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| **Sponsor:** Sanofi<br>**Drug substance(s):** Insulin glargine 300 U/mL | **Study Identifiers:** U1111-1255-5143; NCT04980027<br>**Study code:** LPS16665 |

**Title of the study:**

Multicentre phase IV single arm clinical trial to evaluate the safety and efficacy of Gla-300 in insulin-naïve patients with type 2 diabetes uncontrolled on oral anti-hyperglycemic drugs

**Study center(s):** 15 Centers from India

**Study period:**

Study Initiation date [date of first patient in (FPI)]: 10-Aug-2021

Study completion date [date of last patient out (LPO)]: 26-Dec-2022

Study Status: Completed

**Phase of development:** Phase IV

**Objectives:**

**Primary**

- To evaluate the safety of Gla-300 in insulin naïve T2D participants uncontrolled on oral antihyperglycemic drugs.

**Secondary**

- To assess the efficacy of Gla-300 on glycemic control in insulin naïve T2D participants uncontrolled on oral anti-hyperglycemic drugs
- To assess change in participant's treatment satisfaction using DTSQs (Diabetes Treatment Satisfaction Questionnaire)

**Methodology:**

This study was a single group, multicenter phase IV clinical trial conducted in type 2 diabetes mellitus participants who are uncontrolled on oral anti-hyperglycemic drugs.
The study comprised of 3 periods:
• A screening period of up to 2 weeks
• A 24-week treatment period
• A post-treatment follow-up phone call visit after 3 days after the end of treatment.

The maximum study duration per participant was 27 weeks. Eight on-site visits and 8 telephone contacts were scheduled. Additional on-site visits were scheduled for unexpected investigational medicinal product (IMP) needs and for safety concerns as considered appropriate by the Investigator.

Screening is from signed informed consent (visit 1) to the start of the treatment period (visit 2).

The end of the treatment period is at the end of 24 weeks (visit 15) and the end of the study is at visit 16.

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| **Number of participants:**<br>Planned: 222 participants<br>Screened: 251 participants<br>Eligible: 220 participants<br>Treated: 220 participants<br>**Evaluated:**<br>Full analysis set: 220 participants<br>Safety population: 220 participants<br>Per protocol population: 218 participants |
| **Diagnosis and criteria for inclusion:**<br>Participant must be 18 years of age inclusive, at the time of signing the informed consent.<br>Participants with type 2 diabetes mellitus.<br>Participants who are insulin naïve on at least one oral antihyperglycemic drug (metformin, sulfonylurea, thiazolidinedione, DPP-4 inhibitor, SGLT-2 inhibitor, glinide, α-glucosidase inhibitor) with or without glucagon-like peptide 1 receptor agonists (GLP-1 RAs) for a minimum period of 6 months prior to screening. The background non-insulin antidiabetic drug should be administered at stable dose for at least 8 weeks prior to screening.<br>HbA1c between 7.5% (58 mmol/mol) and 10% (86 mmol/mol) inclusive, during screening.<br>Median of the last 3 consecutive fasting SMBG values prior to baseline, or at least 2 fasting SMBG values in the week prior to baseline >130 mg/dL. |
| **Study products**<br>**Investigational medicinal product:** Insulin glargine U300<br>**Dose formulation:** Prefilled (disposable) pen<br>**Unit dose strength:** Each prefilled pen contains a total of 450 units of insulin glargine (1.5 mL of 300 units/mL insulin glargine) solution.<br>**Dosage level:**<br>Time of administration: The clock time for the injection (hh:mm) will be established at the discretion of the participant/Investigator at baseline and will be maintained for the duration of the study.<br>Dose regimen: recommended starting dose of Gla-300 is 0.2U/kg body weight once daily s.c injection. The insulin dose will be adjusted according to the recommended titration algorithm.<br>**Route of administration:** Subcutaneous |

**Duration of study intervention:** Up to 24 weeks.

**Post-treatment follow-up:** After 3 days after the end of treatment.

**Criteria for evaluation:**

**Primary:**

- Percentage of participants with Treatment Emergent Adverse Events (TEAEs) including serious adverse events (SAEs) and hypoglycemic episodes.

**Secondary:**

- Percentage of participants with at least 1 confirmed (Level 1) hypoglycemia event from baseline to Week 24
- Change in HbA1c from baseline to Week 12 and 24
- Percentage of participants reaching HbA1c target of <7% at Weeks 12 and 24.
- Percentage of participants reaching targeted fasting self-monitored blood glucose (SMBG) of 80 to 110 mg/dL (4.4 to 6.1 mmol/L) at Weeks 12 and 24.
- Change in fasting plasma glucose (FPG) from baseline to Week 24.
- Change in fasting SMBG from baseline to Week 24.
- Change in 7-point SMBG profile from baseline to Week 24.
- Percentage of participants requiring rescue therapy by Weeks 12 and 24
- Change in body weight from baseline to week 12 and week 24
- Change in insulin dose baseline to week 12 and week 24
- Change in DTSQs scores from baseline to week 12 and week 24

**Statistical methods:**

**General Conventions**

All analyses will be done using SAS (version 9.4, SAS Institute Inc., Cary, NC, USA).
Safety and Efficacy endpoints will be analyzed in a descriptive manner. Continuous data will be reported using the following descriptive statistics:

1. Number of observations (n)
2. Mean and Standard deviation (SD)
3. Minimum (min) and Maximum (max)
4. Median

Categorical data will be presented using frequency (n = number of participants; m = number of events) and percentage (%).
Listings will be provided for all data recorded in eCRF to study participant profiles. All listings will be sorted by Participant ID, and date, unless otherwise stated. Unscheduled visit data will only be listed and not included in summaries.

