Pfizer Logo

Merck and Pfizer Announce that Investigational SGLT-2 Inhibitor Ertugliflozin Met Primary Endpoint in Two Phase 3 Studies

Saturday, June 10, 2017 - 09:00am

Ertugliflozin as Add-on to Metformin or in Initial Co-administration with Sitagliptin Showed Significant A1C Reductions in Adults with Type 2 Diabetes

Merck (NYSE:MRK), known as MSD outside the United States and Canada, in partnership with Pfizer Inc. (NYSE:PFE), today announced that two Phase 3 studies (VERTIS MET and VERTIS SITA) of ertugliflozin, an investigational oral SGLT-2 inhibitor in development to help improve glycemic control in adults with type 2 diabetes, met their primary endpoints. In the studies, both doses of ertugliflozin tested (5 mg and 15 mg daily) achieved statistically significant reductions in A1C, a measure of average blood glucose over a two- to three-month timeframe, when added to metformin or in initial co-administration with sitagliptin. The results of these studies, along with 52-week extension data from three other studies in the VERTIS clinical development program of ertugliflozin, will be presented at the 77th Scientific Sessions of the American Diabetes Association (ADA) in San Diego.

“We are pleased to share these new Phase 3 data with the scientific community that support the product profile of ertugliflozin as add-on therapy to metformin or for first-line use when combined with sitagliptin,” said Sam Engel, M.D., associate vice president, Merck clinical research, cardiometabolic and women’s health. “These studies are important milestones on our journey to bring this medicine to adults with type 2 diabetes and the physicians who care for them.”

“These results, combined with findings from other studies in the VERTIS program, underscore the potential of ertugliflozin as an important therapeutic option for adults with type 2 diabetes to help improve their glycemic control,” said James Rusnak, M.D., Ph.D., chief development officer, cardiovascular and metabolic diseases, Pfizer Global Product Development. “As the global burden of diabetes continues to rise, we are committed to meeting patients’ needs with additional treatment options to help manage their condition.”

VERTIS MET, a 26-week study, evaluated the efficacy and safety of ertugliflozin in combination with metformin, compared with placebo and metformin, in adults with type 2 diabetes uncontrolled on metformin monotherapy. The study showed patients taking ertugliflozin 5 mg or 15 mg and metformin experienced greater reductions in A1C compared to placebo (0.7 percent and 0.9 percent, respectively, compared with 0.0 percent for placebo, $p<0.001$, for both comparisons). Ertugliflozin in combination with metformin also met a secondary endpoint in the study, as significantly more patients taking either ertugliflozin 5 mg or 15 mg achieved the ADA’s recommended A1C treatment goal of less than 7.0 percent compared with placebo and metformin. As add-on therapy to metformin, treatment with ertugliflozin also resulted in significant reductions in fasting plasma

glucose (FPG), body weight, systolic blood pressure (SBP) and diastolic blood pressure (DBP), compared with placebo.

The 26-week VERTIS SITA study compared the efficacy and safety of initial combination therapy with ertugliflozin and Merck's DPP-4 inhibitor JANUVIA® (sitagliptin) with placebo. In this study, patients taking ertugliflozin 5 mg or 15 mg, in combination with sitagliptin 100 mg, experienced greater reductions in A1C compared with patients taking placebo alone (1.6 percent and 1.7 percent, respectively, compared with 0.4 percent in patients taking placebo, $p<0.001$ for both comparisons). Additionally, the co-administration of ertugliflozin and sitagliptin met a secondary endpoint in the study, as significantly more patients taking ertugliflozin 5 mg or 15 mg, in combination with sitagliptin 100 mg, achieved the A1C treatment goal of less than 7.0 percent. Treatment with the initial combination of ertugliflozin and sitagliptin also resulted in significant reductions in FPG, body weight and SBP, compared with placebo.
Ertugliflozin is being investigated in the VERTIS clinical development program, which is comprised of nine Phase 3 trials in approximately 12,600 adults with type 2 diabetes. VERTIS CV, the ongoing cardiovascular (CV) outcomes trial of ertugliflozin, recently completed enrollment with approximately 8,000 patients. The primary endpoint of VERTIS CV is to assess the non-inferiority of ertugliflozin to placebo on the composite of CV death, nonfatal myocardial infarction or nonfatal stroke (MACE). In 2016, the trial was expanded and pre-specified secondary endpoints were added to test for superiority on the composite of CV death and hospitalization for heart failure, and for superiority on CV death alone.

