ONGLYZA™ (saxagliptin) When Added to Insulin in Adults with Type 2 Diabetes Maintained Reductions in Blood Sugar Levels (HbA1c) Over 52 Weeks in Investigational Study Extension

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PRINCETON, N.J. & LISBON--(BUSINESS WIRE)--Bristol-Myers Squibb Company (NYSE: BMY) and AstraZeneca (NYSE: AZN) today announced results from an investigational Phase 3b clinical study in which the addition of ONGLYZA™ (saxagliptin) 5 mg to ongoing insulin therapy (with or without metformin) maintained reductions of blood sugar levels (glycosylated hemoglobin levels, or HbA1c) in adult patients with type 2 diabetes compared to the addition of placebo (with or without metformin) from 24 to 52 weeks. These results, presented at the 47th European Association for the Study of Diabetes (EASD) Annual Meeting in Lisbon, Portugal, are from an extension of a 24-week trial, the results of which were presented at the 71st American Diabetes Association (ADA) Scientific Sessions in San Diego, CA in June 2011.

In the 52-week analysis, change from baseline in HbA1c in patients taking ONGLYZA 5 mg added to insulin (with or without metformin) was -0.75% compared to -0.38% for those taking placebo added to insulin (with or without metformin). There was also a greater increase from baseline mean daily insulin dose in patients who received placebo compared to patients who received ONGLYZA 5 mg (with or without metformin). It is unknown whether increased insulin doses by patients in the placebo group could have affected the magnitude of differences seen between the two treatment groups in the efficacy analyses.

The proportion of patients in each treatment group who experienced at least one adverse event over the 52-week treatment period was similar. The most common events included hypoglycemia, urinary tract infection, nasopharyngitis, upper respiratory tract infection, headache and bronchitis.

"Since many patients with type 2 diabetes will eventually require insulin, it is important to assess a compound’s ability to be used in combination with insulin to manage blood glucose control over the long term," said Anthony Barnett, MD, University of Birmingham and Heart of England NHS Foundation Trust and principal investigator of the study. "This is the first longer-term study to report that ONGLYZA 5 mg, used with insulin, maintains improvement in glucose control over 24 to 52 weeks in adult patients with type 2 diabetes."

In Europe, ONGLYZA is indicated as a once-daily 5 mg oral tablet dose in adult patients with type 2 diabetes mellitus to improve glycemic control:

— in combination with metformin, when metformin alone, with diet and exercise, does not provide adequate glycemic control;
— in combination with a sulphonylurea, when sulphonylurea alone, with diet and exercise, does not provide adequate glycemic control in patients for whom use of metformin is considered inappropriate; or
— in combination with a thiazolidinedione, when the thiazolidinedione alone, with diet and exercise, does not provide adequate glycemic control in patients for whom use of a thiazolidinedione is considered appropriate.

ONGLYZA is currently not indicated in combination with insulin therapy.

Please see the Summary of Product Characteristics for the full European Prescribing Information.

In the United States, ONGLYZA is indicated as an adjunct to diet and exercise to improve blood sugar (glycemic) control in adults with type 2 diabetes mellitus in multiple clinical settings. ONGLYZA should not be used for the treatment of patients with type 1 diabetes mellitus or diabetic ketoacidosis (increased levels of ketones in the blood or urine), as it would not be effective in these settings.

About the Study

This was a Phase 3b, multi-center, randomized, placebo-controlled, double-blind 24-week study with a 28-week extension. The primary endpoint at 24 weeks was mean change in HbA1c from baseline of ONGLYZA 5 mg added to insulin (with or without metformin) compared to placebo added to insulin (with or without metformin). The study met the primary endpoint, demonstrating that ONGLYZA 5 mg added to insulin (with or without metformin) achieved a statistically significant HbA1c reduction from baseline of -0.75% compared to -0.38% (p-value < 0.0001) for those receiving placebo added to insulin (with or without metformin). The overall objective of the extension was to assess the long-term safety and efficacy of ONGLYZA over 52 weeks. Efficacy measures included: changes from baseline of HbA1c, mean total daily dose of insulin (MTDDI),...
percent of patients achieving glycemic response of HbA1c < 7%, and body weight. Given the exploratory nature of these analyses, statistical significance testing was not pre-specified in the statistical analysis plan; however, for the primary efficacy measure (HbA1c change from baseline), a post-hoc analysis of significance was conducted.

The study included 455 individuals with type 2 diabetes (ages 18 – 78) with inadequate glycemic control (HbA1c levels ≥ 7.5% and ≤ 11%; mean baseline HbA1c = 8.7%) who were receiving a stable dose of insulin (with or without metformin). Patients were randomly assigned to receive ONGLYZA 5 mg added to insulin (n = 304) or placebo added to insulin (n = 151) once-daily for 52 weeks. During the initial 24-week period, patients were advised to maintain stable insulin doses, which could be decreased to reduce the risk of hypoglycemia. Patients with hyperglycemia or with substantially increased insulin had a rescue visit and remained in the study on a flexible insulin regimen. During the extension period, all patients were able to adopt a flexible insulin regimen. Sixty-nine percent of patients were treated with metformin, and the dose could not be changed in the study.

Of the 455 patients initially randomized and treated in the study, 371 patients completed the extension (81% of patients in the ONGLYZA added to insulin group and 83% of patients in the placebo added to insulin group, of those originally treated).

