the iGlarLixi fixed-ratio combination injected once a day within 1 hour prior to the first meal of the day. iGlarLixi was titrated once weekly by 2 or 4 units until an FPG value of 4.4 to 5.6 mmol/L was reached.

Administration of oral glucose-lowering agents taken at baseline were continued after randomization at the same dose, except for DPP4 inhibitors which was discontinued at randomization (run-in period was not necessary) for both the groups. Additional oral glucose-lowering agents were not permitted.

Stratification factors at baseline included the use of SGLT2 inhibitors, the use of DPP4 inhibitors, and a stratum for baseline HbA1c (< 8.5% vs ≥ 8.5%).

Patients and HCPs participated in the Pen sub-study completed patient-reported outcomes (PRO) Pen questionnaire and HCP questionnaire respectively at Week 4 (Visit 3).

At Visit 7 (Week 12), the Investigator installed another Abbott Freestyle Libre Pro device. The patient wore the device for 2 weeks in order to monitor glucose levels in a continuous fashion. The patient detached the sensor at Week 14 and gave the sensor to the Investigator at Visit 9 (Week 26). During Abbott Freestyle Libre Pro sub-study, patients monitored their glucose level and glycemic variability with the device for 2 weeks at screening and Week 12.

At Visit 9 (Week 26), the patients completed the Diabetes Treatment Satisfaction Questionnaire (change) (DTSQc).

At the last visit of the last patient, physicians completed the HCP satisfaction questionnaire.

Investigators were advised to target self-monitoring plasma glucose (SMPG) levels of 4.4 to 5.6 mmol/L (inclusive) and an A1c ≤ 7%. The Diabetes Canada clinical practice guidelines suggest that the target A1c be reviewed and reinforced with Investigators and research coordinators before and during the study.

No interim analysis was planned for the main study.

An analysis was planned for the Pen sub-study when the last patient included in the sub-study completed Visit 3 (Week 4). To ensure database analysis integrity, a different biostatistician than the one used in the main study accessed the information on the Pen sub-study questionnaire responses.

Approximately 80 patients, previously taking Lantus®, were planned to be included in the Pen sub-study. Patients participated in the sub-study completed a PRO pen questionnaire at Week 4 (Visit 3).

For the Abbott Freestyle Libre Pro sub-study, 50 patients were planned to be monitored in their blood glucose level and glycemic variability with an Abbott Freestyle Libre Pro device for 2 weeks at screening and Week 12.

Impact of the coronavirus disease 2019 (COVID-19) pandemic on study conduct

The COVID-19 pandemic was declared on 11 March 2020 and was ongoing during the conduct of this trial. Contingency measures were implemented to maintain feasibility, data integrity, and participant safety during the COVID 19 pandemic. These included modifications to trial conduct and administration of trial procedures to allow participants to continue in the trial despite challenging circumstances and modifications to monitoring and/or other trial oversight mechanisms. The last patient was enrolled on 17 March 2020. The last patient randomized was on 13 April 2020 to the Daily titration group.

Number of participants:

Planned: 264

Randomized: 265

Treated: 262

Evaluated:

Efficacy: 256

Safety: 262

Diagnosis and criteria for inclusion:

Patients with T2DM were enrolled in the study based on the below eligibility criteria.

Main inclusion criteria:

- Patients >18 years of age (inclusive) at the time of signing the informed consent
- Patients with T2DM based on Diabetes Canada 2018 Clinical Practice Guidance criteria and diagnosed at least 6 months prior to the Screening Visit
- Uncontrolled glycemia with A1c≥7.5% and ≤ 10.5%
- Patients treated for at least 6 months on any basal insulin (including but not limited to insulin glargine, Toujeo®, Degludec®, etc.) ± OADs
    - The total basal insulin dose had to be ≤40 units/day
    - The OADs allowed at inclusion were metformin, insulin secretagogues, DPP4 inhibitors, and SGLT2 inhibitors; with no change in OAD dose for at least 2 months prior to randomization
- BMI between 20 and 40 kg/m2 inclusively
- Signed written informed consent

Study products

Investigational medicinal product(s): Insulin glargine/lixisenatide

Formulation/ Form & composition: Solution for injection

Route(s) of administration: Subcutaneous

Dose regimen:

Entered on Once Daily Dosing:

For patients transferring from once daily basal insulins to the iGlarLixi arm, the starting dose described in the below table were used (80% rule not used).