Marketing applications for ertugliflozin and for two fixed-dose combination products (ertugliflozin and JANUVIA, ertugliflozin and metformin) are under review with the U.S. Food & Drug Administration (FDA) and the European Medicines Agency. The Prescription Drug User Fee Act (PDUFA) action date from the FDA is in December 2017 for the three New Drug Applications.

Results from VERTIS MET: Ertugliflozin When Added to Metformin Therapy (1168-P)
In this randomized, double-blind 26-week investigational multicenter study, 621 patients with type 2 diabetes and a baseline A1C of 7.0 – 10.5 percent, who were inadequately controlled with metformin monotherapy (greater or equal to 1,500 mg/day for more than or equal to 8 weeks), were randomized to receive placebo, ertugliflozin 5 mg/day or ertugliflozin 15 mg/day in a 1:1:1 ratio, as an add-on therapy to metformin. In addition to meeting the study's primary endpoint of improved blood glucose control at 26 weeks, ertugliflozin in combination with metformin also met a key secondary endpoint in the study, as significantly more patients taking ertugliflozin 5 mg and 15 mg in combination with metformin achieved the ADA's recommended A1C treatment goal of less than 7.0 percent (35.3 percent and 40.0 percent, respectively) compared with placebo and metformin (15.8 percent) ($p<0.001$, for both comparisons based on adjusted odds ratio comparisons). The following statistically significant placebo-adjusted reductions were observed for the primary and additional key secondary endpoints for ertugliflozin added to metformin:

- A1C: 0.7 percent (5 mg) and 0.9 percent (15 mg) ($p<0.001$ for both comparisons);
- FPG: 26.7 mg/dL (5 mg) and 38.3 mg/dL (15 mg) ($p<0.001$ for both comparisons);
- Body weight: 3.7 lbs (1.7 kg) (5 mg) and 3.5 lbs (1.6 kg) (15 mg) ($p<0.001$ for both comparisons);
- SBP: 3.7 mmHg (5 mg) ($p=0.002$) and 4.5 mmHg (15 mg) ($p<0.001$); and
- DBP: 1.8 mmHg (5 mg) ($p=0.013$) and 2.4 mmHg (15 mg) ($p=0.001$).

The incidence of adverse events was 42.5 percent, 50.2 percent and 45.0 percent in the ertugliflozin 5 mg and metformin, ertugliflozin 15 mg and metformin, and placebo and metformin groups, respectively. A higher

incidence of genital mycotic infections in females was observed in patients taking ertugliflozin 5 mg (5.5 percent) and 15 mg (6.3 percent) versus placebo (0.9 percent) (p=0.032 for 15 mg) and in males (3.1 percent (5 mg); 3.2 percent (15 mg); 0.0 percent (placebo)), added to metformin. Ertugliflozin had no adverse impact on bone mineral density at week 26 (95 percent CI). Symptomatic urinary tract infections, hypoglycemia and hypovolemia adverse events were similar between treatment groups.

Results from VERTIS SITA: Initial Combination of Ertugliflozin and JANUVIA® (sitagliptin) (1197-P)
In this 26-week, randomized, double-blind investigational multicenter Phase 3 study of 291 patients with an A1C of 8.0 – 10.5 percent inadequately controlled with diet and exercise, patients were randomized to ertugliflozin 5 mg and sitagliptin 100 mg, ertugliflozin 15 mg and sitagliptin 100 mg or placebo. The study met its primary endpoint of improved blood glucose control at 26 weeks with A1C reductions of 1.6 percent (ertugliflozin 5 mg and sitagliptin 100 mg), 1.7 percent (ertugliflozin 15 mg and sitagliptin 100 mg), compared with 0.4 percent in patients taking placebo (p<0.001 for both comparisons). In addition, the study met a key secondary endpoint, with significantly more patients taking ertugliflozin 5 mg or 15 mg in combination with sitagliptin 100 mg achieving the A1C treatment goal of less than 7.0 percent (35.7 percent and 31.3 percent, respectively) compared with placebo (8.3 percent) (p<0.001, for both comparisons based on adjusted odds ratio comparisons).

