Investigational Compound Dapagliflozin Sustained Glycemic Control and Weight Reduction in Study of Type 2 Diabetes Patients Inadequately Controlled with Metformin

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- **Extension of study evaluated safety and efficacy of dapagliflozin plus metformin versus placebo plus metformin at 102 weeks**
- **Update on overall safety profile provided**

SAN DIEGO--(BUSINESS WIRE)--Bristol-Myers Squibb Company (NYSE: BMY) and AstraZeneca (NYSE: AZN) today announced results from an exploratory 78-week study extension of a Phase 3 clinical study that showed the investigational compound dapagliflozin plus metformin sustained greater mean reductions from baseline in blood sugar levels (glycosylated hemoglobin levels, or HbA1c) in patients with type 2 diabetes inadequately controlled with metformin alone, as compared to placebo plus metformin over 102 weeks. The reductions seen in the study ranged from -0.48 percent in patients receiving dapagliflozin 2.5mg plus metformin to -0.78 percent in patients receiving dapagliflozin 10 mg plus metformin, as compared to 0.02 percent in patients taking placebo plus metformin. Efficacy was evaluated only as an exploratory endpoint; the extension was primarily designed to assess safety. Adverse events, serious adverse events and adverse events leading to discontinuation reported in the study were balanced across treatment groups, with events suggestive of genital infections and urinary tract infections more common in the dapagliflozin groups. The results were presented today at the 71st American Diabetes Association Scientific Sessions.

In addition to sustained reductions in blood sugar levels, the 102-week study reported results from additional exploratory endpoints, including fasting plasma glucose (FPG) and mean change from baseline in body weight, which were both sustained at 102 weeks in patients with type 2 diabetes inadequately controlled with metformin alone as compared to placebo plus metformin.

Signs, symptoms and other reports suggestive of genital infections or urinary tract infections were more common in patients taking dapagliflozin added to metformin. These events were proactively monitored, with most patients responding to standard treatment. One event suggestive of a urinary tract infection lead to discontinuation. Other commonly occurring adverse events included back pain, influenza, diarrhea, headache, nasopharyngitis, upper respiratory tract infection, renal impairment or failure and events of hypoglycemia. In addition, one patient treated with dapagliflozin 5 mg was diagnosed with transitional cell bladder cancer. One woman treated with 10 mg dapagliflozin was diagnosed with breast cancer.

“This study of dapagliflozin added to metformin over 102 weeks suggests that this drug has greater and sustained improvements in glycemic control and sustained reductions in body weight compared to placebo,” said Cliff Bailey, Professor of Clinical Science and Head of Diabetes Research at Aston University, Birmingham, UK. “This information adds to the body of dapagliflozin knowledge and could help the medical community better understand the SGLT2 inhibitor mechanism.”

The initial 24-week results for the study were presented during the 45th European Association for the Study of Diabetes (EASD) Annual Meeting in 2009. A New Drug Application (NDA) for dapagliflozin was accepted for review by the U.S. Food and Drug Administration (FDA) in March 2011 with a Prescription Drug User Fee Act (PDUFA) date set for October 28, 2011. In addition, a Marketing Authorisation Application (MAA) was validated by the European Medicines Agency (EMA) in January 2011. If approved, dapagliflozin -- an inhibitor of SGLT2, a target in the kidney -- would potentially be the first in a new class of insulin-independent, oral type 2 diabetes agents.

**About the Study**

This was a 24-week Phase 3, randomized, double-blind, placebo-controlled study with a 78-week extension. The primary endpoint at 24 weeks compared mean HbA1c change from baseline for each dapagliflozin treatment arm compared to placebo. The 78-week extension was designed to assess the safety of long-term treatment with dapagliflozin, as well as changes from baseline in HbA1c, FPG and weight over 102 weeks of treatment.