Entering on Twice Daily Dosing:

The following algorithm (80% rule) was used for patients transferred from twice daily basal insulins to the iGlarLixi arm:

1. The total daily dose of basal insulin was calculated
2. The total daily dose was reduced by 20%
3. The iGlarLixi dose was determined (see table below)

Basal Insulin Dose	iGlarLixi Dose
< 30 units	Start at 15 units
≥ 30 units	Start at 30 units

The dose of the combination product (investigational medicinal product [IMP]) titrated according to the patient's needs for insulin glargine.

DPP4 inhibitors were discontinued at randomization and was acceptable to remove the DPP4 inhibitor at randomization without a run-in period.

Note that only the dose of insulin glargine appeared in the pen dosing window. The dose (µg) of lixisenatide did not appear in the dose window even though lixisenatide was pre-mixed in the cartridge. The lixisenatide dose was increased or decreased along with insulin glargine dose.

Titration for iGlarLixi (DAILY TITRATION)

The dose was titrated using a simple titration algorithm of 1 unit per day based on the amount of insulin required to reach and maintain a fasting SMPG of 4.4 to 5.6 mmol/L (inclusive) while avoiding hypoglycemia. Patients were taught self-titration.

Fasting SMPG (mmol/L)	Dose Change (units/day)
5.7 and above	+1
≤ 5.6	No change in dose

SMPG: self-monitoring plasma glucose

The maximum daily dose is 60 units/20 µg.

The dose of iGlarLixi titrated by increments of 1 unit per day until an FPG of 4.4 to 5.6 mmol/L reached. If an unexplained symptomatic hypoglycemia occurred over past 24 hours, dose was reduced by 1 unit. The up-titration was resumed the following day. If severe hypoglycemia occurred (ie, required a third-party assistance), the patient would seek medical attention immediately and then contacted the research team.

Sound clinical judgment was exercised while titrating patients. Investigators might adjust or stop titration, or temporarily reduced the dose, if they believed further titration was hazardous at that time.

Titration for iGlarLixi (WEEKLY TITRATION)

The iGlarLixi was self-administered once a day within 1 hour prior to the first meal of the day, but titrated only once weekly.

The iGlarLixi was titrated once weekly by 2 or 4 units (see table below) based on the amount of insulin required to reach and maintain a fasting SMPG of 4.4 to 5.6 mmol/L (inclusive) while avoiding hypoglycemia. Patients were taught self-titration.

Fasting SMPG (mmol/L) *	Dose Change (units/day)
> 7.8	+4
> 5.6 and ≤ 7.8	+2
4.4 to 5.6	No change
One value < 4.4	−2

SMPG: self-monitoring plasma glucose

*values are based on median fasting self-measured plasma glucose values from the preceding 3 days. If 1 value over the preceding 3 days is below 4.4 mmol/L the dose change was −2 units/day

The maximum daily dose is 60 units/20 µg.