The following statistically significant placebo-adjusted reductions were observed for the primary and additional key secondary endpoints:

• A1C: 1.2 percent (ertugliflozin 5 mg and sitagliptin 100 mg) and 1.2 percent (ertugliflozin 15 mg and sitagliptin 100 mg) (p<0.001 for both comparisons);
• FPG: 38.9 mg/dL for 5 mg ertugliflozin and 100 mg sitagliptin, 46.1 mg/dL for 15 mg ertugliflozin and 100 mg sitagliptin) (p<0.001 for both comparisons);
• 2-hour PMG: 62.4 mg/dL for ertugliflozin 5 mg and 100 mg sitagliptin and 69.6 mg/dL for ertugliflozin 15 mg and 100 mg sitagliptin (p<0.001 for both comparisons);
• Body weight: 4.4 lbs (2.0 kg) for ertugliflozin 5 mg and sitagliptin 100 mg and 4.6 lbs (2.1 kg) for ertugliflozin 15 mg and sitagliptin 100 mg (p<0.001 for both comparisons);
• SBP: 4.4 mmHg for ertugliflozin 5 mg and sitagliptin 100 mg (p=0.011) and 6.4 mmHg for ertugliflozin 15 mg and sitagliptin 100 mg (p<0.001).
Observed reductions in DBP were not significant (p>0.05). The incidence of adverse events was 44.9 percent, 44.8 percent and 42.3 percent in the ertugliflozin 5 mg and sitagliptin 100 mg, ertugliflozin 15 mg and sitagliptin 100 mg, and placebo groups, respectively. A higher incidence of genital mycotic infections in males was observed in patients taking ertugliflozin 5 mg (5.3 percent) and 15 mg (1.9 percent) versus placebo (0.0 percent) and in females (4.9 percent (5 mg); 7.0 percent (15 mg); 5.0 percent (placebo)) (p?0.05 for all comparisons). Incidence rates of urinary tract infections, symptomatic hypoglycemia and hypovolemia were low and not significantly different across groups.

.
Important Information about JANUVIA® (sitagliptin) 25 mg, 50 mg and 100 mg tablets
JANUVIA (sitagliptin) is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. JANUVIA should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis. JANUVIA has not been studied in patients with a history of pancreatitis. It is unknown whether patients with a history of pancreatitis are at increased risk of developing pancreatitis while taking JANUVIA.

Selected Important Risk Information about JANUVIA® (sitagliptin)

JANUVIA is contraindicated in patients with a history of a serious hypersensitivity reaction to sitagliptin, such as anaphylaxis or angioedema.
There have been postmarketing reports of acute pancreatitis, including fatal and nonfatal hemorrhagic or necrotizing pancreatitis, in patients taking JANUVIA. After initiating JANUVIA, observe patients carefully for signs and symptoms of pancreatitis. If pancreatitis is suspected, promptly discontinue JANUVIA and initiate appropriate management. It is unknown whether patients with a history of pancreatitis are at increased risk of developing pancreatitis while taking JANUVIA.

Assessment of renal function is recommended prior to initiating JANUVIA and periodically thereafter. A dosage adjustment is recommended in patients with moderate or severe renal insufficiency and in patients with end-stage renal disease requiring hemodialysis or peritoneal dialysis. Caution should be used to ensure that the correct dose of JANUVIA is prescribed.
There have been postmarketing reports of worsening renal function, including acute renal failure, sometimes requiring dialysis. A subset of these reports involved patients with renal insufficiency, some of whom were prescribed inappropriate doses of sitagliptin.

When JANUVIA was used in combination with a sulfonylurea or insulin, medications known to cause hypoglycemia, the incidence of hypoglycemia was increased over that of placebo. Therefore, a lower dose of sulfonylurea or insulin may be required to reduce the risk of hypoglycemia.

