

Dapagliflozin as Monotherapy Demonstrated Improved Glycemic Control in Treatment-Naïve Adults with Type 2 Diabetes

(PRINCETON, NJ and WILMINGTON, DE, June 22, 2010) – Findings from a 24-week Phase 3 clinical study published online in the latest issue of *Diabetes Care* demonstrated that the investigational drug dapagliflozin, administered as a monotherapy, achieved statistically significant mean reductions at 5 mg and 10 mg doses once daily in the primary endpoint of glycosylated hemoglobin levels (HbA1c) in treatment-naïve adult patients with newly diagnosed type 2 diabetes, compared to placebo. The study also showed reductions in the secondary endpoint of fasting plasma glucose (FPG) and total body weight compared to placebo in these patients. Signs, symptoms and other reports suggestive of urinary tract infections (UTIs) and genital infection were more frequently noted in the dapagliflozin arms and rarely led to treatment discontinuation. No major episodes of hypoglycemia were reported in the study. This data appears in a pre-print version of the study that is scheduled to be published in the September issue of *Diabetes Care* and is currently available online at <http://diabetes.org/diabetescare>. An abstract of this study was presented at the World Diabetes Congress in 2009.

Dapagliflozin, an investigational compound, is a potential first-in-class sodium-glucose cotransporter-2 (SGLT2) inhibitor currently in Phase 3 trials under joint development by [Bristol-Myers Squibb Company](#) (NYSE: BMY) and [AstraZeneca](#) (LSN, NYSE: AZN) as a once-daily oral therapy for the treatment of adult patients with type 2 diabetes. SGLT2 inhibitors facilitate the elimination of glucose by the kidney, which should result in lowering serum glucose levels.

“These findings of dapagliflozin as a monotherapy, together with an additional Phase 3 study of dapagliflozin in combination with metformin which was presented at the 2009 European Association for the Study of Diabetes annual meeting, show the potential of this agent to help patients with type 2 diabetes,” said Ele Ferrannini, MD, Professor of Internal Medicine, Department of Internal Medicine, University of Pisa School of Medicine (Italy).

About the Study

The study was designed to assess the efficacy and safety of dapagliflozin in treatment-naïve patients with newly diagnosed type 2 diabetes and inadequate glycemic control with diet and exercise alone. The data represent findings from a 24-week, parallel-group, double-blind, placebo-controlled Phase 3 study, with a 2 week diet/exercise placebo lead-in.

Throughout the study, all patients received diet and exercise counseling per American Diabetes Association (ADA) recommendations.

The study included 485 individuals with type 2 diabetes (ages 18 - 77) who were drug naïve and had a HbA1c level between 7.0 and 10.0%. Subjects were randomized equally to one of seven treatment groups to receive either a morning (main cohort) or evening (exploratory cohort) once-daily dose as follows for 24 weeks: Morning dose: placebo (n=75), dapagliflozin 2.5 mg (n=65), dapagliflozin 5 mg (n=64) or dapagliflozin 10 mg (n=70); Evening dose: dapagliflozin 2.5 mg (n=67), dapagliflozin 5 mg (n=68) or dapagliflozin 10 mg (n=76).

The primary endpoint was mean change from baseline at week 24 in HbA1c in the main cohort. Key secondary efficacy measures included change from baseline at week 24 in FPG and body weight.

Study Results

After 24 weeks, individuals in the main cohort receiving dapagliflozin 5 mg and 10 mg demonstrated a statistically significant adjusted mean change in HbA1c from baseline of -0.77% and -0.89% respectively, compared to -0.23% for placebo (p-value less than 0.001 and p-value less than 0.0001 respectively, versus placebo). Individuals receiving dapagliflozin 2.5 mg experienced an adjusted mean change in HbA1c of -0.58% (p-value of 0.02).

Individuals treated with dapagliflozin 5 mg and 10 mg demonstrated statistically significant reductions in FPG, a secondary endpoint, at week 24 from baseline: -24.1 mg/dL for dapagliflozin 5 mg and -28.8 mg/dL for dapagliflozin 10 mg, compared to -4.1 mg/dL for placebo (p-value 0.0007 and p-value less than 0.0001 respectively, versus placebo). Individuals receiving dapagliflozin 2.5 mg experienced a reduction of -15.2 mg/dL.

At week 24, a higher proportion of patients in dapagliflozin groups were able to achieve the American Diabetes Association/European Association for the Study of Diabetes recommended target HbA1c of less than 7% (secondary endpoint: 41%, 44%, 51% with dapagliflozin 2.5 mg, 5 mg and 10 mg respectively, versus 32% with placebo).

In addition, the study evaluated the potential impact of dapagliflozin added to a regimen of diet and exercise on total body weight. At week 24, the decrease in adjusted mean total body weight, a secondary endpoint, was greater with each dapagliflozin dose compared to placebo, although not reaching statistical significance (-3.3 kg, -2.8 kg, -3.2 kg with dapagliflozin 2.5 mg, 5 mg and 10 mg respectively, versus -2.2 kg with placebo).

