Merck Presents New Data from the Comparative Trials with Sitagliptin (CompoSIT) Clinical Trial Program with JANUVIA® (sitagliptin)

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KENILWORTH, N.J.--(BUSINESS WIRE)--Merck (NYSE: MRK), known as MSD outside the United States and Canada, today announced new data from the Comparative Trials with Sitagliptin (CompoSIT) clinical trials with JANUVIA® (sitagliptin). In the CompoSIT-I study, initiation of insulin therapy while continuing treatment with JANUVIA resulted in greater blood glucose reductions and more patients reaching A1C goal compared to those who discontinued JANUVIA. In the CompoSIT-R study, among patients with mild renal impairment inadequately controlled on metformin, with or without a sulfonylurea, treatment with JANUVIA showed non-inferiority and superiority in reducing A1C levels compared with patients treated with dapagliflozin. These results were presented at the 78th Scientific Sessions of the American Diabetes Association (ADA) in Orlando, Florida.

“Taken together, the results offer further insight into JANUVIA as a treatment option in these settings that impact substantial numbers of the type 2 diabetes patient population: those initiating insulin therapy and those with mild renal impairment,” said Dr. Sam Engel, associate vice president, diabetes, endocrinology and women’s health, Merck Research Laboratories. “These studies further support the clinical profile of JANUVIA and may help to inform the individualization of treatment, which is the cornerstone of diabetes care.”

JANUVIA 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. JANUVIA is contraindicated in patients with a history of a serious hypersensitivity reaction to sitagliptin, such as anaphylaxis or angioedema. Selected important risk information is continued below.

Efficacy and Safety of Continuing Sitagliptin When Initiating Insulin Therapy in Subjects with Type 2 Diabetes Mellitus (Abstract #112-LB; CompoSIT-I)

In this randomized, controlled double-blind study of patients with inadequately controlled type 2 diabetes taking metformin in dual combination therapy with JANUVIA (sitagliptin) and initiating insulin treatment, continuing treatment with JANUVIA (n=373) resulted in greater blood glucose reduction at week 30 compared to discontinuing JANUVIA (n=370), with LS mean changes from baseline A1C of -1.88 percent with JANUVIA and -1.42 percent with placebo, a between-group difference of -0.46 percent (95 percent CI [-0.58, -0.34], p<0.001).

More than half of the patients (54 percent) who continued treatment with JANUVIA (n=202) achieved the ADA target A1C goal of less than 7.0 percent, compared to 35 percent of patients who were taking insulin alone (n=131), a between-group difference of 18.8 percent (95 percent CI [11.6, 25.7], p<0.001). Mean change from baseline reductions in fasting plasma glucose were -84.8 mg/dL with JANUVIA and -78.3 mg/dL with placebo, a between-group difference of -6.5 mg/dL (95 percent CI [-11.9, -1.0]).

Furthermore, in this study, there was no increased risk of hypoglycemia with JANUVIA: patients who continued JANUVIA had a rate of documented symptomatic hypoglycemia of 1.55 events per patient-year compared with 2.12 events per patient-year in the group that discontinued JANUVIA, resulting in an event rate ratio of 0.73, (95 percent CI [0.54, 0.98], p=0.039). Additionally, patients continuing JANUVIA required a lower daily insulin dose (53.2 daily units with JANUVIA compared to 61.3 daily units in those who discontinued JANUVIA), a between-group difference of -8.0 units, (95 percent CI [-14.6, -1.5], p=0.016). The Prescribing Information states that when JANUVIA was used in combination with a sulfonylurea or with insulin, medications known to cause hypoglycemia, the incidence of hypoglycemia was increased over that of placebo used in combination with a sulfonylurea or with insulin. Therefore, a lower dose of sulfonylurea or insulin may be required to reduce the risk of hypoglycemia.

