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Prescribing decisions should be made based on the approved package insert in the country of prescription.

Sponsor: Sanofi **Drug substance(s):** Lantus®/insulin glargine	**Study Identifiers:** U1111-1172-1002, NCT02606357 **Study code:** LANTUL07225
Title of the study: Treatment initiation with basal insulin in uncontrolled Type 2 diabetes patients on oral anti-diabetic agent (OAD) in Jordan (NEWLAN)	
Study center(s): 13 sites in Jordan	
Study period: Date first patient enrolled: 22/Nov/2015 Date last patient completed: 27/Nov/2017	
Phase of development: Phase IV	
Objectives: Primary objective • To assess the change in glycosylated hemoglobin (HbA1c) from baseline to 6 months in uncontrolled Type 2 diabetes patients on OAD therapy in Jordan after 6 months of treatment with basal insulin (Insuline glargine 100 U/ml). **Secondary objectives** • To evaluate the percentage of patients achieving target of HbA1c <7.0%, • To evaluate the change in fasting blood glucose (FBG), • To assess the following safety criteria: hypoglycemic events, body weight change, and overall safety. • Describe the titration process: changes in glargine insulin dose at 3 months and 6 months, changes in the titration doses used (if any), and time to reach control	
Methodology: The NEWLAN study was a national, multicenter, open-label, uncontrolled, prospective Phase IV clinical study of 6-month follow-up to gather information on the baseline changes in Jordan patients with type 2 diabetes treated with insulin glargine 100 U/ml (Gla-100).	
Number of patients**:** Planned: 290 Randomized: NA Treated: 242 **Evaluated:** Efficacy: 177 Safety: 242 Pharmacokinetics: NA	
Diagnosis and criteria for inclusion: Male or female patients aged not less than 18 years with Type 2 diabetes Mellitus (type 2 DM) who were uncontrolled with previous therapy (HbA1c >7.0%), evident in HbA1c test within the last 1 month before study entry, also for insulin naïve patients (any patient uncontrolled after one or a maximum of two lines of therapy including: monotherapy (Metformin alone or any other Oral Anti-Diabetic agent (OAD) if contraindicated or intolerance) and/or dual therapy (any OAD combination), at maximum tolerated dose in the last 3 months) and who were willing to sign the informed consent.	

Study treatments

Investigational medicinal product(s): Lantus®/insulin glargine 100 U/ml (Gla-100)

Formulation: 100 units/mL solution in a pre-filled SoloSTAR® pen (3 mL).

Route(s) of administration: Subcutaneous injection

Dose regimen: Starting dose as per the ADA/EASD Consensus Algorithm: the recommended starting dose of insulin glargine was 0.1 - 0.2 units/kg of body weight, although larger amounts (0.3–0.4 U/ kg/day) were also reasonable in patients with severe hyperglycemia.

Time: Administration once a day (od), in the evening, at dinner or at bedtime.

Duration of treatment: 6 months

Duration of observation: 6 months

Criteria for evaluation:

Efficacy:

Primary endpoint

- The change in HbA1c from baseline to study endpoint at 6 months.

Secondary endpoints

- Percentage of patients achieving a target of HbA1c <7.0% at 6 months
- Change in fasting blood glucose (FBG) from baseline to 3 and 6-month follow-up
- CMean daily doses of Gla-100 at baseline, 3 and 6 month, change in daily dose of Gla-100at each visit (3 and 6 months), and time to reach glycemic control (HbA1c <7.0%)

Safety:

- Hypoglycemic events:
  - Asymptomatic hypoglycemia is defined as a measured blood glucose level ≤ 70 mg/dL (3.9 mmol/L) not associated with clinical symptoms.
  - Symptomatic hypoglycemia is defined as an event with clinical symptoms that are considered to result from hypoglycemia (confirmed or not by a blood glucose measurement ≤ 70mg/dL [3.9 mmol/L]).
  - Severe symptomatic hypoglycemia is defined as an event with clinical symptoms that are considered to result from hypoglycemia in which the patient required the assistance of another person because the patient could not treat her/himself due to acute neurological impairment directly resulting from the hypoglycemia (assistance by another person when the patient could have treated her/himself is not considered as requiring assistance) and one of the following criteria:
    - The event was associated with a measured blood glucose level < 36 mg/dL (2.0 mmol/L),
    - Or the event was associated with prompt recovery after oral carbohydrate, intravenous glucose, or glucagon administration.
- Body weight at baseline, 3-month and 6-month follow-up.
- Adverse Events (AEs)/Serious Averse Events (SAEs) /Adverse Events of Special Interest (AESIs).

Statistical methods:

Descriptive statistics were performed according to the type of criterion:

- Quantitative: number of observed values, mean, standard deviation, median, minimum and maximum, first quartile, and third quartile,
- Qualitative: number of observed values and percentages. Missing data or unknown responses were not counted in the percentages. Also, 2-sided 95% Wald CI for primary and secondary variables.

Statistical tests were performed at a two-sided significance level of α=5%. No adjustment for multiple testing was made.

Summary:

In this study, 242 patients with type 2 diabetes mellitus were enrolled. 177patients were included in the efficacy analysis and all enrolled patients were included in the safety analysis.

The study population consisted of 62.5% men and 37.5% women with a mean age of 55.7±10.7 years, mean height of 167.8 ±9.01 cm, mean weight of 85.14 ±15.56 Kg and mean Body Mass Index (BMI) of 30.3 ± 4.92 (range 19.29 -44.9) kg/m².

The mean baseline heart rate was 75.68 ±9.44 beats/minute. The mean baseline systolic and diastolic blood pressure were 129.1 ±12.6 and 77.9 ±9.2 mmHg, respectively.

At baseline mean HbA1c was 9.7 ± 1.4%, (range 7.2 to 14.2%) measured by HbA1c kits in 96.3% of the patients. In addition, the mean fasting blood glucose was 217 ± 73 mg/dL (range 95 to 512 mg/dL).

The most frequent diabetes complications among the study population at baseline were as followed: Retinopathy (6.3%), Sensory Neuropathy (14.2%), Microalbuminuria /Proteinuria (7.9%), Foot ulcer (2.9%), Angina (0.8%), Myocardial Infarction/Acute Coronary Syndrome (1.7%), Heart failure (0.8%), Peripheral Vascular Disease (0.8%), history of revascularization (5%), Coronary artery disease (0.4%), Eye cataract (0.4%), and Numbness (0.4%).

Additionally, 93 (38.8%) patients had medical or surgical comorbidities at baseline as followed:

Other Medical/Surgical History and Co-Morbidities	Percent	Other Medical/Surgical History and Co-Morbidities	Percent
Albuminuria	0.8%	Hypertriglyceridemia	0.4%
Ankylosing Spondylitis	0.4%	Hyperuricemia	2.8%
Aortic Surgery	0.4%	Hypothyroidism	2.8%
Asthma	0.4%	Hysterectomy	0.8%
Benign Prostate Hyperplasia	0.8%	Kidney Stones	1.6%
Cardio Vascular Disease	10.8%	Left Leg Pain	0.4%
Cholecystectomy	0.4%	Lower Limb Stenting	0.4%
Constipation	0.4%	Lymphoma	0.4%
Diabetic Foot Infection	0.4%	Neuropathy	0.4%
Disc	1.6%	Osteoarthritis	0.8%
Dyslipidemia	32.1%	Osteoporosis	0.4%
Erectile Dysfunction	1.7%	Pelvic Fracture Fixation	0.4%
Fatty Liver Disease	0.4%	Peptic Ulcer	0.4%
G6 PD	0.4%	Planned Eye Surgery	1.2%
GERD	0.4%	Retinopathy	0.4%
Glaucoma	0.4%	Sinusitis	0.4%
Hip Replacement	0.4%	Urinary Tract Infection UTI	0.4%
hypercholesterolemia	0.4%	Varicocele Surgery	0.4%
Hypertension	42.9%	Vertigo	0.4%
Hyperthyroidism	1.6%	Vitamin D Deficiency	1.2%

