

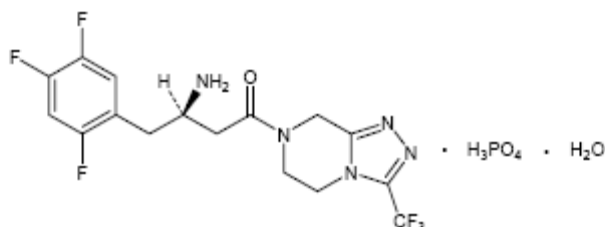
Bon Secours Richmond
Pharmacy & Therapeutics Committees
Sitagliptin (Januvia)
3/2007

Recommendations:

- Sitagliptin (Januvia®) is recommended for formulary inclusion. It is FDA approved for patients 18 years of age and older for the following:
 - Monotherapy: Adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus
 - Combination Therapy: In patients with type 2 diabetes mellitus to improve glycemic control in combination with metformin or a thiazolidinedione when the single agent alone, with diet and exercise, does not provide adequate glycemic control
 - Advantages include:
 - limited or no weight gain/loss
 - low rates of hypoglycemia when compared to placebo
 - few drug interactions
 - possible regeneration of pancreatic beta cells
 - once daily oral dose
 - few gastrointestinal side effects as opposed to the GLP-1 analogues, and few adverse side effects (sore throat, upper respiratory infection, and headache)
 - Disadvantages include:
 - modest decreases in A1C when compared to other anti-diabetic agents
 - dosage adjustments for renal impairment
 - high cost
 - lack of long term safety data on immune modulating effects
 - DPP-4 is widely distributed in numerous tissues and T-cells, B-cells, and natural killer cells.
 - Long term effects on immune system are unknown. DPP-4 inhibitors have been shown to inhibit T-cell activity in vitro at high concentration; but unlikely to achieve these levels in-vivo. DPP-4 cleaves hormones, neuropeptides, and chemokines. DPP-4 inhibitors prolong the action of hormone YY, neuropeptides (substance P), and macrophage-derived chemokines. Potential adverse effects include increased BP, inflammation, and allergic reactions.
- Pharmacy monitoring
 - Dosing adjustment for renal dysfunction.
 - Doses greater than 100 mg per day are not recommended as additional improvement in blood glucose is not provided. Pharmacokinetics are not effected by BMI.

Dosing adjustment for renal dysfunction			
Creatinine Clearance (ml/min)	Greater Than 50	30-50	Less than 30 including hemodialysis or peritoneal dialysis
Daily Dose	100 mg	50 mg	25 mg

BSR Patient Cost Per Day				
Januvia	Metformin (Generic)	Glipizide (Generic)	Rosiglitazone (Avandia)	Pioglitazone (Actos)
25-100 mg daily \$4.58	500 mg TID \$0.30	5-20 mg Daily \$0.03-\$0.09	4-8 mg Daily \$2.65-\$4.90	15-45 mg Daily \$3.10-\$5.38



Findings:

- Sitagliptin is a highly selective competitive reversible inhibitor of DPP-4 (dipeptidyl peptidase-4), the enzyme responsible for inactivation and degradation of the incretin hormones *glucagon-like peptide-1* (GLP-1) and *glucose-dependent insulinotropic polypeptide* (GIP). These hormones are released by the intestine throughout the day, with an increase postprandially; they potentiate insulin synthesis and release by pancreatic beta cells and decrease glucagon production by pancreatic alpha cells in a glucose-dependent manner, lowering serum glucose concentrations. They also inhibit gastric emptying, and reduce appetite and food intake. GLP-1 is released in a glucose dependent manner. Diabetics have lower levels of GLP-1 than normal individuals.
- DPP-4 is widely distributed in numerous tissues and T-cells, B-cells, and natural killer cells.
- Long term effects on immune system are unknown. DPP-4 inhibitors have been shown to inhibit T-cell activity in vitro at high concentration; but unlikely to achieve these levels in-vivo. DPP-4 cleaves hormones, neuropeptides, and chemokines. DPP-4 inhibitors prolong the action of hormone YY, neuropeptides (substance P), and macrophage-derived chemokines. Potential adverse effects include increased BP, inflammation, and allergic reactions.
- Sitagliptin is selective for DPP-4 and does not inhibit DPP-8 (located on activated T-cells) or DPP-9 (located in skeletal muscle, heart, and liver) at therapeutic concentrations.
- Actions of GLP-1 receptor

