

**FOR IMMEDIATE RELEASE**

**NEW DATA ON SITAGLIPTIN, AN INVESTIGATIONAL ONCE-DAILY MEDICINE  
FOR TYPE 2 DIABETES**

**SITAGLIPTIN SHOWED THE SAME GLUCOSE LOWERING EFFECT  
AS A STANDARD THERAPY WITH SIGNIFICANT DIFFERENCES  
IN WEIGHT CHANGE AND HYPOGLYCEMIA**

**WASHINGTON, D.C. - June 13, 2006** – Results from a late-breaking oral presentation at today's American Diabetes Association (ADA) 66<sup>th</sup> Annual Scientific Sessions, showed that sitagliptin was non-inferior to glipizide (a sulfonylurea) in significantly reducing blood sugar levels at 52 weeks when added to the regimen of patients with type 2 diabetes who were inadequately controlled on metformin monotherapy. Study results also showed that patients taking sitagliptin experienced a significant weight loss while those taking glipizide experienced weight gain. Sitagliptin, a DPP-4 (dipeptidyl peptidase-4) inhibitor, is in a new class of oral drugs that enhances the body's own ability to lower blood sugar (glucose) when it is elevated.

“What's exciting about DPP-4 inhibitors is that they are a completely new way to treat type 2 diabetes, something that's never been done before that will be complementary to existing therapies we use today,” explained Dr. Daniel Drucker, Professor of Medicine and Director of the Banting and Best Diabetes Centre in Toronto. “One in two patients in Canada being treated for type 2 diabetes does not achieve targeted blood sugar levels suggesting that current therapies have significant limitations. Sitagliptin may provide a promising new option as it effectively lowers blood sugar levels, enabling patients to better achieve their A1C target levels, and this, with less side effects such as weight gain and hypoglycemia.”

**Summary of findings at primary time point**

In this double-blind, randomized study 1,172 patients were given either sitagliptin (100 mg once daily) or glipizide (up to 20 mg daily, the maximum titrated dose). At 52 weeks, the primary time point analysis (n= 793) for this study which continues for another year (104 weeks), sitagliptin achieved the pre-specified bounds for non-inferiority vs. glipizide.

Results showed that:

- Mean reduction in A1C\* was identical between the two groups: (0.67 per cent vs. baseline, p<0.001); in patients with mildly to moderately elevated baseline A1C levels (mean baseline 7.5 per cent);

\* A1C is a measure of a person's blood average blood glucose over a two- to three-month period. An important predictive factor in the magnitude of A1C reduction in response to anti-hypoglycemic therapy is a patient's A1C level at baseline.

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## **ADA late-breaking results on sitagliptin / 2**

- Similar proportions of patients in each group achieved A1C goal (<7 per cent) (63 per cent for sitagliptin vs. 59 per cent for glipizide);
- Patients in the sitagliptin group experienced significant weight loss (mean -1.5 kg) from baseline while those treated with glipizide had significant weight gain from baseline (mean +1.1 kg) — the between-treatment difference was statistically significant ( $p<0.001$ );
- Patients treated with sitagliptin had a significantly lower incidence of hypoglycemia (low blood sugar) while those taking glipizide experienced a significantly higher rate: 4.9 per cent vs. 32.0 per cent respectively ( $p<0.001$ ).

### **Sitagliptin achieves A1C goal across phase III clinical program**

In other phase III studies also presented during the ADA meeting, sitagliptin, when used as monotherapy or in combination with two commonly used therapies (metformin and pioglitazone), significantly reduced blood sugar levels. Additionally, treatment with sitagliptin improved beta cell function. Beta cells are cells in the pancreas that make and release insulin.

### **Results from monotherapy studies**

#### **Study #021**

The efficacy and safety of sitagliptin were assessed in a 24-week, randomized, double-blind, placebo-controlled phase III study of 741 patients with primarily mild to moderate type 2 diabetes (mean baseline A1C 8 per cent). After a drug washout period for those on an anti-hyperglycemic agent and a 2-week single-blind placebo run-in period, the patients, ages 18 to 75 years, with an A1C between 7 per cent and 10 per cent were randomized (1:1:1) to placebo, sitagliptin 100 mg once daily, or sitagliptin 200 mg once daily. At the proposed registration dose of 100 mg, sitagliptin produced significant mean glucose-lowering results:

<u>Measurement</u>	<u>Value (placebo-subtracted)</u>
HbA1c	-0.79 per cent (p<0.001)
FPG	-17.1 mg/dL or 0.96 mmol/L (p<0.001)
2-hour PPG	-46.7 mg/dL or 2.62 mmol/L (p<0.001)

In a pre-specified stratification of patients based on their baseline A1C, patients with a higher baseline A1C experienced greater mean reductions of A1C than those with lower baseline levels. The following table provides the range of responses seen with sitagliptin 100 mg in patients with different baseline A1C values:

<u>Baseline HbA1c</u>	<u>Reduction (placebo-subtracted)</u>
≥ 9 (mean 9.58 per cent)	-1.52 per cent (p<0.001)
8 to 8.9 per cent (mean 8.36 per cent)	-0.80 per cent (p<0.001)
<8 per cent (mean 7.39 per cent)	-0.57 per cent (p<0.001)

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### **ADA late-breaking results on sitagliptin / 3**

In this 24-week monotherapy study, the rate of hypoglycemia or gastrointestinal adverse experiences was similar between sitagliptin and placebo. Body weight decreased from baseline by -0.2 kg with the proposed registration dose of sitagliptin 100 mg and by -1.1 kg in patients on placebo (p=0.008, difference between treatment groups).

