

**FOR IMMEDIATE RELEASE**

*Clinical update presented at ADA*

**Data Released at ADA Showed that Sitagliptin and Metformin as Initial Combination Therapy Provided Significant Glucose Lowering Efficacy over 54 Weeks in Patients with Type 2 Diabetes**

- *Investigational Use of Initial Combination Therapy with Sitagliptin and Metformin Significantly Improved Blood Sugar Control Compared with Metformin Alone Over One Year*
- *A Separate, Investigational Study showed Sitagliptin Significantly Improved Blood Sugar Control When Added to Sulfonylurea or to Sulfonylurea and Metformin vs. Sulfonylurea or Sulfonylurea and Metformin Alone*
- *New Study with Sitagliptin Suggests that Metformin Acts in a Different Manner than DPP-4 Inhibitors to Increase Total GLP-1 Levels*
- *Additional Data Suggested that, When Used Together, Sitagliptin and Metformin Had a Complementary Effect on Active GLP-1 Levels in Healthy Adults*
- *A Pooled Analysis of 5,141 Patients Showed Overall Incidence of Adverse Experiences, Incidence of Serious Adverse Experiences, and Incidence of Discontinuations Due to Adverse Experiences were Similar in the Sitagliptin and Non-Exposed Groups For Up to Two Years*

**CHICAGO, Ill - June 26, 2007** – Clinical studies presented at the American Diabetes Association (ADA) 67<sup>th</sup> Annual Scientific Sessions showed that, with investigational use as initial therapy, sitagliptin in combination with metformin provided significant glycemic improvement over 54 weeks and demonstrated significant improvement in markers of beta cell function in patients with type 2 diabetes. New data from investigational studies presented also showed that sitagliptin significantly improved blood sugar control in patients with type 2 diabetes when added to a sulfonylurea, glimepiride (dual combination therapy), or when added to a sulfonylurea and metformin (triple combination therapy). Additional efficacy and safety data for sitagliptin were also presented at the meeting. Sitagliptin is a selective, once daily agent in a new class of anti-hyperglycemic agents known as DPP-4 (dipeptidyl peptidase-4) inhibitors, and is not currently available or approved in Canada.

**Initial Combination Therapy with Sitagliptin and Metformin Significantly Improved Blood Sugar Control Compared with Metformin Alone Over One Year (LB-04; Study #036)**

"Initial therapy with one agent is often unsuccessful at getting patients to blood sugar goals. Many patients may require initial combination therapy, in addition to diet and exercise, in order to achieve and maintain blood sugar control," said Dr. Daniel Drucker, Professor of Medicine and Director of the Banting and Best Diabetes Centre in Toronto. "Sitagliptin in combination with metformin significantly improved blood sugar control for over one year. This has important implications for patients with moderate to severe type 2 diabetes who need to achieve optimal blood sugar targets in order to help slow disease progression and associated complications."

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After completing an initial 24-week placebo-controlled phase 'A' (n=1091), 762 patients with a mean baseline HbA1c\* of 8.7 per cent continued in a 30-week, double-blind, active-controlled phase 'B' on their previous active treatments: sitagliptin 50 mg/metformin 1000 mg twice daily (n=161); sitagliptin 50 mg/metformin 500 mg twice daily (n=160); metformin 1000 mg twice daily (n=153); metformin 500 mg twice daily (n=147); and sitagliptin 100 mg once-daily (n=141). Results showed a mean HbA1c reduction from baseline of 1.8 per cent in patients treated with sitagliptin 50 mg/metformin 1000 mg twice daily for up to 54 weeks.

Two-thirds (67 per cent) of patients continuing past 24 weeks in this study achieved the American Diabetes Association (ADA) target HbA1c goal of less than seven per cent on sitagliptin 50 mg/metformin 1000 mg twice daily (n=153) compared to 44 per cent on metformin 1000 mg twice daily alone (n=134). Further, 48 per cent of patients treated with sitagliptin 50 mg/metformin 500 mg twice daily (n=147), 25 per cent of patients treated with metformin 500 mg twice daily (n=117), and 23 per cent of patients treated with sitagliptin 100 mg once daily (n=106) reached the ADA target HbA1c goal. The Canadian Diabetes Association's recommended HbA1c goal level is  $\leq 7$  per cent.

Duration of response was demonstrated by data showing that 85 per cent of patients treated with sitagliptin 50 mg/metformin 1000 mg twice daily and 70 per cent of patients treated with sitagliptin 100 mg once daily who achieved the target HbA1c goal of less than seven per cent at Week 24 had a Week 54 HbA1c value of less than seven per cent (n=96 and 33, respectively). In addition, 80 per cent of patients treated with sitagliptin 50 mg/metformin 500 mg twice daily (n=65), 79 per cent of patients treated with metformin 1000 mg twice daily (n=63), and 59 per cent of patients treated with metformin 500 mg twice daily (n=34) who reached a goal HbA1c of less than seven per cent at Week 24 had a Week 54 HbA1c value of less than seven per cent.