In this study, change in body weight was similar in the two treatment groups after 30 weeks. The mean change in body weight was 3.3 ± 7.5 lbs with JANUVIA and 3.7 ± 8.6 lbs with placebo. Adverse events (AEs) were also similar in the two groups (five patients taking JANUVIA and six patients taking placebo discontinued due to an AE; 216 patients taking JANUVIA and 222 patients taking placebo experienced one or more AEs).

“Though continuation with oral agents upon initiation of insulin is consistent with treatment guidelines, when insulin therapy is
initiated, physicians may still choose to discontinue the use of oral agents,” said Dr. Ronan Roussel, Clinical Professor of Diabetology, Université Paris Diderot, Hôpital Bichat, Centre de Recherche des Cordeliers, Paris, France. “This study could help physicians as they consider treatment options for patients whose disease has progressed and require treatment with insulin.”

In this study, 746 patients with a mean A1C of 8.8 percent and disease duration of 10.6 years were randomized to continuing or discontinuing JANUVIA (sitagliptin), with both groups initiating insulin glargine. Eligible patients had inadequately controlled type 2 diabetes taking metformin greater or equal to 1500 mg/day in dual or triple combination therapy with a DPP-4 inhibitor with or without a sulfonylurea. Those taking metformin and JANUVIA 100 mg/day directly entered the trial; all others were switched to metformin and JANUVIA and stabilized during a run-in period.

Safety and Efficacy of Sitagliptin Compared with Dapagliflozin in Subjects with Type 2 Diabetes, Mild Renal Impairment and Inadequate Glycemic Control on Metformin ± a Sulfonylurea (Abstract #1142-P; CompoSIT-R)

In this randomized, double-blind, active comparator-controlled clinical study of patients with mild renal impairment taking metformin with or without a sulfonylurea, LS mean changes from baseline A1C were -0.51 percent with the addition of JANUVIA (n=307) and -0.36 percent with the addition of dapagliflozin (n=306), a between-group difference of -0.15 percent (95 percent CI [0.26, -0.04], p=0.006), meeting both non-inferiority and superiority criteria for JANUVIA at week 24. The ADA-recommended A1C goal of less than 7.0 percent was met by 43 percent of patients with JANUVIA (n=116) and 27 percent with dapagliflozin (n=71), a between-group difference of 16 percent (95 percent CI [7.7, 23.2]), a secondary outcome.

The pre-specified analysis of two-hour post-prandial glucose showed no significant difference between groups (mean change from baseline -42.9 mg/dL with JANUVIA and -39.3 mg/dL with dapagliflozin, a between-group difference of -3.6 mg/dL (95 percent CI [-12.3, 5.0]). Mean reductions from baseline in fasting plasma glucose were -16.5 mg/dL with JANUVIA and -20.1 mg/dL with dapagliflozin, a between-group difference of 3.5 mg/dL (95 percent CI [-1.2, 8.3]). Mean change from baseline in systolic blood pressure was -0.6 ± 0.8 mm Hg with JANUVIA and -3.3 ± 0.7 mm Hg with dapagliflozin. Mean reduction from baseline in body weight was 0.9 ± 0.4 lbs with JANUVIA and 5.3± 0.4 lbs with dapagliflozin.

There were significantly fewer patients with drug-related AEs with JANUVIA than with dapagliflozin (24 vs. 42 patients).

Summary AE profiles were generally similar: discontinuation due to an AE, 10 patients taking JANUVIA (sitagliptin) and 10 patients taking dapagliflozin; one or more events of hypoglycemia, seven patients taking JANUVIA and metformin and eight patients taking dapagliflozin and metformin, and 15 patients taking JANUVIA, metformin and a sulfonylurea and 13 patients taking dapagliflozin, metformin and a sulfonylurea.