In terms of previous antihyperglycemic therapy at baseline, 56.7% of the patients were on Metformin plus Glimepiride combination, 15.4% were on Metformin plus Glibenclamide combination, 7.6% were on Metformin plus Vildagliptin combination, 4.6% were on Metformin plus Gliclazide or Metformin plus Sitagliptin combination, 2.5% were on Metformin plus linagliptin, 0.8% were on Metformin plus Gliclazide plus Linagliptin/ Vidagliptin, 0.4% were on Metformin plus Pioglitazone, 0.4% were on Metformin plus Repaglinide, 0.4% were on Metformin plus Gliclazide plus Pioglitazone, 0.4% were on Metformin plus Glimepiride plus Vildagliptin, and 5% received Metformin alone. The average metformin dose was 2133 ± 525 mg. Mean Gla-100 dose at visit one (baseline) was 17.46 ± 5.14 units/day (range 7-30 units/day). At visit 2 (3 months) and visit 3 (6 months), the mean dose increased to 29.14 ±12.) Units/day and 33.16 ±14.1 units/day, respectively. Friedman test was used to assess the change in Gla-100 dose throughout study visits and revealed a statistically significant change in dose throughout study visits ($\chi 2$= 128.4, P <0.001).

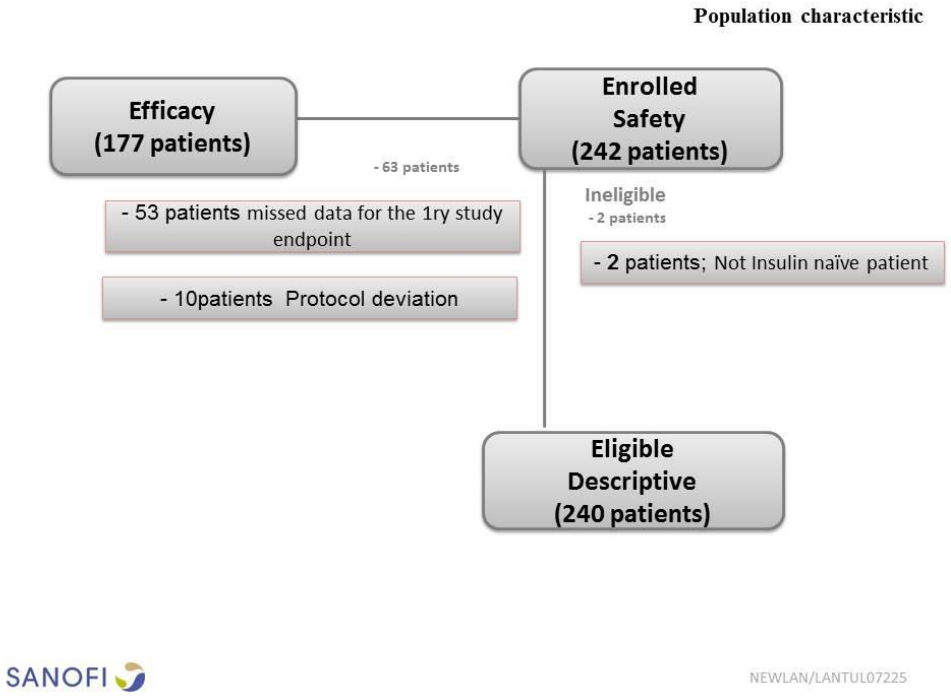
Overall, 136 (80%) of the patients at visit 2 and 108 (86.4%) of the patients at visit 3 were up-titrated with mean dose increments of 15.1 ±12.3 U/day at visit 2 and 18.4 ±12.9 U/day at visit 3. In addition, 12 (7.1%) patients at visit 2 and 10 (8%) patients at visit 3 were down-titrated with a mean dose decrement of -5.9 ± 4.6 U/day at visit 2 and -5.7 ±3.1 U/day at visit 3. A stable Gla-100dose (no titration) was observed in 22 (12.9%) of the patients at visit 2 (vs. visit 1) and 7 (5.6%) at visit 3 (vs. visit 2).