The dose of iGlarLixi was titrated according to the product label, in increments of 2 or 4 units per week until an FPG of 4.4 to 5.6 mmol/L was reached. FPG values were based on the median fasting SMPG values from the preceding 3 days. If one value over the preceding 3 days was below 4.4 mmol/L, the dose change was −2 units/day. The dose would not be increased if the patient experienced an episode of symptomatic hypoglycemia or any episode of nocturnal or severe hypoglycemia for no obvious reason (eg, decreased food intake, increased physical activity, etc.). If sever hypoglycemia occurred (ie, required a third-party assistance), the patient would seek medical attention immediately and then contacted the research team. The maximum daily dose was 60 units/20 µg.
Non investigational medicinal product (s): The patients were treated with basal insulin for at least 6 months prior to inclusion in the study. The OADs allowed at inclusion were metformin, insulin secretagogues, DPP4 inhibitors, and SGLT2 inhibitors. The dose of the OAD was stabilized for the last 2 months prior to screening. Administration of OADs taken at baseline were continued after randomization at the same dose, except for DPP4 inhibitors, which were discontinued at randomization (no run-in period necessary). Doses were reduced at the discretion of the Investigator in response to biochemical or clinical hypoglycemia. Additional OAD agents were not allowed.
Duration of treatment: 26 weeks **Duration of observation:** A 3 day post treatment safety follow up period (phone contact)
Criteria for evaluation: **Efficacy:** <u>Primary efficacy endpoint:</u> • Change in HbA1c (%) from baseline to Week 26 <u>Secondary efficacy endpoints:</u> The hierarchical sequential approach was used to manage the analysis of the first 2 secondary endpoints as per order showed below while the additional secondary endpoints were evaluated descriptively: • Change in body weight from baseline to Week 26 • Percentage of patients reaching A1c ≤ 7% with no body weight gain and/or hypoglycemia (severe or documented symptomatic [≤ 3.9 mmol/L]) at Week 26 • Percentage of patients reaching A1c ≤ 7% at Week 26 • Change in FPG and fasting SMPG from baseline to Week 12 and 26 • Change in 7-point SMPG profile from baseline to Week 12 and 26 • Insulin glargine dose at Week 26 • Percentage of patients requiring rescue therapy during the 26-week open-label treatment period **Safety:** Safety endpoints were evaluated by • Hypoglycemia • Adverse events (AE), serious adverse events, adverse events of special interest, AEs leading to discontinuation • Potentially clinically significant abnormality(ies) in laboratory values or vital signs

Other endpoints:

- Patient reported outcomes DTSQ change at Week 26 based on DTSQc
- Health Care Practitioner Satisfaction Questionnaire at the last visit of the last patient
- Patient evaluation of pen's ease of use and ease of learning of SoloStar (Pen sub-study) at Week 4
- Health Care Practitioner assessment of ease of instruction on the use of the SoloStar pen (Pen sub-study) at Week 4

Statistical methods:

Primary Efficacy Analysis:

The primary efficacy variable, the change from baseline in HbA1c up to Week 26, was analyzed using a mixed-effect model with repeated measures under the missing at random framework using modified intention-to-treat (mITT) population. The model included titration method, DPP4 use (Yes, No), and SGLT2 use (Yes, No), visit (Week 12, and Week 26), and treatment by visit interaction as fixed effects and baseline HbA1c and HbA1c by visit as covariates. Non-inferiority of Daily titration with regards to Weekly titration was demonstrated using the least square (LS) mean difference and 95% confidence interval (CI), If the lower limit of 95% CI for the difference was greater than −0.4% then non-inferiority was met. The p-value was based on the non-inferiority test with a non-inferiority margin of −0.4%.

Secondary Efficacy Endpoint Analysis

As first secondary endpoint in the hierarchical approach, change in weight was analyzed in a manner similar to the primary endpoint considering a non-inferiority margin of 1 kilogram. The lower limit of 95% CI for the difference was greater than -1 kilogram and non-inferiority was met. The p-value was based on the non-inferiority test and the pre-specified non-inferiority margin. The last endpoint tested as per hierarchical approach, composite secondary endpoint HbA1c ≤ 7.0%, no hypoglycemia, and no weight gain was analyzed using the mITT population considering a non-inferiority margin of 5%. A generalized liner model procedure was used; distribution equal to binomial, to evaluate the non-inferiority of the simple daily titration versus iGlarLixi titrated weekly according to Canadian product monograph. Class effects included titration group, randomization strata of HbA1c (< 8.5%, ≥ 8.5%), DPP4 use (Yes, No), and SGT2 use (Yes, No). Non-inferiority was demonstrated using the LS mean difference and 95% CI. Based on hierarchical approach, if primary endpoint was met

Descriptive statistics were used to display the results of the remaining secondary variables.

