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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):** not applicable	**Study Identifiers:** U1111-1200-1995, NCT03312478 **Study code:** LANTUL08473 / SHINE
Title of the study: To evaluate the aSsociation between T1DM in offspring witH posItive pareNtal history of diabetes (SHINE)	
Study center(s): 5 sites in Pakistan	
Study period: Date first patient enrolled: 13-Oct-2017 Date last patient completed: 19-Aug-2018	
Phase of development: 4	
Objectives: Primary Objective: • To measure the association between a parental history of diabetes and the odds of an offspring being T1DM Secondary objective(s): • To document the profile of T1DM patients • To document the glycemic parameters (HbA1c) of T1DM • To capture the current therapeutic management	
Methodology: SHINE was a phase 4, national, multi-center, case control study, with a ratio of 1:2 (case: control). Case control study design had been selected to determine the exposure to the risk factor of interest from each of the two groups of individuals. Age matched controls were inducted for each case fulfilling with similar inclusion and exclusion criteria as explained in section 7. The enrollment duration of the study was 12 months. Each patient underwent laboratory test for insulin autoantibodies (IAA, GAD, or IA2) and HbA1c. Primary data had been collected at the time of enrolment. Subsequently telephonic follow up was performed 15 days ± 5 days to ensure the well-being of patients.	
Number of patients**:** Planned: 375 Randomized: Not applicable Treated: Not applicable **Evaluated:** Efficacy/pharmacodynamics: Not applicable Safety: 5 unsolicited adverse events were reported	
Diagnosis and criteria for inclusion: **Inclusion Criteria for Cases** • Age ≥ 2 years and ≤ 20 years	

• T1DM at any stage of life assessed as:

- Insulin initiated within one year of diagnosis.

- One or more islet autoantibodies (IAA, GAD, or IA2) positive at the time of enrolment. The laboratory value for IAA ≥ 2.4 units/ml, ≥ 10 IU/ml for IA2 and ≥ 5 IU/ml for anti-GAD had been labelled as positive.

• Consenting to participate in the study or care giver ready to sign data release consent if the patient was less than legal limit which was 18 years of age.

Inclusion Criteria for Controls

• Age ≥ 2 years and ≤ 20 years. Every control had been matched for a specific patient within ± two years of age.

• Non diabetic

• All islet autoantibodies negative at the time of enrolment (IAA, GAD, or IA2). The laboratory value for IAA < 2.4 units/ml, <10 IU/ml for IA2 and < 5 IU/ml for anti-GAD had been labelled as negative.

• Consenting to participate in the study or care giver ready to sign data release consent if the patient was less than 18 years of age.

Exclusion criteria for cases

• Age ≤ 2 years and >20 years

• Patient with any other pre-existing auto-immune disease

• Gestational Diabetes

• Pregnant Woman

Exclusion criteria for controls:

• Age ≤ 2 years and > 20 years

• Patient with history of T1 and T2DM

• History of T1 and T2DM in siblings

• Gestational Diabetes

• Pregnancy

Study treatments

Investigational medicinal product(s): Not applicable

Formulation: Not applicable

Route(s) of administration: Not applicable

Dose regimen: Not applicable

Duration of treatment: Not applicable

Duration of observation: Not applicable

Criteria for evaluation:

A table to calculate measures of disease frequency and association from dichotomous categorical variables. A typical 2 x 2 table.

The odds ratio (OR) was calculated by 2x2 table which was a measure of the relative magnitude of disease in matched case–controls pairs (1:2). The concordant pairs were ignored since they don't contribute in calculation of OR and discordant pairs of cases and controls were used to calculate the matched OR. From a 2 x 2 table.

Matched OR= Ratio of discordant pairs= (b/c).

Variables such as gender, socio economic status, distribution of prescribed therapies by type of insulin was treated as categorical and FBG (mg/dl) and HAb1c (%) were treated as continuous and their levels were treated as categorical.

Efficacy/pharmacodynamics: Not applicable

Safety: Incidence of serious and non- serious adverse events and nature of adverse events were recorded by investigators throughout the study period for each study participants.

Those adverse events resulted from the laboratory intervention were dealt as solicited and those resulting from the used of Sanofi products were dealt as unsolicited.

Statistical methods:

Population characteristics were summarized using descriptive statistics such as mean, standard deviation for continuous variables, and frequencies and percentages for categorical variables. A table to calculate measures of disease frequency and association from dichotomous categorical variables. A typical 2 x 2 table.

The odds ratio (OR) were calculated from 2x2 table which was a measure of the relative magnitude of disease in matched case–controls pairs (1:2). The concordant pairs were ignored since they don't contribute in calculation of OR and discordant pairs of cases and controls were used to calculate the matched OR. From a 2 x 2 table

Matched OR= Ratio of discordant pairs= (b/c).

Categorical variables such as gender, socio economic status, distribution of prescribed therapies by type of insulin were presented as frequencies and percentages, while continuous variable like FBG (mg/dl) and HbA1c (%) was presented as mean and standard deviation

Summary:

Population characteristics:

Three seventy five (125 cases and 250 controls) participants were enrolled in this study over a period of 12 months. Most of the study participants were male 58% (n=218). The mean age of the participants were 10.63 (SD =3.4) years. The mean HbA1c was recorded as 7.05 (SD +2.8) %.

No association was found between T1DM with positive parental history of diabetes.

Eleven percent of the cases (n=14) were reported to have positive family history of diabetes and among them T1DM was reported in 10.4% (n=13) of parents and T2DM in 0.8% (n=1) of parents. In regards to parental diabetic history, 8% (n=10) mothers were reported to have diabetes as compared to 3.2% (n=4) fathers.

Diabetes related complications were reported in 16% (n=60) of cases. The most common diabetes related complications were Diabetic ketoacidosis 86% (n=52), sensory neuropathy 10% (n=6) and retinopathy 3% (n=2), respectively.

Severe episode of hypoglycemia over the period of 3 months were reported in 41.6% (n=53) cases.

Human regular/ Human NPH were found to be most commonly prescribed insulin combination therapy taken by 53 % (n=66) of cases and premix insulin therapy alone were taken by 32% (n-40) cases.

Healthy lifestyle modification practices were effectively prevalent among cases and face to face diabetic education was imparted to this population by their health care providers. The data also suggest that people with T1DM were paying consistent visits to health care providers for diabetes related management.

Safety results:

Five unsolicited adverse events were reported from three investigations sites. The reported adverse events were hypoglycemia, hyperglycemia, raised HbA1c level, raised FBG level and diabetes ketoacidosis.

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