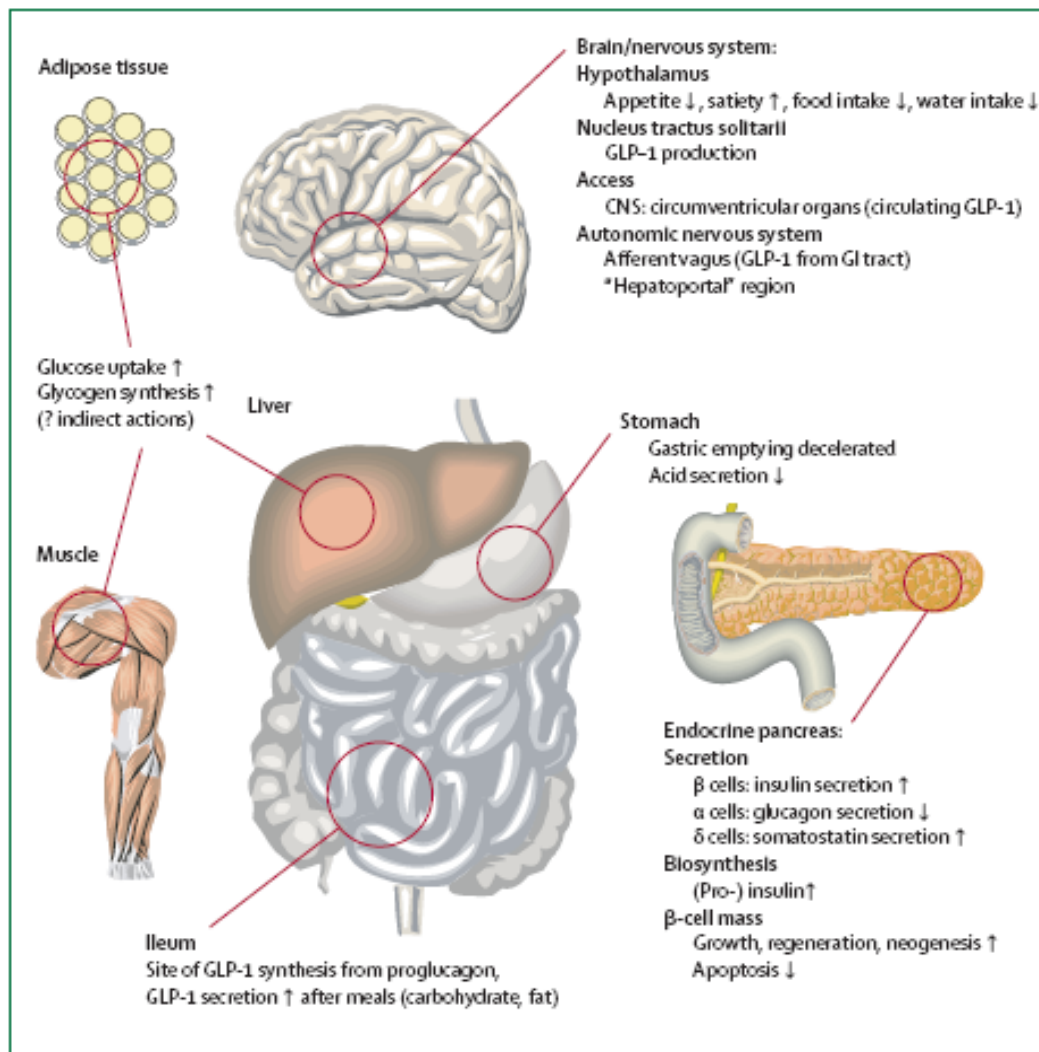


Figure 1: Physiology of GLP-1 secretion and action on GLP-1 receptors in different organs and tissues

- Recommended dose for healthy adults is 100 mg once daily as monotherapy or as combination therapy

Dosage Adjustment in Patients With Moderate, Severe and End Stage Renal Disease (ESRD) (2.2)	
50 mg once daily	25 mg once daily
Moderate	Severe and ESRD
CrCl ≥ 30 to < 50 mL/min ~Serum Cr levels [mg/dL] Men: $> 1.7 - \leq 3.0$; Women: $> 1.5 - \leq 2.5$	CrCl < 30 mL/min ~Serum Cr levels [mg/dL] Men: > 3.0 ; Women: > 2.5 ; or on dialysis