Safety Analysis

Safety analyses other than hypoglycemia for the 26-week treatment period was descriptive, based on the safety population (randomized and exposed). The primary focus of AE reporting was on-treatment-emergent adverse events.

Hypoglycemia

The number (%) of patients and rate in patient years (2 types: the number of patients with events and the total number of events per patient-year) of each type of hypoglycemia were summarized by treatment group.

- Documented [level 1 (≤ 3.9 mmol/L) and level 2 (< 3.0 mmol/L)] and severe
- All day and nocturnal (defined as midnight to 6 AM, and midnight to 8 AM)

The pattern of hypoglycemia occurrence over time was also assessed, as appropriate.

Other Variables analysis

Diabetes treatment satisfaction questionnaires

The DTSQs and DTSQc covered 8 items about diabetes treatment over the past weeks and measured overall satisfaction, convenience, flexibility, understanding of diabetes, was willing to recommend ongoing treatment to others and had willingness to continue the ongoing treatment. Descriptive statistics were used to summarize the DTSQs score at baseline within each treatment group while at Week 26 the DTSQc score was analyzed.

Health care professional satisfaction questionnaire

Descriptive statistics were used to summarize the HCP satisfaction questionnaire components overall and by qualification (Specialist, General Practitioners, Nurse, Pharmacist and Other).

Pen questionnaire

Patient evaluation of pen's ease of use and ease of learning of SoloStar was summarized using descriptive statistics on subset of patients participating to the sub-study. A histogram was provided showing the percentages of every answers for each item.

The HCP assessment of ease of instruction on the use of the SoloStar pen was analyzed by means of descriptive statistics on HCP involved on sub-study. The questionnaire assessed the proportion (%) of HCP who rated ease to train patients on the use of the SoloStar pen.

Summary Results:

Population characteristics:

- A total of 31 study centers in Canada participated in the study where patients were randomized and treated at 30 study centers, and at 1 study center, all the patients (n=4) screened were considered as screen failures.
- A total of 398 patients were enrolled in the study where 133 were considered as screening failure and the remaining 265 eligible patients were randomized to either to the Daily titration group (132 patients) or Weekly titration group (133 patients). Out of 265 randomized patients, 262 (98.9%) patients were treated and 231 (87.2%) patients completed all 26 weeks of the treatment period. A total of 222 (83.8%) patients completed the study period.
- Demographic and baseline characteristics were comparable across both treatment groups. Overall, the mean (SD) age, BMI and HbA1c of the study population was 64.1 (10.96) years, 29.26 (4.411) kg/m^2, and 8.51 (0.805) %, respectively. Most of the patients were White (58.0%) followed by Asian (28.0%). The majority of the patients were not Hispanic or Latino (97.3%).
- Overall, the mean (SD) daily dose of basal insulin (units) was 24.3 (9.93) units. The mean (SD) duration of diabetes was 16.52 (7.961) years (ie, 17.25 [9.042] years in Weekly titration group and 15.79 [6.652] years in the Daily titration group, respectively). The mean (SD) daily dose of basal insulin (units) was comparable in both groups, 25.1 (10.06) units in the Daily titration group and 23.6 (9.78) units in the Weekly titration group. A higher proportion of patients in the Weekly titration group had allergies in comparison with patients in the Daily titration group (25 [18.8%] versus 12 [9.1%], respectively). Across both groups, the higher proportion of patients were on metformin than on other OADs (117 [88.6%] and 114 [85.7%], respectively). A total of 214 (80.8%) patients received 2 or more OADs where 111 (84.1%) patients were from the Daily titration group and 103 (77.4%) patients were from the Weekly titration group.
- There were no notable differences between the 2 groups with respect to age at onset of diabetes, number of OADs, duration of first and second OADs, diabetic microvascular complications, and creatinine clearance.
- All 265 patients (100%) eligible in the study had a medical history/surgical history at screening. Across both groups, osteoarthropathies was the most common musculoskeletal and connective tissue disorder (Daily titration group: 30.3%; Weekly titration group: 34.6%) followed by depressive disorders among psychiatric disorders (Daily titration group: 15.9%; Weekly titration group: 18.8%), and anaemia NEC among blood and lymphatic system disorder (Daily titration group: 9.8%; Weekly titration group: 5.3%).
- More than 80% of the patients across the Daily and Weekly titration groups reported the use of prior medications (112 [84.8%] and 112 [84.2%] patients, respectively). Apart from drugs used in diabetes across the Daily and Weekly titration groups (112 [84.8%] and 109 [82.0%] patients, respectively), the most frequently used prior non-diabetic medication was analgesics (2 [1.5%] and 1 [0.8%] patients, respectively). All other non-diabetic therapeutic class were reported either in ≤ 2 patients in the study.
- All patients reported the use of concomitant medications during the study. The most common non-diabetic concomitant medications across the Daily and Weekly titration groups were lipid modifying agents (119 [90.2%] and 119 [89.5%] patients, respectively) and agents acting on the renin-angiotensin system (101 [76.5%] and 97 [72.9%] patients, respectively). Rosuvastatin (67 [50.8%] and 71 [53.4%] patients, respectively) and atorvastatin (37 [28.0%] and 39 [29.3%] patients, respectively) were the most common lipid modifying agents and perindopril (21 [15.9%] and 27

