Dapagliflozin Clinical Trial Results Indicate Improvement In Key Glycemic Measures In Treatment-Naïve Type 2 Diabetes Patients

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PRINCETON, N.J. & LONDON--(BUSINESS WIRE)--Findings published today in Diabetes Care from a 12-week, Phase IIb dose-ranging study showed that dapagliflozin, a novel, selective, sodium glucose co-transporter2 (SGLT2) inhibitor, produced clinically meaningful reductions across all key glycemic measures studied (glycosylated hemoglobin level (HbA1c), fasting plasma glucose (FPG), and postprandial plasma glucose (PPG)) in treatment-naïve type 2 diabetes patients, compared to placebo. The study findings also showed that patients receiving dapagliflozin experienced greater reductions in body weight compared to patients on placebo. Adverse events across dapagliflozin and metformin doses were reported at a similar rate, which was somewhat higher than placebo.

Dapagliflozin is an investigational SGLT2 inhibitor currently in Phase III trials under joint development by Bristol-Myers Squibb Company (NYSE: BMY) and AstraZeneca (NYSE: AZN) as a once-daily therapy for the treatment of type 2 diabetes. SGLT2 inhibitors act by inhibiting the reabsorption of glucose in the kidney, thereby reducing the return of filtered glucose to the circulation.

“These data suggest that dapagliflozin, the first SGLT2 to be studied in Phase III clinical trials, may reduce important glycemic measures and facilitate weight loss in patients with type 2 diabetes,” said Elisabeth Svanberg, M.D., Ph.D., vice president, Development Lead, Bristol-Myers Squibb. “We look forward to further studies of dapagliflozin to fully understand its potential in the treatment of people with type 2 diabetes,” said William Mezzanotte, M.D., M.P.H., vice president, Global Products, AstraZeneca.

About the Study
This Phase IIb study, presented at the 2008 American Diabetes Association annual meeting, was designed to assess the efficacy and safety of dapagliflozin across a wide range of doses. The data represent findings from a prospective, randomized, double-blind, placebo-controlled, parallel-group study of 389 individuals with type 2 diabetes (ages 18-79) who were treatment-naïve and whose HbA1c was greater than or equal to 7 percent and less than or equal to 10 percent. After a two-week lead-in phase that included diet, exercise and placebo, individuals were randomized to one of seven separate treatment arms: dapagliflozin 2.5 mg (n=59), 5 mg (n=58), 10 mg (n=47), 20 mg (n=59), 50 mg (n=56), metformin extended release 750 mg force-titrated at Week 2 to 1500 mg (n=56) or placebo (n=54), once daily for 12 weeks. Metformin was included as a positive control benchmark; no statistical comparison was made to the metformin arm.

The primary endpoint of the study compared mean HbA1c change from baseline for each dapagliflozin group versus placebo. The secondary endpoints included FPG change from baseline as compared to placebo, dose-dependent trends in glycemic efficacy, the proportion of individuals achieving the American Diabetes Association recommended HbA1c target of less than 7 percent and the change in 24-hour urinary glucose-to-creatinine ratio.

Study Results
After 12 weeks, individuals receiving dapagliflozin demonstrated a significant adjusted mean decrease in HbA1c from baseline of -0.71 percent for dapagliflozin 2.5 mg, -0.72 percent for dapagliflozin 5 mg, -0.85 percent for dapagliflozin 10 mg, -0.55 percent for dapagliflozin 20 mg and -0.90 percent for dapagliflozin 50 mg, compared to -0.18 percent for placebo (p-value at the 2.5, 5, 10 and 50 mg dose levels less than 0.001; p-value at the 20 mg dose level equal to 0.007). The adjusted mean decrease for metformin was -0.73 percent. No log-linear dose response relationship was demonstrated (P trend = 0.41).

Dapagliflozin also demonstrated a clinically meaningful adjusted mean decrease in FPG from baseline of -16 mg/dL for dapagliflozin 2.5 mg, -19 mg/dL for dapagliflozin 5 mg, -21 mg/dL for dapagliflozin 10 mg, -24 mg/dL for dapagliflozin 20 mg and -31 mg/dL for dapagliflozin 50 mg, compared to -6 mg/dL for placebo (p-value at the 2.5 mg dose level equal to 0.03; p-value at the 5 mg dose level equal to 0.005; p-value at the 10 mg dose level equal to 0.002; p-value at the 20 mg and 50 mg dose levels less than or equal to 0.001). The adjusted mean decrease for metformin was -18 mg/dL.

The percentage of individuals treated with dapagliflozin that achieved HbA1c of less than 7 percent after the 12 week treatment period was 46 percent for dapagliflozin 2.5 mg, 40 percent for dapagliflozin 5 mg, 52 percent for dapagliflozin 10 mg, 46 percent for dapagliflozin 20 mg and 59 percent for dapagliflozin 50 mg, compared to 32 percent for placebo and 54 percent for metformin. The 50 mg result was the only statistically significant result, with a p-value equal to 0.01.