The study included 546 adults with type 2 diabetes (aged ≥18) whose HbA1c was between 7% and 10%. After a two-week lead-in phase, individuals were randomized to one of four treatment groups at the onset of the study: dapagliflozin 2.5 mg (n=137), dapagliflozin 5 mg (n=137), dapagliflozin 10 mg (n=135), or placebo (n=137). Patients in all arms also received at least 1,500 mg/d of metformin. Four hundred and eighty-three patients completed the initial 24-week study. Four hundred
and seventy-six patients entered the 78-week extension period, and of these 339 patients completed the extension. The completion rate was lower for the placebo group (63.5%) than for the dapagliflozin groups (68.3% – 79.8%).

More patients on placebo (23.5%) withdrew during the extension period for lack of efficacy compared to the dapagliflozin groups (13.3%, 13.9%, and 7.6% for dapagliflozin 2.5 mg, 5 mg, and 10 mg, respectively). The proportion of patients rescued or discontinued for failing to achieve glycemic targets was larger for the placebo group (83/137 [60.6%]) than for the dapagliflozin 2.5 mg (71/137 [51.8%]), dapagliflozin 5 mg (63/137 [46.0%]) and dapagliflozin 10 mg (57/135 [42.2%]) groups at week 102.

**Study Results: Efficacy Findings**

At the end of 102 weeks, change from baseline in HbA1c in patients receiving placebo plus metformin was 0.02 percent, compared to -0.48 percent for patients receiving dapagliflozin 2.5 mg plus metformin, -0.58 percent for patients receiving dapagliflozin 5 mg plus metformin and -0.78 percent for patients receiving dapagliflozin 10 mg plus metformin.

The mean change from baseline in FPG at Week 102 in patients receiving placebo plus metformin was -10.4 mg/dL, compared to -19.3 mg/dL for patients receiving dapagliflozin 2.5 mg plus metformin, -24.5 mg/dL for patients receiving dapagliflozin 5 mg plus metformin and -26.4 mg/dL for patients receiving dapagliflozin 10 mg plus metformin.

The mean change from baseline in body weight at Week 102 in patients receiving placebo plus metformin was -1.36 kg, compared to -1.10 kg for patients receiving dapagliflozin 2.5 mg plus metformin, -1.70 kg for patients receiving dapagliflozin 5 mg plus metformin and -1.74 kg for patients receiving dapagliflozin 10 mg plus metformin.

The adjusted percentage of patients receiving placebo plus metformin who achieved HbA1c of less than 7 percent at 102 weeks was 15.4 percent, compared to 20.7 percent for patients receiving dapagliflozin 2.5 mg plus metformin, 26.4 percent for patients receiving dapagliflozin 5 mg plus metformin and 31.5 percent for patients receiving dapagliflozin 10 mg plus metformin.

**Study Results: Safety Findings**

One hundred and eleven subjects per group (81.0% – 82.2%) reported at least one adverse event.

The rate of events suggestive of urinary tract infections for patients receiving placebo plus metformin was 8.0%, compared to 8.0% for patients receiving dapagliflozin 2.5 mg plus metformin, 8.8% for patients receiving dapagliflozin 5 mg plus metformin and 13.3% for patients receiving dapagliflozin 10 mg plus metformin.

The rate of events suggestive of genital infections for patients receiving placebo plus metformin was 5.1%, compared to 11.7% for patients receiving dapagliflozin 2.5 mg plus metformin, 14.6% for patients receiving dapagliflozin 5 mg plus metformin and 12.6% for patients receiving dapagliflozin 10 mg plus metformin.

Of patients treated with placebo plus metformin, 5.8% experienced at least one hypoglycemic event, compared to 3.6% of patients receiving dapagliflozin 2.5 mg plus metformin, 5.1% of patients receiving dapagliflozin 5 mg plus metformin and 5.2% of patients receiving dapagliflozin 10 mg plus metformin. There were no major episodes of hypoglycemia.

Events of renal impairment or failure were reported in 1.5% of patients treated with placebo plus metformin, compared to 4.4% of patients receiving dapagliflozin 2.5 mg plus metformin, 2.9% of patients receiving dapagliflozin 5 mg plus metformin and 1.5% of patients receiving dapagliflozin 10 mg plus metformin.