The incidence (and rate) of hypoglycemia based on all reports of symptomatic hypoglycemia were: 12.2% (0.59 episodes/patient-year) for JANUVIA 100 mg in combination with glimepiride (with or without metformin), 1.8% (0.24 episodes/patient-year) for placebo in combination with glimepiride (with or without metformin), 15.5% (1.06 episodes/patient-year) for JANUVIA 100 mg in combination with insulin (with or without metformin), and 7.8% (0.51 episodes/patient-year) for placebo in combination with insulin (with or without metformin).
There have been postmarketing reports of serious hypersensitivity reactions in patients treated with JANUVIA (sitagliptin), such as anaphylaxis, angioedema, and exfoliative skin conditions including Stevens-Johnson syndrome. Onset of these reactions occurred within the first 3 months after initiation of treatment with JANUVIA, with some reports occurring after the first dose. If a hypersensitivity reaction is suspected, discontinue JANUVIA, assess for other potential causes for the event, and institute alternative treatment for diabetes.

Angioedema has also been reported with other dipeptidyl peptidase-4 (DPP-4) inhibitors. Use caution in a patient with a history of angioedema with another DPP-4 inhibitor because it is unknown whether such patients will be predisposed to angioedema with JANUVIA.

There have been postmarketing reports of severe and disabling arthralgia in patients taking DPP-4 inhibitors. The time to onset of symptoms following initiation of drug therapy varied from 1 day to years. Patients experienced relief of symptoms upon discontinuation of the medication. A subset of patients experienced a recurrence of symptoms when restarting the same drug or a different DPP-4 inhibitor. Consider DPP-4 inhibitors as a possible cause for severe joint pain and discontinue drug if appropriate.

Postmarketing cases of bullous pemphigoid requiring hospitalization have been reported with DPP-4 inhibitor use. In reported cases, patients typically recovered with topical or systemic immunosuppressive treatment and

discontinuation of the DPP-4 inhibitor. Tell patients to report development of blisters or erosions while receiving JANUVIA. If bullous pemphigoid is suspected, JANUVIA should be discontinued and referral to a dermatologist should be considered for diagnosis and appropriate treatment.

There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with JANUVIA or with any other antidiabetic drug.
In clinical studies, the adverse reactions reported, regardless of investigator assessment of causality, in ?5% of patients treated with JANUVIA as monotherapy and in combination therapy and more commonly than in patients treated with placebo, were upper respiratory tract infection, nasopharyngitis, and headache.

About Merck

For more than a century, Merck, a leading global biopharmaceutical company known as MSD outside of the United States and Canada, has been inventing for life, bringing forward medicines and vaccines for many of the world's most challenging diseases. Through our prescription medicines, vaccines, biologic therapies and animal health products, we work with customers and operate in more than 140 countries to deliver innovative health solutions. We also demonstrate our commitment to increasing access to health care through far-reaching policies, programs and partnerships. Today, Merck continues to be at the forefront of research to advance the prevention and treatment of diseases that threaten people and communities around the world - including cancer, cardio-metabolic diseases, emerging animal diseases, Alzheimer's disease and infectious diseases including HIV and Ebola. For more information, visit www.merck.com and connect with us on Twitter, Facebook, Instagram,YouTube and LinkedIn.

About Pfizer Inc.: Working together for a healthier world®

At Pfizer, we apply science and our global resources to bring therapies to people that extend and significantly improve their lives. We strive to set the standard for quality, safety and value in the discovery, development and manufacture of health care products. Our global portfolio includes medicines and vaccines as well as many of the world's best-known consumer health care products. Every day, Pfizer colleagues work across developed and emerging markets to advance wellness, prevention, treatments and cures that challenge the most feared diseases of our time. Consistent with our responsibility as one of the world's premier innovative biopharmaceutical companies, we collaborate with health care providers, governments and local communities to support and expand access to reliable, affordable health care around the world. For more than 150 years, we have worked to make a difference for all who rely on us. We routinely post information that may be important to investors on our website at www.pfizer.com. In addition, to learn more, please visit us on www.pfizer.com and follow us on Twitter at @Pfizer and @PfizerNews, LinkedIn, YouTube and like us on Facebook at Facebook.com/Pfizer.