Minimum and maximum values will be reported in the units of collection with 3 decimals being maximum value; the mean will be presented with 1 decimal place more and the standard deviation 2 decimal places more than the units of collection. Percentages for categorical summaries will be represented to 1 decimal place.

**Summary Results:**

**Demographic and other baseline characteristics:**

The demographics and other baseline characteristics were analyzed for the patients belonging to the full analysis set (FAS) population (N=220 participants). The population predominantly consists of male participants (139, 63.2%, N=220). Amongst 81 female participants, there were 5 (6.2%) participants with childbearing potential. The participants were of age ranging from 29 years to 76 years, height 137 cm to 187.1 cm and weight 42.5 kg to 111.8 kg.

The mean (SD) for the systolic blood pressure was 125.4 (10.38) mmHg, diastolic blood pressure 78.4 (6.43) mmHg, heart rate was 82.5 (10.09). The physical examination result was normal for all participants (220, 100%, N=220). The electrocardiogram result was abnormal non-clinically significant (NCS) for 11 (5%, N=220) participants.

**Exposure:**

In safety population (N=220 patients), a mean (SD) of cumulative planned dose 4316.6 (1584.41) U and mean (SD) of cumulative actual dose 4269 (1575.83) U was observed.

**Safety results:**

In safety population, there were 55 participants who reported a total of 65 adverse events (AEs) (25.0%, N=220). Among the 65 AEs, a majority of 64 events were treatment emergent (24.5%, N=220), which includes 1 SAE (0.5%, N=220) (urethral stenosis). Most of the event reported were under SOC 'Infections and infestations' (10.9%, N=220). None of the events were fatal, led to study discontinuation or were related to the IMP.

A total of 2 participants (0.9%, N=218) reported 2 instances of level 1 hypoglycemic event before IMP was administered. A total of 64 participants (29.4%, N=218) reported 211 instances of level 1 hypoglycemic event after IMP. Among them, 63 participants (28.9%, N=218) 209 instances of level 1 hypoglycemic event only after IMP administration. None of the participants reported level 2 hypoglycemia event.

**Efficacy results**

**HbA1c:** The mean change from baseline to Week 12 of HbA1c was -0.9% ranging from -6.3% to 3.0% and the mean change from baseline to Week 24 of HbA1c was -1.14% ranging from -5.6% to 3.9%. HbA1c target of <7% was reached by 40 participants (18.8%, N=213) at the end of 12 weeks and 53 participants (24.3%, N=218) at the end of 24 weeks.

**FBG:** At baseline, the mean (SD) FBG was 169.09 (35.761) mg/dL, which at the end of 12 weeks and 24 weeks was 121.08 (29.866) mg/dL and 118.28 (32.743) mg/dL respectively. The change in FBG at the end of 12 weeks and 24 weeks was -48.38 (40.945) mg/dL and - 50.98 (44.510) mg/dL.

**SMBG:** At the end of week 12 and week 24, the mean (SD) change in fasting SMBG was -48.38 (40.945) and -52.01 (44.140) mg/dL respectively. The percentage of participants reaching targeted fasting SMBG of 80 to 110 mg/dL (4.4 to 6.1 mmol/L) was 38.4% (n=81, N=211) at the end of week 12 and 50.0% (n=108, N=216) at the end of week 24.

Change in 7-point SMBG profile from baseline to Week 24:

• Before breakfast, 212 participants reported a mean (SD) of 116.7 (32.27) mg/dL and a mean (SD) change of -48.4 (53.48) mg/dL change from baseline measured for 212 participants.

• 2 hours after breakfast, 212 participants reported a mean (SD) of 177.2 (52.23) mg/dL and a mean (SD) change of -43.6 (78.39) mg/dL change from baseline measured for 209 participants.

• Before lunch, 211 participants reported a mean (SD) of 148.2 (47.35) mg/dL and a mean (SD) change -30.7 (73.27) mg/dL change from baseline measured for 209 participants.

• 2 hours after lunch, 212 participants reported a mean (SD) of 186.3 (55.67) mg/dL and a mean (SD) change of -32.1 (72.96) mg/dL change from baseline measured for all 212 participants.

• Before dinner, 212 participants reported a mean (SD) of 151.2 (47.86) mg/dL and a mean (SD) change of -26.0 (64.89) mg/dL change from baseline measured for 208 participants.

• 2 hours after dinner, 212 participants reported a mean (SD) of 182.1 (51.74) mg/dL and a mean (SD) change of -35.4 (71.59) mg/dL change from baseline measured for 203 participants.

• At bedtime, 200 participants reported a mean (SD) of 175.6 (44.62) mg/dL and a mean (SD) change of -37.7 (66.32) mg/dL change from baseline measured for 186 participants.

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| **Body weight:** At baseline, the mean (SD) body weight was 72.73 (12.195) kg. At week 12, the mean (SD) body weight was 72.85 (11.817) kg with a mean (SD) change of -0.02 (3.290) kg as compared to baseline. At week 24, the mean (SD) body weight was 72.76 (11.556) kg with a mean (SD) change of 0.07 (3.573) kg as compared to baseline.<br>**Insulin dose:** At baseline, the mean insulin dose per day (U) was reported to be 14.211 (± 3.1628) U. At the end of 24 weeks, the mean insulin dose per day (U) was reported to be a mean (SD) of 29.924 (15.0122) U and the mean (SD) change of 15.725 (14.0349) U from baseline.<br>**Rescue therapy:** By visit 11, none of the participants required rescue therapy whereas by visit 15, 1 participant (0.5%, N=218) required rescue therapy. DTSQ scores: The DTSQ scores showed an increase from baseline through visit 11 and visit 15. The mean (SD) change from baseline at visit 11 and visit 15 was 8.2 (9.38) and 10.1 (10.58) respectively. |
| **Issue date:** 27-Nov-2023 |