One case of transitional cell bladder cancer was reported in the dapagliflozin 5 mg treatment group; none were reported in the placebo, dapagliflozin 2.5 mg or dapagliflozin 10 mg treatment groups. One case of breast cancer was reported in dapagliflozin 10 mg treatment group; none were reported in the placebo, dapagliflozin 2.5 mg or 5 mg groups.

**Update on Malignancies in the Overall Dapagliflozin Safety Profile**

In the overall dapagliflozin clinical program, there was no overall imbalance in malignant tumors. However, there were imbalances in two tumor types in the dapagliflozin clinical trial program. Nine bladder cancers have been observed in 5,478 patients on dapagliflozin and one bladder cancer has been observed in 3,156 patients in control groups. Six of these 10 subjects had hematuria (blood in the urine) at baseline and five were diagnosed within a year after study start. Nine breast cancers have been observed in 2,223 women on dapagliflozin and one has been observed in 1,053 women in control groups. All were diagnosed within a year after study start.

In preclinical studies, dapagliflozin was not shown to be genotoxic or carcinogenic and the investigational agent has no known off-target pharmacology. SGLT2 is not expressed in the breast or in the bladder.

These clinical and preclinical data have been shared with FDA and other health authorities and will be reviewed fully at the scheduled Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) on July 19, 2011.

**About Type 2 Diabetes**

In 2010, diabetes was estimated to affect nearly 300 million people aged 20-79 worldwide. Because of the aging population and the growing trend of obesity, the prevalence of diabetes is projected to reach nearly 440 million by 2030. Type 2 diabetes accounts for approximately 90 to 95% of all cases of diagnosed diabetes in adults. Type 2 diabetes is a chronic, progressive disease characterized by insulin resistance and/or dysfunction of beta cells in the pancreas, which decreases insulin sensitivity and secretion, leading to elevated glucose levels. Over time, this sustained hyperglycemia contributes to worsening insulin resistance and further beta cell dysfunction. To date, treatments for type 2 diabetes have focused primarily on insulin-dependent mechanisms. Dapagliflozin acts independently of insulin.

Significant unmet needs exist as nearly half of treated patients remain uncontrolled on their current glucose-lowering regimen. Many patients with type 2 diabetes have additional co-morbidities (such as obesity) which may complicate glycemic control.
About SGLT2 Inhibition

The kidney plays an important role in glucose balance, normally filtering ~180g of glucose each day, with virtually all glucose being reabsorbed back into circulation. SGLT2 is the major sodium-glucose cotransporter in the kidney and is an insulin-independent pathway for the reabsorption of glucose back into the blood.

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.

About AstraZeneca

AstraZeneca is a global, innovation-driven biopharmaceutical business with a primary focus on the discovery, development and commercialization of prescription medicines for gastrointestinal, cardiovascular, neuroscience, respiratory and inflammation, oncology and infectious disease. AstraZeneca operates in over 100 countries and its innovative medicines are used by millions of patients worldwide.

For more information about AstraZeneca in the U.S. or our AZ&Me™ Prescription Savings programs, please visit: www.astrazeneca-us.com or call 1-800-AZandMe (292-6363).

Bristol-Myers Squibb Forward-Looking Statement

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, 2010, 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.

AstraZeneca Forward-Looking Statement

The statements contained herein include forward-looking statements. Although we believe our expectations are based on reasonable assumptions, any forward-looking statements, by their very nature, involve risks and uncertainties and may be influenced by factors that could cause actual outcomes and results to be materially different from those predicted. The forward-looking statements reflect knowledge and information available at the date of the preparation of this press release and the Company undertakes no obligation to update these forward-looking statements. Important factors that could cause actual results to differ materially from those contained in forward-looking statements, certain of which are beyond our control, include, among other things, those risk factors identified in the Company’s Annual Report and Form 20-F Information 2010. Nothing contained herein should be construed as a profit forecast.

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