Mean body weight at baseline was 84.7 ± 14.95 kg and increased significantly to 85.8 ± 14.7 kg at visit 2 (p<0.001), and further increased to 87.1 ± 14.7 kg at visit 3 as (p<0.001 vs. baseline).

Mean BMI increased significantly during the study with baseline values from 30.3 ± 4.83 kg/m² to reach 30.8 ± 4.6 kg/m² at visit 2 (p<0.001) and 31.1 ± 4.69 kg/m² at visit 3 (p<0.001 vs. baseline).

Population characteristics:

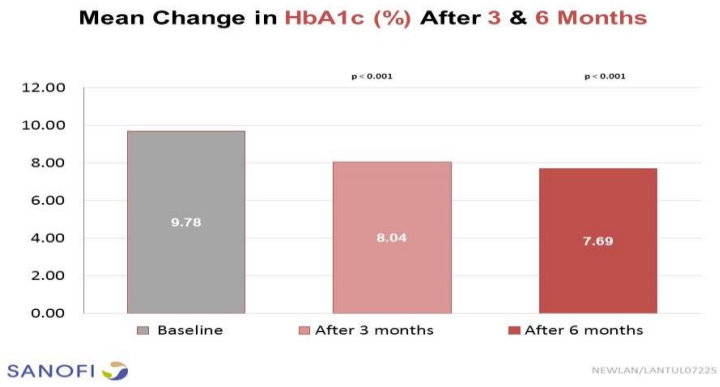
In the present multicenter prospective study, 242 patients were screened for eligibility 240 patients were eligible and started study's treatment. At the end of the sixth month of follow-up, the HbA1c values were missed for 53 (22%) patients; 10 (4.2%) patients violated the study protocol. Protocol deviation was in the form of treatment discontinuation before the visit 3 (N =7), taking insulin from other sources (N=2), and started insulin glargine more than 14 days after inclusion date (N =1). Thus, only 177 patients were included in the efficacy analysis.



Efficacy results:

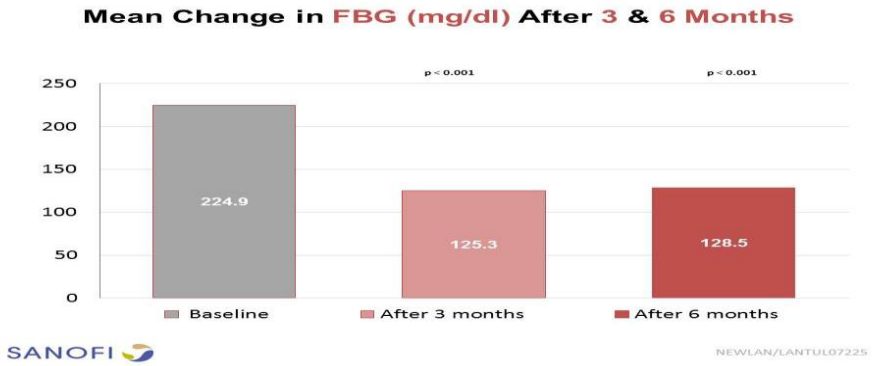
HbA1c change over study visits

With regard to the primary outcome of the study, the mean baseline HbA1c level decreased significantly from 9.78 ± 1.36 % to 8.04 ± 1.23 % by the end of third month of treatment; the mean change in HbA1c was -1.76 ± 1.46% (p <0.001). Moreover, the mean HbA1c level continued to decrease significantly by the end of sixth month of treatment to reach 7.69 ± 1.23%; the mean change from baseline was -2.09 ± 1.54%. Thirty-three (18%) patients achieved the targeted HbA1c (<7.0%) at visit 2 and 45 (25.4%) patients achieved the targeted HbA1c (<7.0%) at visit3.



