52-Week Phase 3 Study Found Investigational Drug Dapagliflozin Plus Metformin Similar to Glipizide Plus Metformin in Improving Glycosylated Hemoglobin (HbA1c) in Adults with Type 2 Diabetes Mellitus

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STOCKHOLM--(BUSINESS WIRE)--Bristol-Myers Squibb Company (NYSE: BMY) and AstraZeneca (NYSE: AZN) today announced results from a randomized, double-blind Phase 3 clinical study in adults with type 2 diabetes inadequately controlled on metformin therapy alone. The study demonstrated dapagliflozin was non-inferior compared to glipizide (sulphonylurea) in improving glycosylated hemoglobin levels (HbA1c) when added to existing metformin therapy during a 52-week treatment period. The study also demonstrated that dapagliflozin plus metformin achieved significant reductions in key efficacy secondary endpoints: reduction in total body weight from baseline, compared with a weight gain on glipizide plus metformin therapy and a reduced number of patients reporting one or more hypoglycemic events. Treatments were titrated during the first 18 weeks, up to 10 mg/day for dapagliflozin plus metformin (median dose 10 mg/day) or 20 mg/day for glipizide (median dose 20 mg/day). Results from the study were presented at the 46th European Association for the Study of Diabetes (EASD) Annual Meeting.

Overall, the frequencies of adverse events, serious adverse events and study discontinuations were comparable across the two treatment groups; although signs, symptoms and other reports suggestive of urinary tract or genital infections were more common in dapagliflozin treated subjects.

Dapagliflozin, an investigational compound, is a first-in-class sodium-glucose cotransporter-2 (SGLT2) inhibitor and is currently in Phase 3 trials under joint development by Bristol-Myers Squibb and AstraZeneca as a once-daily oral therapy for the treatment of adult patients with type 2 diabetes. SGLT2 inhibitors, which act independently of insulin mechanisms, facilitate the excretion of glucose and associated calories in the urine, thereby lowering blood glucose levels.

“Type 2 diabetes patients often present with multiple co-morbidities in addition to their blood sugar levels,” said Michael A. Nauck, MD, Head of Diabetes Center, Bad Lauterberg (Germany), principle investigator of the study. “We are pleased to see the results from this Phase 3 study found that dapagliflozin plus metformin compared favorably to glipizide plus metformin, helping patients lower their HbA1c levels with a lower risk of hypoglycemia.”

About The Study

This Phase 3 study was designed to assess whether, after 52 weeks, the change from baseline in HbA1c levels with dapagliflozin plus metformin was non-inferior to glipizide plus metformin in adult patients with type 2 diabetes who had inadequate glycemic control on 1500 mg/day or higher doses of metformin therapy alone. Non-inferiority was defined in the study protocol as a treatment group numerical difference in the HbA1c reduction of less than 0.35% for the upper limit of the two-sided 95% confidence interval [CI] when either dapagliflozin or glipizide were added to a stable dose of metformin. Key secondary endpoints included the change from baseline in body weight and number of patients reporting hypoglycemic events at week 52.

The study was a 52-week, multicenter, randomized, parallel-group, double-blind, active-controlled Phase 3 study, which included 814 adult patients with type 2 diabetes (aged ≥ 18) whose HbA1c was greater than 6.5% and less than or equal to 10% at baseline. Individuals were randomized to one of two treatment groups: dapagliflozin plus metformin (n=406; starting 2.5 mg per day) or glipizide plus metformin (n=408; starting 5 mg per day). For the first 18 weeks, study drugs were up-titrated as needed (dapagliflozin to less than or equal to 10 mg per day; glipizide to less than or equal to 20 mg per day). The median dose of dapagliflozin was 10 mg. The median dose of glipizide was 20 mg.

Study Results

Using the full analysis, after 52 weeks, individuals taking dapagliflozin plus metformin, compared to those taking glipizide plus metformin, achieved an identical adjusted mean reduction in HbA1c from baseline of -0.52%. Results of the study demonstrated that therapy with dapagliflozin was non-inferior to glipizide when added to existing metformin therapy (difference in adjusted mean change from baseline vs. glipizide as added to existing metformin therapy was 0.00%, 95% CI -0.11 to 0.11).