[20.3%] patients, respectively) and ramipril (28 [21.2%] and 19 [14.3%] patients, respectively) were the most common agents acting on the renin-angiotensin system.

- All patients reported the use of post-treatment medications during the study. The most common post-treatment medications across the Daily and Weekly titration groups were the drugs used in diabetes (130 [98.5%] and 128 [96.2%] patients, respectively), lipid modifying agents (119 [90.2%] and 118 [88.7%] patients, respectively), and agents acting on the renin-angiotensin system (101 [76.5%] and 96 [72.2%] patients, respectively).

Primary Efficacy Endpoint

The primary objective of this study was met as statistical non-inferiority of the Daily titration group over the Weekly titration group was demonstrated in change in HbA1c% from baseline to Week 26:

- Patients in both groups had a mean HbA1c decrease by -1.26% for the Daily titration group and by −0.94% for the Weekly titration group, reaching mean HbA1c values at Week 26 of 7.25% and 7.56%, respectively. The difference between the 2 treatment groups was 0.32% (95% CI: 0.07%, 0.57%) demonstrating statistical non-inferiority (considering a non-inferiority margin of -0.4%) of the Daily titration when compared with the Weekly titration ($p<0.0001$ for non-inferiority test). The primary analysis was further confirmed by the sensitivity analysis.
- The primary efficacy analysis was repeated in the population without trial impact (disruption) due to COVID 19. The reductions in mean HbA1c from baseline to Week 26 were consistent with those observed in the primary efficacy analysis, with LS mean changes from baseline of −1.25% (95% CI: −1.44%, −1.06%) in the Daily titration group and −0.86% (95% CI: −1.06%, −0.67%) in the Weekly titration group. The difference between the 2 treatment groups was 0.39% (95% CI: 0.12%, 0.66%), confirming statistical non-inferiority of the Daily titration when compared with the Weekly titration ($p<0.0001$ for non-inferiority test).