**Study Results**

Over 52 weeks, patients receiving ONGLYZA 5 mg added to insulin (with or without metformin) compared to patients receiving placebo added to insulin (with or without metformin) showed the following:

- Maintained reductions of blood sugar levels over 52 weeks in HbA1c from baseline:
  - -0.75% vs. -0.38% (p < 0.0001, n = 244, baseline 8.67% for ONGLYZA 5 mg added to insulin; n = 124, baseline 8.66% for placebo added to insulin).
  - Similar HbA1c reduction was reported for patients with or without metformin use at baseline.

- Increase in mean total daily dose of insulin from baseline of +5.67 units/day vs. +6.67 units/day.

- Of patients on ONGLYZA 5 mg, 21.3% achieved a therapeutic glycemic response of HbA1c < 7%, and of patients on placebo, 8.7% achieved a therapeutic glycemic response of HbA1c < 7%.

- Increases in mean change in body weight from baseline of 0.8 kg for ONGLYZA 5 mg vs. 0.5 kg for placebo (95% CI: -0.3, 0.9; n = 246, baseline 87.7 kg for ONGLYZA 5 mg added to insulin; n = 125, baseline 86.2 kg for placebo added to insulin)

Most patients completed the study through week 52 (81% and 83% of patients in the ONGLYZA and placebo groups, respectively).

Over the 52-week treatment period, 66.4% of patients in the ONGLYZA 5 mg added to insulin group had at least one adverse event compared to 71.5% in the placebo added to insulin group.

Hypoglycemia was reported in 22.7% of patients in the ONGLYZA 5 mg added to insulin group compared to 26.5% in the placebo added to insulin group, with confirmed hypoglycemia of 7.6% and 6.6%, respectively. Confirmed hypoglycemia was defined as hypoglycemic symptoms associated with a fingerstick glucose measurement of ≤ 50 mg/dL at the time of the event.

The other most common adverse events (incidence ≥ 5% for ONGLYZA 5 mg) were as follows for ONGLYZA 5 mg added to insulin (with or without metformin) compared to placebo added to insulin (with or without metformin) respectively:

- Urinary tract infections (7.9% vs. 7.9%)
- Nasopharyngitis (6.3% vs. 6.6%)
- Upper respiratory tract infections (6.3% vs. 7.3%)
- Headache (5.9% vs. 4.0%)
- Bronchitis (5.3% vs. 3.3%)

Twenty-five (8.2%) patients in the ONGLYZA 5 mg added to insulin group reported at least one serious adverse event (SAE), as compared to 13 (8.6%) patients in the placebo added to insulin group. Treatment-related SAEs were reported in three patients in the ONGLYZA 5 mg added to insulin group vs. zero in the placebo added to insulin group. In the ONGLYZA 5 mg added to insulin group, nine (3.0%) patients discontinued the study due to adverse events, of which four were considered serious adverse events. In the placebo added to insulin group, three (2.0%) patients discontinued due to adverse events, of which zero were considered serious adverse events. There were also two deaths in the ONGLYZA added to insulin group, in which both events were considered unrelated to treatment.

**About ONGLYZA™ (saxagliptin)**

As of September 2011, ONGLYZA has been submitted for regulatory review in more than 90 countries and is approved in 66 countries, including the U.S., Canada, Mexico, 30 European countries, India, Brazil and China.

**IMPORTANT SAFETY INFORMATION for ONGLYZA™ (saxagliptin) in the United States**

**Warnings and Precautions**

- **Use with Medications Known to Cause Hypoglycemia:** Insulin secretagogues, such as sulfonylureas, cause hypoglycemia. Therefore, a lower dose of the insulin secretagogue may be required to reduce the risk of hypoglycemia when used in combination with ONGLYZA.

- **Macrovascular Outcomes:** There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with ONGLYZA or any other antidiabetic drug.
Most Common Adverse Reactions

- Most common adverse reactions (regardless of investigator assessment of causality) reported in ≥ 5% of patients treated with ONGLYZA and more commonly than in patients treated with control were upper respiratory tract infection (7.7%, 7.6%), headache (7.5%, 5.2%), nasopharyngitis (6.9%, 4.0%) and urinary tract infection (6.8%, 6.1%).

- When used as add-on combination therapy with a thiazolidinedione, the incidence of peripheral edema for ONGLYZA 2.5 mg, 5 mg, and placebo was 3.1%, 8.1% and 4.3%, respectively.

Drug Interactions

Because ketoconazole, a strong CYP3A4/5 inhibitor, increased saxagliptin exposure, the dose of ONGLYZA should be limited to 2.5 mg when coadministered with a strong CYP3A4/5 inhibitor (e.g., atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir and telithromycin).

Use in Specific Populations

- **Patients with Renal Impairment**: The dose of ONGLYZA (saxagliptin) is 2.5 mg once daily for patients with moderate or severe renal impairment, or with end-stage renal disease requiring hemodialysis (creatinine clearance [CrCl] ≤ 50 mL/min). ONGLYZA should be administered following hemodialysis. ONGLYZA has not been studied in patients undergoing peritoneal dialysis. Assessment of renal function is recommended prior to initiation of ONGLYZA and periodically thereafter.

- **Pregnant and Nursing Women**: There are no adequate and well-controlled studies in pregnant women. ONGLYZA, like other antidiabetic medications, should be used during pregnancy only if clearly needed. It is not known whether saxagliptin is secreted in human milk. Because many drugs are secreted in human milk, caution should be exercised when ONGLYZA is administered to a nursing woman.

- **Pediatric Patients**: Safety and effectiveness of ONGLYZA in pediatric patients have not been established.

Click here for full U.S. Prescribing Information.

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. Significant unmet needs exist as nearly half of treated patients remain uncontrolled on their current glucose-lowering regimen.

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 commercialise 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 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 please visit: www.astrazeneca.com.

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