#### **Study #023**

The efficacy and safety of sitagliptin were assessed in a randomized, double-blind, placebo-controlled, 18-week study in patients, ages 27 to 76 years, with type 2 diabetes. After a drug washout period for those on an anti-hyperglycemic agent and a two-week, single-blind, placebo run-in period, the 521 patients with A1C between 7 per cent and 10 per cent were randomized in a 1:2:2 ratio to placebo, sitagliptin 100 mg once daily or sitagliptin 200 mg once daily. In this study, sitagliptin 100 mg once daily produced significant mean reductions in A1C, FPG, and PPG in the patients with primarily mild to moderate type 2 diabetes (mean baseline A1C 8.1 per cent). The mean reductions observed were:

<u>Measurement</u>	<u>Value (placebo-subtracted)</u>
HbA1c	-0.60 per cent (p<0.001)
FPG	-19.7 mg/dL or 1.10 mmol/L (p<0.001)
2-hour PPG	-46.3 mg/dL or 2.59 mmol/L (p<0.05)

When stratified according to their baseline A1C values, patients demonstrated the following range of response for mean reduction of A1C:

<u>Baseline HbA1c</u>	<u>Reduction (placebo-subtracted)</u>
≥ 9 (mean 9.48 per cent)	-1.20 per cent (p<0.001)
8 to 8.9 per cent (mean 8.40 per cent)	-0.61 per cent (p=0.004)
<8 per cent (mean 7.37 per cent)	-0.44 per cent (p=0.003)

In this 18-week monotherapy study, there was no significant increase in hypoglycemia or gastrointestinal adverse events with sitagliptin compared to placebo. Body weight was similarly reduced with sitagliptin 100 mg (-0.6 kg) and placebo (-0.7 kg).

#### **Improvement in beta cell function**

Beta cell dysfunction, characterized by a decreased ability to produce adequate levels of insulin, occurs early in the disease process and is required for the development of type 2 diabetes. In the monotherapy studies, sitagliptin produced significant improvements in measures of beta cell function: HOMA-Beta and the fasting proinsulin/insulin ratio.

#### **Results from add-on therapy**

In two separate 24-week, phase III add-on studies, sitagliptin 100 mg once daily significantly improved A1C levels when added to therapy for patients inadequately controlled on metformin or a pioglitazone (a TZD) alone. In these studies, patients had mildly to moderately elevated A1C levels (mean baseline A1C of approximately 8 per cent).

**Study #020**

In a 24-week, double-blind study, 701 patients who had inadequate glycemic control with metformin (at least 1500 mg daily) were randomized to add either sitagliptin 100 mg once daily or placebo. Sitagliptin 100 mg once daily added to patients inadequately controlled on metformin and with mildly to moderately elevated A1C levels (mean baseline A1C 8.0 per cent) led to a significant additional mean reduction in A1C, FPG, and PPG at 24 weeks, as shown:

<u>Measurement</u>	<u>Value (placebo-subtracted)</u>
HbA1c	-0.65 per cent (p<0.001)
FPG	-25.4 mg/dL or 1.42 mmol/L (p<0.001)
2 hour PPG	-50.6 mg/dL or 2.83 mmol/L (p<0.001)

When added to patients inadequately controlled on metformin, sitagliptin was generally well tolerated, with no increased incidence of hypoglycemia or gastrointestinal adverse events compared with the placebo arm of the study. Body weight was similarly reduced with the treatment group with sitagliptin 100 mg + metformin and placebo + metformin.

**Study #019**

In another 24-week, double-blind study, 353 patients who had not achieved glycemic control with pioglitazone 30 mg or 45 mg daily were randomized to receive pioglitazone with sitagliptin 100 mg once daily or pioglitazone with placebo. The patients had mildly to moderately elevated A1C levels (mean baseline A1C 8.05 per cent). Sitagliptin 100 mg once daily added to pioglitazone resulted in significant additional reductions in A1C and FPG when compared to pioglitazone with placebo, as shown:

<u>Measurement</u>	<u>Value (placebo-subtracted)</u>
HbA1c	-0.70 per cent (p<0.001)
FPG	-17.7 mg/dL or 0.99 mmol/L (p<0.001)

Sitagliptin 100 mg in combination with pioglitazone was generally well tolerated with an overall incidence of adverse events and hypoglycemia similar to the placebo plus pioglitazone combination. A slightly higher incidence of abdominal pain, and of the overall incidence of pre-specified, selected gastrointestinal adverse experiences, was observed with patients receiving sitagliptin. Body weight changes were similar between the treatment group of sitagliptin 100 mg + pioglitazone and placebo + pioglitazone.

**Safety and tolerability profiles across the clinical program**

The overall incidence of clinical and laboratory adverse experiences was similar between sitagliptin and placebo with the most common side effects ( $\geq 3$  per cent and greater than placebo) being stuffy or runny nose and sore throat; headache; diarrhea; upper respiratory infection; joint pain; and urinary tract infection (with differences ranging from 0.1 per cent to 1.5 per cent vs. placebo).

**Novel mode of action**

Sitagliptin is Merck's investigational oral, once daily DPP-4 inhibitor for the treatment of type 2 diabetes. A potent and highly selective DPP-4 inhibitor, it works by enhancing a natural body system that lowers blood sugar, the incretin system. When blood sugar is elevated, incretins work in two ways to help the body regulate high blood sugar levels: they trigger the pancreas to increase insulin and signal the liver to reduce glucose production. DPP-4 inhibitors enhance the body's own ability to control blood sugar levels by increasing the active levels of these incretin hormones in the body, helping to decrease blood sugar levels in patients with type 2 diabetes. The mechanism of action is distinct from any existing class of glucose lowering agents. Sitagliptin is not approved in Canada.

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