Secondary Efficacy Endpoints

- There was an increase in body weight in the Weekly titration group whereas in the Daily treatment group the body weight was reduced (LS mean [SE], 0.81 [0.37] kg, versus −0.22 [0.37] kg,], respectively) from Baseline to Week 26. The LS mean (SE) difference between the 2 treatment groups was 1.03 [0.52] kg (95% CI: 0.01 kg, 2.06 kg) demonstrating statistical non-inferiority (with reference to non-inferiority margin of – 1 kilogram) of the Daily titration when compared with Weekly titration ($p<0.0001$ for non-inferiority test).
- The percentage of patients reaching HbA1c ≤ 7% with no body weight gain, and without hypoglycemia (severe or documented symptomatic [< 3.9 mmol/L]) was numerically higher in the Daily titration group (15.2%) compared with the Weekly titration group (7.6%) at Week 26. The logistic regression analysis shows a difference in LS mean of composite endpoint between the 2 groups (LS [SE]) of −0.07 (0.04) with 95% CI: −0.13, 0.00 and $p<0.001$ demonstrating statistically significant non-inferiority (with reference to non-inferiority margin of 5%) of Daily titration with reference to Weekly titration.
- The percentage of patients reaching HbA1c ≤ 7% was numerically higher in the Daily titration group (53 [42.4%]) compared with the Weekly titration group (44 [33.6%]) at Week 26.
- There was a decrease in mean FPG and SMPG levels, and 7-point SMPG profile from baseline to Weeks 12 and 26 across both groups.
- The mean insulin glargine dose was comparable between the Daily titration group and the Weekly titration group at Week 26. However, it took longer time to reach mean insulin glargine dose in the Weekly titration group compared to Daily titration group.
- The percentage of patients requiring rescue therapy visit was numerically lower in the Daily titration group compared with the Weekly titration group (4 [3.2%] patients versus 6 [4.6%] patients).

Other Outcomes

- The mean (SD) treatment satisfaction scores at Week 26 comparison to the satisfaction score at baseline was comparable between the Daily (12.7 [5.75]) and Weekly titration (13.1 [5.99]) groups.

- In overall, 22 HCPs provided responses for the types of titration algorithms they preferred; 11 (50.0%) HCPs each preferred daily (1 unit/day) and weekly (+2 or +4 units weekly) titration algorithms. On a scale ranging from 3 (indicating agreement) to −3 (indicating disagreement), the mean HCP scores for the Daily titration algorithm were numerically higher than those for the Weekly titration algorithm for 4 of 7 questions in the HCP Satisfaction Questionnaire.
- Majority of the patients found it either very easy or easy of use and Learning of SoloStar® (Pen Sub-study) through questionnaire. A total of 88 (97.8%) patients responded that they would like to continue to use the SoloStar® pen after the study and 88 (96.7%) patients responded that they would recommend the SoloStar® pen to others.
- Majority of the HCPs found it either very easy or easy to train patients to use the SoloStar® pen through questionnaire. On average, HCPs took 10.7 min to train patients to use the SoloStar® pen, and 96.3% HCPs would recommend the SoloStar® pen to others.

Impact of COVID-19 Pandemic on Efficacy Results

- The COVID-19 pandemic was not considered to have had a sizeable impact on the efficacy results, as judged by the sensitivity analysis performed on the primary endpoint that excluded patients impacted by the COVID 19 pandemic.

Safety Endpoints

In overall, the safety profile of the study drug was comparable when it was titrated using a simple titration algorithm (Daily titration group) or by weekly adjustment (Weekly titration group) in patients with T2DM.

Extent of Exposure

- The median duration of treatment was comparable between the 2 treatment groups (181 days in the Daily titration group and 182 days in the Weekly titration group).
- The mean (SD) starting dose of IMP when basal insulin was < 30 U and ≥ 30 U was comparable between the Daily and Weekly titration groups (16.8 [5.59] U versus 17.4 [5.53] U and 30.1 [2.68] U versus 30.6 [4.01] U, respectively).

Hypoglycemic Events

- The percentage of patients with any hypoglycemia was comparable across the 2 treatment groups (65.1% in the Daily titration group and 60.9% in the Weekly titration group).
- The patient rates with any hypoglycemia, severe hypoglycemia, symptomatic hypoglycemia, documented hypoglycemia, documented and symptomatic hypoglycemia, and severe and/or documented symptomatic hypoglycemia were comparable across the treatment groups.
- Two severe hypoglycemia events (1 in each group) were captured as SAEs, which were severe, related to IMP, and were resolved.