The percentages of the most frequent adverse events (greater than 10%) with dapagliflozin 2.5 mg, 5 mg and 10 mg, compared to placebo, were as follows: nasopharyngitis (10.8, 4.7, 2.9, 5.3), diarrhea (6.2, 1.6, 1.4, 1.3), headache (7.7, 4.7, 5.7, 6.7). Patients were actively monitored for clinical signs and symptoms suggestive of urinary tract infections and genital infections. An increased incidence of signs, symptoms and other reports suggestive of UTIs and genital infections was noted with dapagliflozin treatment. Events suggestive of UTI were as follows: 4.6%, 12.5%, 5.7% with dapagliflozin 2.5 mg, 5 mg and 10 mg respectively, versus 4.0% with placebo. Events suggestive of genital infections were as follows: 7.7%, 7.8%, 12.9% with dapagliflozin 2.5 mg, 5 mg and 10 mg respectively compared to 1.3% with placebo. The reported signs, symptoms and other events suggestive of UTI and genital infections rarely led to treatment discontinuation.

The occurrence of hypoglycemia was as follows: 1 case (1.5%) in the dapagliflozin 2.5 mg group, 0 cases in the dapagliflozin 5 mg group, 2 cases (2.9%) in the dapagliflozin 10 mg group, compared with 2 cases (2.7%) in the placebo group. There were no reports of major episodes of hypoglycemia in any treatment group and no patients discontinued study medication due to hypoglycemia.

At week 24, the seated systolic mean change in blood pressure was greater for each dapagliflozin treatment group compared to placebo: -4.6 mmHg for dapagliflozin 2.5 mg, -2.3 mmHg for dapagliflozin 5 mg, -3.6mm Hg for dapagliflozin 10 mg compared to -0.9 mm Hg for placebo.

Additional Exploratory Analyses

In the exploratory evening dose cohort, changes from baseline in HbA1c, FPG and body weight at week 24 were similar to those seen in the main dapagliflozin patient cohort.

An additional exploratory analysis was conducted in patients with a HbA1c level between 10.1 and 12.0% (high-HbA1c exploratory cohort, n=73), who were randomly assigned to receive blinded treatment with a morning dose of either dapagliflozin 5 mg or 10 mg once-daily. This analysis showed that treatment with dapagliflozin lead to numerically greater reductions in mean HbA1c and FPG from baseline than those observed in other cohorts.

About Type 2 Diabetes

Type 2 diabetes (diabetes mellitus) is a complex, progressive disease characterized by elevated glucose which is frequently associated with other co-morbidities such as obesity, hypertension and dyslipidemia. Significant unmet needs exist as nearly half of the patients remain uncontrolled on their current treatment regimen.

The kidneys play a key but underappreciated 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. Glucose reabsorption is necessary to retain calories, but becomes counterproductive in type 2 diabetes. In patients with type 2 diabetes who have hyperglycemia, a greater amount of glucose is filtered and reabsorbed by the kidneys, which contributes to sustained hyperglycemia in diabetes.

Over time, sustained hyperglycemia worsens insulin resistance and contributes to dysfunction in the beta cells of the pancreas further undermining control of the disease. Sustained hyperglycemia is also directly related to diabetic microvascular complications such as blindness and may also contribute to macrovascular complications.

About SGLT2 Inhibition

The kidney continuously filters glucose through the glomerulus; however, nearly all of this glucose is reabsorbed. A protein called SGLT2 is responsible for the majority of glucose reabsorption and helps the body retain glucose for its energy requirements. For patients with diabetes, retention of excess glucose by this pathway contributes to persistent hyperglycemia.

Bristol-Myers Squibb and AstraZeneca Collaboration

Bristol-Myers Squibb and AstraZeneca entered into a collaboration in January 2007 to enable the companies to research, develop and commercialize select investigational drugs for type 2 diabetes. 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 discover, develop and deliver innovative medicines that help patients prevail over serious diseases.

For more information about Bristol-Myers Squibb, visit www.bms.com or follow us on Twitter at <http://twitter.com/bmsnews>.

This press release contains "forward-looking statements" as that term is defined in the Private Securities Litigation Reform Act of 1995 regarding product development. Such forward-looking statements are based on current expectations and involve inherent risks and uncertainties, including factors that could delay, divert or change any of them, and could cause actual outcomes and results to differ materially from current expectations. No forward-looking statement can be guaranteed. Among other risks, there can be no guarantee that dapagliflozin will receive regulatory approval or, if approved, that it will become a commercially successful product. Forward-looking statements in this press release should be evaluated together with the many uncertainties that affect Bristol-Myers Squibb's business, particularly those identified in the cautionary factors discussion in Bristol-Myers Squibb's Annual Report on Form 10-K for the year ended December 31, 2009, in our Quarterly Reports on Form 10-Q and our Current Reports on Form 8-K. Bristol-Myers Squibb undertakes no obligation to publicly update any forward-looking statement, whether as a result of new information, future events or otherwise.

About AstraZeneca

AstraZeneca is a global, innovation-driven biopharmaceutical business with a primary focus on the discovery, development and commercialization of prescription medicines. As a leader in gastrointestinal, cardiovascular, neuroscience, respiratory and inflammation, oncology and infectious disease medicines, AstraZeneca generated global revenues of \$32.8 billion in 2009. In the United States, AstraZeneca is a \$14.8 billion healthcare business.

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