The study also demonstrated that patients treated with dapagliflozin plus metformin achieved a statistically significant weight loss at 52 weeks when compared to those treated with glipizide plus metformin (-3.22 kg vs. +1.44 kg respectively; p-value less than 0.0001). Significantly more patients achieved a weight loss of greater than or equal to 5% at baseline with dapagliflozin plus metformin (33.3%) compared to glipizide plus metformin (25%; p-value less than 0.0001) at week 52.
The number of individuals with any hypoglycemic event was significantly lower for patients treated with dapagliflozin plus metformin as compared to those treated with glipizide plus metformin (3.5% vs. 40.8% respectively; p-value less than 0.0001) at week 52.

The overall proportions of individuals experiencing adverse events after 52 weeks were similar between the two treatment groups: 78.3% for dapagliflozin plus metformin vs. 77.9% for glipizide plus metformin. The most common adverse events for dapagliflozin plus metformin compared to glipizide plus metformin were nasopharyngitis (10.6% vs. 15.0%), hypertension (7.4% vs. 8.6%) and influenza (7.4% vs. 7.4%). Discontinuations due to adverse events were 9.1% for dapagliflozin plus metformin vs. 5.9% for glipizide plus metformin.

Adverse events suggestive of urinary tract infection and genital infection were analyzed based on predefined groupings of preferred terms for each of these two categories. The percentage of patients with signs, symptoms and other reports suggestive of urinary tract and genital infections was higher for dapagliflozin plus metformin compared to glipizide plus metformin. Signs, symptoms and other reports suggestive of urinary tract infections were 10.8% with dapagliflozin plus metformin vs. 6.4% with glipizide plus metformin. Signs, symptoms and other reports suggestive of genital infections were 12.3% with dapagliflozin plus metformin compared to 2.7% with glipizide plus metformin and most were mild to moderate in intensity. One case of urinary tract infection led to discontinuation in the dapagliflozin group and one case in the glipizide group. Three cases of genital infections led to discontinuation in the dapagliflozin treatment group. Two cases of pyelonephritis were reported in the glipizide group.

The overall proportions of individuals experiencing serious adverse events after 52 weeks were similar between the two treatment groups: 8.6% for dapagliflozin plus metformin vs. 11.3% for glipizide plus metformin.

Effects upon blood pressure were examined as exploratory endpoints. Reductions in systolic and diastolic blood pressure by 4.3 mmHg and 1.6 mmHg, respectively, were observed in the dapagliflozin plus metformin group. Glimepiride plus metformin group was associated with an increase of 0.8 mmHg and a reduction of 0.4 mmHg, in systolic and diastolic blood pressure, respectively. Orthostatic hypotension was not observed.

About Type 2 Diabetes

Type 2 diabetes (diabetes mellitus) is a chronic, progressive disease that is characterized by dysfunction of beta cells in the pancreas, which decreases insulin secretion and leads to elevated glucose levels. Over time, this sustained hyperglycemia contributes to worsening insulin resistance and further beta cell dysfunction.

Many patients with type 2 diabetes have additional co-morbidities such as obesity and hypertension. Significant unmet needs exist as nearly half of treated patients remain uncontrolled on their current glucose-lowering regimen and even fewer are controlled across multiple parameters. In the past, treatments for type 2 diabetes have focused primarily on insulin-dependent mechanisms. An approach that acts independently of insulin may provide an option for adults with type 2 diabetes in helping manage their glucose levels.

About SGLT2 Inhibition

The renal SGLT system plays a major role in overall glucose balance in the body. Normally, the kidney filters ~180g of glucose each day, and virtually all is reabsorbed back into circulation. Glucose reabsorption occurs in the proximal tubule of the kidney via the SGLT system. Selective inhibition of SGLT2 by an insulin independent mechanism of action facilitates the excretion of glucose and associated calories in the urine, thereby lowering blood glucose levels.

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 commercialisation of prescription medicines. As a leader in gastrointestinal, cardiovascular, neuroscience, respiratory and inflammation, oncology and infectious disease medicines, AstraZeneca generated global revenues of US $32.8 billion in 2009. For more information please visit: www.astrazeneca.com

Language:
English

**Contact:**

**Media:**
Bristol-Myers Squibb
Ken Dominski, +1 609-252-5251
ken.dominski@bms.com

or
AstraZeneca
Jim Minnick, +1 302-885-5135
jim.minnick@astrazeneca.com

or

**Investors:**
Bristol-Myers Squibb
John Elicker, +1 609-252-4611
john.elicker@bms.com

or
AstraZeneca
Karl Hard, +44-20-7304-5322
karl.hard@astrazeneca.com

or
AstraZeneca
Clive Morris, +44-20-7304-5084
clive.morris@astrazeneca.com

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