Dapagliflozin Monotherapy in Type 2 Diabetic Patients With Indadequate Glycemic Control by Diet and Exercise

BACKGROUND:

- The need for optimal management of glycemia in patients with type 2 diabetes has long been recognized
- As metabolic risk factors frequently occur as a cluster, it is difficult to control glycemia without negatively affecting one or more of the associated risk factors
- The need for new treatment strategies for glycemic control has led to the development of a new class of compounds referred to as sodium-glucose cotransporter 2 (SGLT2) inhibitors such as dapagliflozin

OBJECTIVE:

- To evaluate the safety and efficacy of dapagliflozin (a highly selective SGLT2 inhibitor)in treatment naïve type 2 diabetes patients

METHODS:

- **Design:** 24 week, randomized, double-blind, parallel group, placebo controlled phase III trial
- **Inclusion/Exclusion criteria:**
  - Inclusion – treatment naïve type 2 diabetic patients age 18-77 whose hyperglycemia was inadequately controlled with diet and exercise alone; BMI $\leq 45 kg/m^2$; Fasting c-peptide ≥ 1.0 ng/mL
  - Exclusion – history of type 1 diabetes; serum creatinine ≥ 133 micromol/L or 124 micromol/L (in men and women respectively); urine albumin to creatinine ratio> 200mg/mmol; AST or ALT > 3 times ULN; creatine kinase ≥ 3 times ULN; symptoms of severely uncontrolled diabetes; significant renal, hepatic, hematological, oncological, endocrine, psychiatric, or rheumatic diseases; a cardiovascular event within 6 months of enrollment; severe uncontrolled hypertension (systolic $\geq$180mmHg, diastolic ≥ 110mmHg)
- **Number of patients enrolled/drug regimens and dosages used**
  - Main Patient Cohort: morning dose – 274 patients enrolled
    - Placebo – 75; Dapagliflozin 2.5mg – 65; Dapagliflozin 5mg – 64; Dapagliflozin 10mg – 70
  - Exploratory Patient Cohort: evening dose – 211 patients enrolled
    - Dapagliflozin 2.5mg – 67; Dapagliflozin 5mg – 68; Dapagliflozin 10mg – 76
  - Exploratory Patient Cohort: High A1c group; morning dose – 74 patients enrolled
    - Dapagliflozin 5mg – 35; Dapagliflozin 10mg – 39
- **Primary outcome measure**:
  - Change in A1c from baseline to week 24 in main patient cohort
- **Secondary outcome measure**:
  - Change in fasting plasma glucose (FPG)and body weight from baseline to week 24 in main patient cohort
- **Other outcomes**
  - Change in A1c, FPG, and body weight from baseline to week 24 in exploratory patient cohorts
- **Data handling method used:**
  - Intent to treat with last observation carried forward in patients with baseline values for the primary and secondary outcome measures

RESULTS:

- **Number of patients who completed the study:**
  - Main Patient Cohort: morning dose – 232 (84.7%)
  - Exploratory Patient Cohort: evening dose – 180 (85.3%)
  - Exploratory Patient Cohort: High A1c group; morning dose – 62 (83.8%)

- **Primary outcome measure:**
    - Mean reductions in A1c from baseline to week 24 ranged from -0.58% to -0.89% with dapagliflozin compared to -0.23% with placebo.
    - These reductions in A1c were statistically significant for the 5mg dapagliflozin and 10mg dapagliflozin groups vs. placebo ($p=0.0005$ and $p<0.0001$ respectively)
    - At the end of the study, a higher proportion of patients in dapagliflozin groups reached the target A1c goal of <7% as compared to placebo
- **Secondary outcome measure:**
    - Reductions in FPG were statistically significant in the 5mg dapagliflozin and 10 mg dapagliflozin groups vs. placebo ($p<0.001$ and $p<0.0001$ respectively)
    - Mean body weight decreases were greater with all dapagliflozin doses than placebo, but did not reach statistical significance
- **Other outcomes (exploratory patient cohort groups):**
    - In the exploratory evening dose cohort, changes from baseline to week 24 in A1c, FPG, and body weight were similar to those seen in the main patient cohort
    - In the exploratory high A1c cohort, treatment with dapagliflozin led to numerically greater reductions in mean A1c and FPG from baseline than those observed in other cohorts
- **Authors stated conclusion:** administration of dapagliflozin as monotherapy to treatment-naïve patients with type 2 diabetes resulted in clinically meaningful decreases in A1c and fasting plasma glucose, along with favorable effects on weight, blood pressure and other metabolic parameters

STRENGTHS:

- Diet/exercise/placebo lead in prior to study drug implementation for all patients
- Exclusion of subjects with inadequate or compromised renal function as well as those with comorbid conditions linked to renal function
- Diet and exercise counseling per ADA recommendations for all patients throughout the study

LIMITATIONS:

- Lack of explicit definition of all inclusion criteria and inclusion of subjects who did not meet all inclusion criteria
- Numerous conflicts of interest
- Manufacturer involvement in study design, conduct, data collection, and data management
- Incomplete statistical analysis
- Incomplete disclosure and monitoring of adverse events
- Inclusion of subjects requiring medication rescue in efficacy analysis without distinction

CONCLUSION:

- Treatment with dapagliflozin at doses of 5mg and 10mg in the morning in combination with diet and exercise counseling resulted in greater decreases in A1c levels and FPG levels than diet and exercise counseling alone in treatment naïve type 2 diabetic patients. However, due to the vast limitations in this study, the clinical utility of this data is extremely limited. The use of this medication in the routine treatment of these patients is not warranted without further study.
- Future research
    - Limited manufacturer involvement in the collection, management, and interpretation of study data
    - Trials of sufficient length to determine safety and tolerability as well as the long term effects of the study drug on plasma glucose, diabetes, and renal function
    - Explicitly defined and followed inclusion and exclusion criteria

- Statistical analysis on all data generated from treatment groups including outcome measures and adverse events

REFERENCE:

Ferrannini E, Ramos SJ, Salsali A, Tang W, List JF. Dapagliflozin Monotherapy in Type 2 Diabetic Patients With Inadequate Glycemic Control by Diet and Exercise. *Diabetes Care*. 2010 Oct; 33(10): 2217-2224.

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