Forward-Looking Statement of Merck & Co., Inc., Kenilworth, N.J., USA

This news release of Merck & Co., Inc., Kenilworth, N.J., USA (the "company") includes "forward-looking statements" within the meaning of the safe harbor provisions of the U.S. Private Securities Litigation Reform Act of 1995. These statements are based upon the current beliefs and expectations of the company's management and are subject to significant risks and uncertainties. There can be no guarantees with respect to pipeline products that the products will receive the necessary regulatory approvals or that they will prove to be commercially successful. If underlying assumptions prove inaccurate or risks or uncertainties materialize, actual results may differ materially from those set forth in the forward-looking statements.
Risks and uncertainties include but are not limited to, general industry conditions and competition; general economic factors, including interest rate and currency exchange rate fluctuations; the impact of pharmaceutical

industry regulation and health care legislation in the United States and internationally; global trends toward health care cost containment; technological advances, new products and patents attained by competitors; challenges inherent in new product development, including obtaining regulatory approval; the company's ability to accurately predict future market conditions; manufacturing difficulties or delays; financial instability of international economies and sovereign risk; dependence on the effectiveness of the company's patents and other protections for innovative products; and the exposure to litigation, including patent litigation, and/or regulatory actions.

The company undertakes no obligation to publicly update any forward-looking statement, whether as a result of new information, future events or otherwise. Additional factors that could cause results to differ materially from those described in the forward-looking statements can be found in the company's 2016 Annual Report on Form 10-K and the company's other filings with the Securities and Exchange Commission (SEC) available at the SEC's Internet site (www.sec.gov).

Pfizer Disclosure Notice

The information contained in this release is as of June 10, 2017. Pfizer assumes no obligation to update forward-looking statements contained in this release as the result of new information or future events or developments. This release contains forward-looking information about a product candidate, ertugliflozin, and applications submitted to the FDA and the EMA for monotherapy and fixed-dose combinations, including their potential benefits, that involves substantial risks and uncertainties that could cause actual results to differ materially from those expressed or implied by such statements. Risks and uncertainties include, among other things, the uncertainties inherent in research and development, including the ability to meet anticipated trial commencement and completion dates and regulatory submission dates, as well as the possibility of unfavorable clinical trial results, including unfavorable new clinical data and additional analyses of existing clinical data; whether and when any applications for ertugliflozin may be filed with regulatory authorities in any other jurisdictions; whether and when the FDA and EMA may approve the pending applications and whether and when regulatory authorities in any other jurisdictions may approve any such other applications, which will depend on the assessment by such regulatory authorities of the benefit-risk profile suggested by the totality of the efficacy and safety information submitted; decisions by regulatory authorities regarding labeling and other matters that could affect the availability or commercial potential of ertugliflozin in monotherapy or in fixed-dose combination; and competitive developments. The competitive landscape for type 2 diabetes therapies, including SGLT2 inhibitors, continues to evolve. The success of our ertugliflozin program is dependent on developments in that space.

A further description of risks and uncertainties can be found in Pfizer's Annual Report on Form 10-K for the fiscal year ended December 31, 2016 and in its subsequent reports on Form 10-Q, including in the sections thereof captioned "Risk Factors" and "Forward-Looking Information and Factors That May Affect Future Results", as well as in its subsequent reports on Form 8-K, all of which are filed with the U.S. Securities and Exchange Commission and available at www.sec.gov and www.pfizer.com.

Please see Prescribing Information for JANUVIA® (sitagliptin) at http://www.merck.com/product/usa/pi_circulars/j/januvia/januvia_pi.pdf and Medication Guide for JANUVIA at http://www.merck.com/product/usa/pi_circulars/j/januvia/januvia_mg.pdf

Merck Media Contacts: Doris Li, 908-246-5701 Kristen Drake, 908-334-4688 or Pfizer Media Contact: Steve Danehy, 212-733-1538 or Merck Investor Contact: Amy Klug, 908-740-1898 or Pfizer Investor Contact: Ryan Crowe, 212-733-8160