Fasting Blood Glucose (FBG) change over study visits

Additionally, the mean baseline FBG level decreased significantly from 224.9 ± 75.3 mg/dL at baseline to 125.3 ± 38 mg/dL at the end of month 3 and to 128.5 ± 45.8 mg/dL at the end of month 6 of treatment; the reduction in FBG level was statistically significant (p <0.001).



Weight change over study visits

Mean body weight at baseline was 84.7 ± 14.95 kg and increased significantly to 85.8 ± 14.7 kg at visit 2 (p<0.001). Also, significantly increased to 87.1 ± 14.7 kg at visit 3 (p<0.001) compared to baseline.

BMI change over study visits

Mean BMI increased significantly during the study with baseline values from 30.3 ± 4.83 kg/m² to reach 30.8 ± 4.6 kg/m² at visit 2 (p<0.001) and 31.1 ± 4.69 kg/m² at visit 3 (p<0.001).

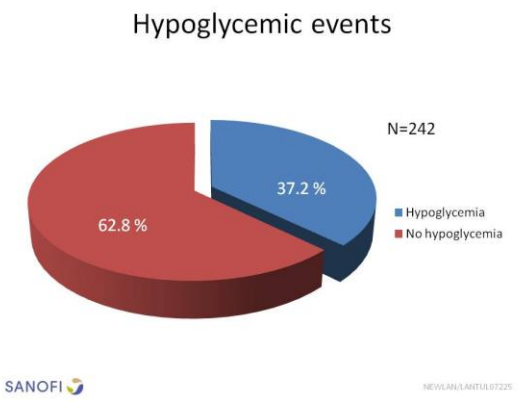
Safety results:

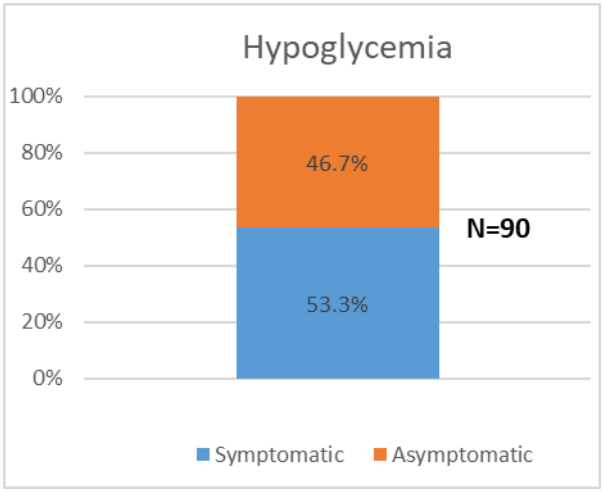
Adverse events

The incidence of adverse events was 8.7% throughout the study period, the encountered adverse events were intentional product misuse (9.5%), dry mouth (9.5%), hypertension (9.5%), and upper respiratory tract infection (9.5%), Stroke (0.4%), Asthenia (0.4%), Myocardial Infarction (0.4%), Hip Fracture (0.4%), Injury (0.4%), Oedema (0.4%), Arthralgia (0.4%), Musculoskeletal Pain (0.4%), Sinusitis (0.4%), Upper Abdominal Pain (0.4%), Joint Swelling (0.4%), Urinary Tract Infection (0.4%), and Skin Ulcer (0.4%).

Hypoglycemic events

In terms of safety outcomes, 90 (37%) patients experienced hypoglycemic events. The hypoglycemia was symptomatic in 48 (53.3%) patients. However, only 6 of these symptomatic events were severe (12.5%); none of the hypoglycemic events was classified as serious.





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