Adverse Events

- The overall number of patients with treatment-emergent adverse events (TEAEs) were comparable across the treatment groups (58.1% in the Daily titration group and 63.9% in the Weekly titration group) in the safety population while the incidence of TEAEs was higher in the Daily titration group as compared with the Weekly titration group (76.9% versus 55.6%) in the population with trial impact due to COVID-19.
- The most commonly reported TEAEs (≥ 5% in overall patients) were nausea (overall: 11.8%; [13.2% in the Daily titration group versus 10.5% in the Weekly titration group]), and diarrhoea (overall: 6.9%; [6.2% in the Daily titration group versus 7.5% in the Weekly titration group]). All other PTs were reported in < 5% of patients in both treatment groups and overall patients. One (0.8%) patient in the Daily titration group was SARS-CoV-2 test positive.
- The incidence of patients who experienced at least 1 TEAE was higher in the Daily titration group as compared with the Weekly titration group (76.9% versus 55.6%) in the population with trial impact due to COVID-19. The most commonly reported TEAEs by PT in ≥ 3 patients were diarrhea (3 patients in overall; [2 patients in the Daily titration group versus 1 patient in the Weekly titration group]). All other PTs were reported in < 3 patients in overall group.

- A total of 26.4% of patients in the Daily titration group and 24.8% of patients in the Weekly titration group experienced TEAEs considered by the Investigator to be related to the IMP. The most frequently reported related AEs across both treatment groups were diarrhea and nausea
- Treatment emergent SAEs (TESAEs) were reported in a total of 17 (6.5%) patients with a higher incidence of TESAEs in the Weekly treatment group (8.3%) compared with the Daily titration group (4.7%). All the TESAEs were reported in 1 patient each except hypoglycemia, which was reported in 3 patients. One death was reported in the Weekly titration group due to pancreatic carcinoma metastatic (SOC: Neoplasms benign, malignant, and unspecified (including cysts and polyps). This SAE was not considered to be related to IMP by the Investigator
- A total of 11 (4.2%) patients had TEAEs that led to IMP discontinuation where 5 patients were in the Daily titration group and 6 patients in the Weekly titration group. The most frequent TEAEs that led to IMP discontinuation were diarrhea and nausea in the Daily titration group
- A total of 3 (1.1%) patients had any local intolerability at injection site where 1 patient each in the Daily titration group had injection site bruising and injection site pruritus (2 events), and injection site pain and 1 patient in the Weekly titration group had injection site discoloration. All the TEAEs were reported as mild, related to IMP (except second occurrence of injection site pruritus), non-serious, and were resolved (except injection site bruising)
- One patient each in the Daily and Weekly titration groups had lipase and amylase increase >2 times upper limit of normal (ULN). All the events were reported as mild, not related to IMP, non-serious and were resolved (except lipase increased in the patient in the Weekly titration group)
- A total of 3 (1.1%) patients had blood calcitonin increased ≥ 20 pg/mL where 1 patient was in the Daily titration group and 2 patients were in the Weekly titration group. All the events were reported as mild, not related to IMP, non-serious, and were not resolved (except the event in the patient the Daily titration group)
- No case of ALT increase, symptomatic overdose, or pregnancy was reported in the study.

Vital signs

- Potentially clinically significant abnormalities (PCSA) identified during the TEAE period included SBP ≤ 95 mmHg and decrease from baseline ≥ 20 mmHg, SBP ≥ 160 mmHg and increase from baseline ≥ 20 mmHg, ≥ 5% increase or decrease in body weight from baseline. All the PCSAs except ≥ 5% decrease in body weight from baseline were present in numerically higher proportion of patients in the Weekly titration group compared with the Daily titration group. One patient in the Weekly titration group had elevated BP, which was reported as mild, not related to IMP, non-serious, and was resolved.

Physical Findings

- Twelve abnormal clinically significant physical findings were captured as AEs including 7 patients in the Daily titration group and 5 patients in the Weekly titration group. All the abnormal clinically significant physical findings were reported as mild (except edema and carotid artery stenosis, which was reported as moderate), not related to IMP (except stasis dermatitis and carotid artery stenosis), non-serious (except carotid artery stenosis), and were not resolved (except upper respiratory tract infection, stasis dermatitis, and thyroid mass, which were considered as resolving).

Impact of the COVID-19 Pandemic on Safety Results

- There was no COVID-19 pandemic related TEAEs, SAEs or death reported in the study.

Issue date: 29-Sep-2021