Over the 54 week study, five out of 182 patients (3 per cent) treated with sitagliptin 50 mg/metformin 1000 mg twice daily and two out of 182 patients (one per cent) treated with metformin 1000 mg twice daily had at least one episode of hypoglycemia. Incidences of gastrointestinal adverse experiences were similar to those observed with metformin alone (26 per cent vs. 31 per cent with metformin 1000 mg twice daily).

**Investigational Study Showed Sitagliptin Significantly Improved Blood Sugar Control When Added to Sulfonylurea or to Sulfonylurea and Metformin vs. Sulfonylurea or Sulfonylurea and Metformin Alone (Poster #535-P; Study #035)**

In this study, which was designed to examine the efficacy and safety of sitagliptin in patients with type 2 diabetes whose blood glucose levels were inadequately controlled (HbA1c levels of 7.5 per cent to 10.5 per cent) on a sulfonylurea (glimepiride) alone or on a sulfonylurea (glimepiride) plus metformin, sitagliptin demonstrated a significant mean difference from placebo in HbA1c of 0.9 per cent in patients on glimepiride and metformin and 0.6 per cent in patients on glimepiride alone (p<0.001 for both comparisons to the addition of placebo).

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\* HbA1c is a measure of a person's average blood glucose over a two-to-three month period. An important predictive factor in the magnitude of HbA1c reduction in response to anti-hyperglycemic therapy is a patient's HbA1c at baseline.

After a titration/stabilization period on glimepiride (at least 4 mg/day) with or without metformin (at least 1500 mg/day) and a 2-week placebo run-in, 441 patients with a mean baseline HbA1c of 8.3 per cent were randomized to the addition of sitagliptin 100 mg once-daily or placebo for 24 weeks. Of these patients, 212 were on glimepiride alone (106 each on sitagliptin or placebo), and 229 on glimepiride and metformin (116 on sitagliptin, 113 on placebo). The primary endpoint was HbA1c change from baseline for the entire cohort.

The addition of sitagliptin to a sulfonylurea with or without metformin was generally well-tolerated in this study. A higher incidence of overall adverse experiences (60 vs. 47 per cent) and drug-related adverse experiences (15 vs. 7 per cent) were reported with sitagliptin compared to placebo in patients treated with glimepiride with or without metformin. These higher rates were partly related to a higher incidence of hypoglycaemia with sitagliptin compared to placebo (12 vs. two per cent, respectively). The higher rate of hypoglycaemia has commonly been seen when antihyperglycaemic agents are used in combination with sulfonylurea agents. After 24 weeks, body weight was increased more with sitagliptin than with placebo (mean change from baseline of +0.8 vs. -0.4 kg, respectively;  $p < 0.001$ ).

### **Investigational Use of Sitagliptin and Metformin as Initial Combination Therapy Led to Improvement in Markers of Beta Cell Function in Patients with Type 2 Diabetes (0533-P; Study #036)**

"Type 2 diabetes is caused by the progressive and inevitable failure of the insulin-producing cells of the pancreas known as the beta cells. Beta cell failure is progressive despite diet, exercise and currently available therapies," explained Dr. Drucker. "Sitagliptin in combination with metformin led to improvement in markers of beta cell function which is a potentially important development in the treatment of type 2 diabetes."

In this investigational study, the effects of sitagliptin and metformin on beta cell function were examined in patients with type 2 diabetes who participated in a 24-week, placebo-controlled study in which 1,091 patients were randomized to one of six treatments: sitagliptin 50 mg/metformin 1000 mg twice daily ( $n=182$ ); sitagliptin 50 mg/metformin 500 mg twice daily ( $n=190$ ); metformin 1000 mg twice daily ( $n=182$ ); metformin 500 mg twice daily ( $n=182$ ); sitagliptin 100 mg once-daily ( $n=179$ ); or placebo ( $n=176$ ). Of these, a subset of 500 patients underwent frequently sampled meal tolerance tests. Beta cell function was measured using a computer model based evaluation. Parameters of beta cell function from this model allowed for the estimation of the insulin secretion rate (ISR) and the characterization of the ISR into static (beta cell responsiveness to above-basal glucose following a meal) and dynamic (beta cell responsiveness to the rate of increase in above-basal glucose following a meal) components.