The study assessed the safety and efficacy of adding JANUVIA (sitagliptin) 100 mg once-daily or dapagliflozin 10 mg once-daily to treatment of patients with mild renal impairment (eGFR ≥60 and <90 mL/min/1.73 m²) and A1C between 7.0 and 9.5 percent while on metformin with or without a sulfonylurea. Patients initiated dapagliflozin 5 mg once-daily at randomization and were up-titrated to dapagliflozin 10 mg once-daily at week 4. The primary efficacy endpoint was change from baseline A1C at week 24, with a primary hypothesis of non-inferiority of JANUVIA to dapagliflozin based on the pre-specified criterion of the upper bound of the between-treatment difference 95 percent CI (JANUVIA minus dapagliflozin) of less than 0.3 percent; if the upper bound was less than 0.0 percent, JANUVIA would be declared superior. Treatment groups were well-balanced at baseline (n=307 and 306, mean A1C of 7.7 and 7.8 percent, mean eGFR [mL/min/1.73 m²] of 79.4 and 76.9 for JANUVIA and dapagliflozin, respectively).

“Approximately 38 percent of patients with type 2 diabetes in the U.S. have mild renal impairment, said Dr. Russell Scott, clinical professor, University of Otago, and director, Lipid and Diabetes Research, Christchurch Hospital, Christchurch, New Zealand. “These data from the study of sitagliptin and dapagliflozin in those with mild renal impairment may help physicians to evaluate how to individualize diabetes treatment for their patients.”

Selected Important Risk Information about JANUVIA (sitagliptin) (continued)

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.

An association between dipeptidyl peptidase-4 (DPP-4) inhibitor treatment and heart failure has been observed in cardiovascular outcomes trials for two other members of the DPP-4 inhibitor class. These trials evaluated patients with type 2 diabetes mellitus and atherosclerotic cardiovascular disease. Consider the risks and benefits of JANUVIA prior to initiating treatment in patients at risk for heart failure, such as those with a prior history of heart failure and a history of renal impairment, and observe these patients for signs and symptoms of heart failure during therapy. Advise patients of the characteristic symptoms of heart failure and to immediately report such symptoms. If heart failure develops, evaluate and manage according to current standards of care and consider discontinuation of JANUVIA (sitagliptin).

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 impairment 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 impairment, 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
The incidence (and rate) of hypoglycemia based on all reports of symptomatic hypoglycemia were: 12.2 percent (0.59 episodes/patient-year) for JANUVIA 100 mg in combination with glimepiride (with or without metformin), 1.8 percent (0.24 episodes/patient-year) for placebo in combination with glimepiride (with or without metformin), 15.5 percent (1.06 episodes/patient-year) for JANUVIA 100 mg in combination with insulin (with or without metformin), and 7.8 percent (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, 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 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 one 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 (sitagliptin). 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.

In clinical studies, the adverse reactions reported, regardless of investigator assessment of causality, in ≥5 percent 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 the Comparative Trials with Sitagliptin (CompoSIT) Clinical Trial Program

Merck has continued to invest in the sitagliptin clinical development program. The objective of the Comparative Trials with Sitagliptin (CompoSIT) Clinical Trial Program is to better understand the use of JANUVIA in certain patient populations, specifically in patients already on JANUVIA who are initiating insulin (CompoSIT-I), patients with mild renal impairment (CompoSIT-R), and patients not at A1C goal on a submaximal dose of metformin (CompoSIT-M). For more information about these studies, visit https://clinicaltrials.gov/.

Our Commitment to Diabetes

At Merck, we're committed to scientific innovation, and we believe it's our responsibility to help address the global diabetes epidemic, one community and one patient at a time.iii

Our legacy in diabetes is rooted in research, which led to the first FDA approval in 2006 of a DPP-4 inhibitor in the U.S., JANUVIA (sitagliptin), but our work didn't stop there.iv We continue to invest our resources and capabilities and collaborate with others to develop and deliver a range of treatments and educational tools for patients and healthcare providers to help address this public health challenge.

For more information about our commitment to diabetes, visit www.merck.com/about/our-work/diabetes.html.

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.

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. 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 2017 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).


Language:
English

Contact:
Merck
Media:
Pam Eisele, 267-305-3558
or
Megan Wilkinson, 267-305-6463
or
Investors:
Michael DeCarbo, 908-740-1807

Ticker Slug:
Ticker: MRK
Exchange: NYSE
@merck