Over 12 weeks, the incidence of adverse events was 59 percent for dapagliflozin 2.5 mg, 60 percent for dapagliflozin 5 mg, 68 percent for dapagliflozin 10 mg, 68 percent for dapagliflozin 20 mg and 63 percent for dapagliflozin 50 mg; the incidence
of events was 54 percent for placebo and 68 percent for metformin. The percentages of the most commonly reported (greater than or equal to 10 percent in any group) adverse events for dapagliflozin 2.5 mg, 5 mg, 10 mg, 20 mg, and 50 mg doses and placebo and metformin, respectively, were: urinary tract infection [5, 9, 11, 7, 7, 6, 7], nausea [5, 7, 6, 3, 5, 6, 11], headache [7, 5, 4, 5, 2, 11, 4], and diarrhea [2, 2, 7, 2, 7, 13].

The rate of reported hypoglycemic events was 7 percent for dapagliflozin 2.5 mg, 10 percent for dapagliflozin 5 mg, 6 percent for dapagliflozin 10 mg, 7 percent for dapagliflozin 20 mg and 7 percent for dapagliflozin 50 mg; the incidence of reported hypoglycemic events was 4 percent for placebo and 9 percent for metformin. There was no occurrence of confirmed hypoglycemia (symptoms of hypoglycemia with a fingerstick glucose less than or equal to 50 mg/dL).

**Effects of Dapagliflozin on Weight Loss**

The Phase IIb study also evaluated the potential impact of dapagliflozin-induced glucosuria on weight loss in people with type 2 diabetes, compared to placebo. These findings included data measuring changes in total body weight and body mass index over the 12-week study period.

Overall, greater percent decreases in total body weight occurred in the dapagliflozin treatment groups: -2.7 percent for dapagliflozin 2.5 mg, -2.5 percent for dapagliflozin 5 mg, -2.7 percent for dapagliflozin 10 mg, -3.4 percent for dapagliflozin 20 mg and -3.4 percent for dapagliflozin 50 mg compared to -1.2 percent for placebo and -1.7 percent for metformin.

**About Type 2 Diabetes**

Diabetes (diabetes mellitus) is a chronic disease in which the body does not produce enough insulin (insulin deficiency), and the cells ignore the insulin (insulin resistance). Symptoms of type 2 diabetes develop gradually, and their onset is not as sudden as in type 1 diabetes. Symptoms may include fatigue, frequent urination, increased thirst and hunger, weight loss, blurred vision, and slow healing of wounds or sores. Some people, however, have no symptoms.

There are two primary underlying causes associated with type 2 diabetes: the body does not produce enough insulin (insulin deficiency), and the cells ignore the insulin (insulin resistance). Symptoms of type 2 diabetes develop gradually, and their onset is not as sudden as in type 1 diabetes. Symptoms may include fatigue, frequent urination, increased thirst and hunger, weight loss, blurred vision, and slow healing of wounds or sores. Some people, however, have no symptoms.

The kidneys play a key role in the overall regulation of blood glucose levels in the body. Normally, in healthy individuals, the kidneys filter a large volume of glucose and actively reabsorb virtually all of it. In patients with type 2 diabetes that have hyperglycemia, a greater amount of glucose is filtered and reabsorbed by the kidneys despite the fact that this perpetuates the hyperglycemia.

Over time, the factors that contribute to sustained hyperglycemia lead to glucotoxicity, which worsens insulin resistance and contributes to dysfunction in the beta cells of the pancreas. In this way, hyperglycemia appears to perpetuate a vicious cycle of deleterious effects that exacerbate type 2 diabetes.

Type 2 diabetes is most often associated with older age, obesity, family history of diabetes, previous history of gestational diabetes, physical inactivity and certain ethnicities. People with type 2 diabetes often are characterized with: insulin resistance, abdominal obesity, a sedentary lifestyle, having low HDL-C (“good”) cholesterol levels and high triglyceride levels and hypertension.

**About SGLT2 Inhibitors**

The kidney continuously filters glucose through the glomerulus; however, nearly all of this glucose is reabsorbed in a separate part of the kidney called the proximal tubule. A protein called SGLT2 is responsible for the majority of glucose reabsorption and helps the body retain glucose for its energy requirements. Inhibiting the activity of SGLT2 helps limit the amount of glucose that is reabsorbed and retained in the body, thereby leading to the excretion of glucose in the urine.

**Bristol-Myers Squibb and AstraZeneca Partnership**

Bristol-Myers Squibb and AstraZeneca entered into collaboration in January 2007 to enable the companies to research, develop and commercialize two investigational drugs for type 2 diabetes – saxagliptin and dapagliflozin. The Bristol-Myers Squibb/AstraZeneca Diabetes collaboration is dedicated to global patient care, improving patient outcomes and creating a new vision for the treatment of type 2 diabetes.

**About Bristol-Myers Squibb**

Bristol-Myers Squibb is a global biopharmaceutical company whose mission is to extend and enhance human life. For more information visit www.bms.com.

**About AstraZeneca**

AstraZeneca is a major international healthcare business engaged in the research, development, manufacturing and marketing of meaningful prescription medicines and supplier for healthcare services. AstraZeneca is one of the world’s leading pharmaceutical companies with healthcare sales of US$ 31.6 billion and is a leader in gastrointestinal, neuroscience, respiratory, oncology and infectious disease medicines. For more information about AstraZeneca, please visit: www.astrazeneca.com.

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