Non-Interventional Study (NIS) Report Synopsis	
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Usage of DapagliFlozin - a Sodium Glucose CO-transporter inhibitoR, in the managEment oF Type-2 Diabetes Mellitus: A Real wOrld evidence study in IndiaN patienTs (FOREFRONT)

Study dates:	**First Subject In:** 4th March 2017 **Last Subject Last Visit:** 3rd March 2018
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Study dates:	**First Subject In:** 4th March 2017 **Last Subject Last Visit:** 3rd March 2018

NIS REPORT SYNOPSIS

FOREFRONT NIS Study

Background/Rationale:

Diabetes is now endemic to India with an estimated 67 million Indians living with this condition in the year 2014. Metformin is a 1st line oral antidiabetic drug in most cases. Sulfonylureas (SU) are a frequent first add-on after the failure of metformin monotherapy. Sodium Glucose Co-transporter 2 (SGLT2) inhibitors are a newer class of oral hypoglycemic agents which has a lower incidence of hypoglycemia and in addition helps in weight and blood pressure (BP) reduction. In India, SGLT2 inhibitors were introduced in early 2015. Its usage is still not optimized for various reasons including lack of wide clinical experience in Indian patients and safety concerns particularly related to infections and some rare Diabetic Ketoacidosis (DKA). Also, usage of SGLT2 inhibitors is limited in the early stage of diabetes as they are usually preferred as 3rd or 4th add-on therapy.

The existing clinical trial programs on SGLT2 inhibitors included a limited number of subjects from India. Same is the case with the dapagliflozin phase-3 program where only few hundred Indian subjects are studied. There was no study available which evaluates the effect of dapagliflozin in real-world scenario in India. Key opinion leaders in diabetes in India had also identified the need for a study on Indian subjects to observe the usage pattern and effect of dapagliflozin, an SGLT2 inhibitor, in this specific real-world setting. Therefore, there was a need for data on real-world setting in larger group of subjects across India. With this aim in mind, the present study had been planned.

Objectives and Hypotheses:

Primary Objective

1. To record the mean change in glycated hemoglobin (HbA1c) from baseline.

Secondary Objectives

1. To record the HbA1c change (%) as per different baseline HbA1c levels (<8%, 8-10% and >10%).

2. To record the change in weight (kg) as per different baseline body mass index (BMI) (kg/m^2) (<25, 25-30, >30).
3. To record the change in blood pressure (mmHg) from baseline.
4. To record adverse events during the study, if any.
5. To describe the usage of concomitant anti-diabetic medications.

Methods:

Study design:

This study was a non-interventional, multicentre, prospective, observational study conducted at 50 sites in India. The study targeted to enroll 2000 subjects with 40 subjects per site. The study was initiated after obtaining written approval of Independent Ethics Committee (IEC) and written informed consent of the subject.

Study Population:

Inclusion Criteria

1. Male or female patients with 18 years and above.
2. Patients who provided written informed consent.
3. Patients with previously diagnosed Type-2 diabetes mellitus (T2DM).
4. Patients with inadequately controlled diabetes (HbA1c>7%) with existing anti-diabetic medications, prior to initiation of dapagliflozin treatment.
5. Patients who were taking dapagliflozin three months prior to initiation of the study.
6. Patients who were having past medical records for demographic information, weight, blood pressure, HbA1c value, and concomitant medications at the time of dapagliflozin prescribed.

Exclusion Criteria

1. Patients with Type-1 diabetes mellitus.
2. Patients with any medical condition which in the opinion of the investigator would interfere with safe completion of the study.
3. Pregnant or lactating women.
4. Patients with other severe conditions/elements which required hospitalization, during study participation period.

Exposure:

This was an observational, non-interventional study and aimed to capture the data from patients who were already taking dapagliflozin. The study was not aimed to expose patients to any intervention.

Statistical Analysis:

The primary objective was analyzed using paired t-test at 5% level of significance. Secondary objectives were analyzed using paired t-test at 5% level of significance. Number and

percentages of incidence of adverse events and patients using different anti-diabetic medications were presented.

Results:

A total of 1978 T2DM subjects were enrolled in the study. The mean (±SD) age and BMI of all enrolled subjects were 52.31 (±10.43) years and 29.30 (±5.28) (kg/m²). Majority of the subjects (88.6%) were on metformin. Dapagliflozin demonstrated statistically significant reductions in mean (±SD) HbA1c -1.49 (±1.18) % and BW -1.86 (±3.04) kg after six months of treatment from baseline ($p<0.001$). Further, in all baseline HbA1c (<8%, 8-10%, >10%) and BMI (<25, 25-30, >30 kg/m^2) categories, dapagliflozin demonstrated a statistically significant reduction in HbA1c and BW at Month 3 and 6 ($p<0.001$). The mean (±SD) reduction in systolic BP, diastolic BP, and heart rate at Month 3 was -3.24 (±11.44) mmHg, -1.13 (±7.67) mmHg and -0.51 (±6.22) beats/min, respectively. The reductions were maintained at Month 6. The study observed a total of 76 adverse events (AEs) in 58 (2.9%) subjects. Majority of the AEs were of mild severity and were recovered without sequelae. No increased incidence of AE was seen compared to existing liturature.The proportion of subjects who experienced vulvovaginitis and urinary tract infections (UTI) were 8/1978 (0.4%) and 4/1978 (0.2%), respectively over six months. Most of the genital infection or UTI events were of mild or moderate intensity except for one subject (0.1%) who experienced serious UTI. Hypoglycemia was observed in 3/1978 (0.2%) subjects.

Conclusion:

In conclusion, the six months of dapagliflozin therapy in T2DM patients significantly improved HbA1c and was well tolerated. Also, a significant reduction in body weight and blood pressure was demonstrated with dapagliflozin.