After 24 weeks, the changes in static and dynamic beta cell responsiveness were increased across all active treatments relative to placebo, and appeared to be increased in an approximately additive fashion with co-administration with sitagliptin and high dose metformin compared to each as monotherapy. The results of the beta cell modeling analysis showed that the addition of sitagliptin to metformin resulted in a 49 per cent increase in measured change in static beta cell responsiveness compared with metformin alone (20.1, sitagliptin 50 mg/metformin 1000 mg twice daily vs. 13.5, metformin 1000 mg twice daily). Further, the addition of sitagliptin to metformin resulted in a 114 per cent increase in measured change in dynamic beta cell responsiveness compared with metformin alone (151.0, sitagliptin 50 mg/metformin 1000 mg twice daily vs. 70.7, metformin 1000 mg twice daily).

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**Sitagliptin and Metformin Had a Complementary Effect to Increase Active GLP-1 Concentrations in Healthy Adults (0286-OR; Study #050)**

A randomized, placebo-controlled, double-blind, clinical pharmacology study was conducted in 16 healthy adults to assess the potential complementary effects of sitagliptin and metformin on GLP-1, an important incretin hormone. In each 2-day treatment period, subjects received one of four treatments: sitagliptin, metformin, the co-administration of sitagliptin and metformin, or placebo.

In this study, sitagliptin and metformin, when taken separately, increased overall, post-meal, active concentrations of GLP-1 levels by 1.95- and 1.76-fold, respectively ( $p < 0.001$ ), compared with placebo. When administered together, sitagliptin and metformin increased active concentrations of GLP-1 by 4.12-fold ( $p < 0.001$ ) compared with placebo. In contrast to active GLP-1 levels that were increased by both drugs, the levels of total GLP-1 (which includes both active and inactive GLP-1) were increased by metformin only and not by sitagliptin. These observations are consistent with the effect of sitagliptin to raise active GLP-1 levels by reducing the clearance, but suggest that metformin acts in a different manner to increase active GLP-1 levels. This study provides evidence that the two drugs may have complementary effects on GLP-1.

"This is the first study in humans that showed that metformin increases the concentration of the incretin hormone, GLP-1; thus increasing the total GLP-1 available. When used together with sitagliptin, a DPP-4 inhibitor that blocks the degradation of GLP-1 by inhibiting its breakdown, there was an increase in GLP-1 levels greater than what either agent provided alone," said Dr. Daniel Drucker. "It appears as though metformin allows for more total GLP-1 to be available, and sitagliptin helps GLP-1 to remain active thus acting in a complementary way."

GLP-1 plays an important role in regulating the body's blood sugar levels. When food is consumed, GLP-1 is released by the gastrointestinal tract to stimulate the pancreatic beta cells to secrete insulin, a hormone that helps the body to use glucose for energy. GLP-1 also suppresses the release of glucagon from the pancreatic alpha cells, which, in turn, tells the liver to reduce its production of sugar.

**A Pooled Analysis of 5,141 Patients Showed Overall Incidence of Adverse Experiences, Incidence of Serious Adverse Experiences, and Incidence of Discontinuations Due to Adverse Experiences were Similar in the Sitagliptin and Non-Exposed Groups For Up to Two Years (Poster #534-P)**

The safety and tolerability of sitagliptin was assessed by pooling data from nine completed Phase IIB and III studies, including the studies discussed above, ranging from 24 to 104 weeks in duration, and including 5,141 patients treated with either sitagliptin 100 mg once-daily ( $n=2,786$ ) or other treatments (placebo or an active comparator) ( $n=2,355$ ). The studies assessed sitagliptin as monotherapy, initial combination therapy with metformin, or add-on to another oral agent (metformin, pioglitazone, sulfonylurea, or sulfonylurea and metformin).

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Sitagliptin 100 mg once daily was generally well-tolerated as monotherapy, as initial combination therapy, or as add-on therapy. For adverse experiences (either clinical or laboratory), the overall incidence of adverse experiences, the incidence of serious adverse experiences, and the incidence of discontinuations due to adverse experiences were similar in the sitagliptin treated patients and in patients who received other therapies (patients on placebo or active comparator). Drug-related adverse experiences were higher in the non-exposed group due to hypoglycemia reported in sulfonylurea-treated patients (since studies in which a sulfonylurea agent was a treatment in patients not receiving sitagliptin were included in this pooled analysis).

Specific clinical adverse experiences, expressed as a rate of  $\geq 1$  event per 100 patient-years of exposure, in the sitagliptin population included nasopharyngitis [12 vs. 9], hypoglycaemia [9 vs. 58], increased blood glucose [5 vs. 9], osteoarthritis [2 vs. 1], contact dermatitis [1 vs. <1], tremor [1 vs. <1], nasal congestion [1 vs. <1], and reduced blood glucose [1 vs. 3] for sitagliptin and non-exposed patients, respectively.

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### **Forward-Looking Statement**

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### **FOR MORE INFORMATION PLEASE CONTACT:**

**Martine Drolet**  
Public Affairs  
Merck Frosst Canada Ltd.  
(514) 428-3037

**Melissa Maloul**  
Cohn and Wolfe  
(514)-845-2257 ext. 228