- Doses greater than or equal to 100 mg every day of sitagliptin will result in sustained DPP-4 inhibition greater than or equal to 80% over a 24-hour dosing interval and may provide near-maximal glucose lowering. GLP-1 and GIP are increased 2-3 fold.
- May be administered without regard to timing of hemodialysis
- Sitagliptin is not effective for treatment of type 1 diabetes or for the treatment of diabetic ketoacidosis
- Rates of hypoglycemia with Januvia as monotherapy and in combination with metformin or pioglitazone were similar to those patients taking placebo. Combination with other medications known to cause hypoglycemia is unknown at this time. Low rates of hypoglycemia are theoretically due to the fact that the DPP-4 inhibitors only work in response to a meal because that is when the incretin levels rise. Minimizing hypoglycemia results in prevention of weight gain.
- Counter-regulatory release of glucagon in response to hypoglycemia is fully preserved even in the presence of pharmacological concentrations of GLP-1.
- Body weight did not increase from baseline with Januvia in the monotherapy studies published in the package insert. A similar decrease in body weight was observed for both placebo and Januvia/Metformin combination treatment groups. There was no significant difference between Januvia/Pioglitazone combination therapy and placebo in body weight change.
- Sitagliptin is well tolerated; gastrointestinal side effects are minimal as compared to the GLP-1 mimetics. DPP-4 inhibitors only increase active GLP-1 levels as compared to total GLP-1 levels. This only modestly increases GLP-1, which supports the role of GLP-1 in diabetes treatment without producing the concentrations that induce the GLP-1 related side effects.
- Adverse Drug Reactions
 - Overall incidence of adverse reactions with Januvia was similar to placebo. Discontinuation of therapy due to adverse reactions was also similar to placebo
 - In patients receiving Januvia with metformin, there were no adverse reactions in $\geq 5\%$ of patients and more commonly than in patients given placebo

Table 1
Placebo-Controlled Clinical Studies of JANUVIA Monotherapy or Combination with Pioglitazone:
Adverse Reactions Reported in $\geq 5\%$ of Patients and More Commonly than in Patients
Given Placebo, Regardless of Investigator Assessment of Causality[†]

	Number of Patients (%)	
	JANUVIA 100 mg	Placebo
Monotherapy	N = 443	N = 363
Nasopharyngitis	23 (5.2)	12 (3.3)
Combination with Pioglitazone	JANUVIA 100 mg + Pioglitazone	Placebo + Pioglitazone
	N = 175	N = 178
Upper Respiratory Tract Infection	11 (6.3)	6 (3.4)
Headache	9 (5.1)	7 (3.9)

[†] Intent to treat population

- Drug Interactions
 - Digoxin AUC increased 11%, monitor appropriately in patients receiving digoxin and sitagliptin concurrently as digoxin levels may be increased. No dosage adjustment of either drug is recommended.
- Thiazolidinediones lower glucose concentrations primarily by decreasing insulin resistance. Because sitagliptin lowers glucose by increasing insulin release and lowering glucagon concentrations rather than by directly improving insulin resistance, the glucose-lowering mechanisms of sitagliptin and thiazolidinediones may be complementary.
- Studies suggest that sitagliptin exhibits disease-modifying potential due to the beneficial effects GLP-1 exerts on the differentiation, proliferation, and survival of beta cells.
- Improved fasting and postprandial glucose levels. Improvement in pancreatic beta cell function and increase insulin release may be responsible for the decreases in fasting plasma glucose as opposed to the postprandial decreases in glucose which would be consistent with how incretins are released in response to a meal to lower glucagons and increase insulin.
- No improvement in insulin resistance or sensitivity as shown by no changes in HOMA-IR in sitagliptin treatment groups
- Theoretical safety concerns: DPP-4 also has effects on T-cell activation and proliferation. A number of neuropeptides, growth factors, cytokines, and chemokines are all potential substrates. Unknown at this time if clinically relevant. Side effects of prolongation of these substrates have not been observed in preclinical or clinical studies.

- Selective for DPP-4. Toxicities associated with inhibition of DPP-8 and DPP-9 have not been observed thus far
- Trough levels of doses greater than or equal to 100 mg produced target inhibition of DPP-4 activity greater than or equal to 80%. This inhibition has been shown to produce maximal or near maximal acute lowering of glucose levels.
- Clinical studies have shown that patients with type 2 diabetes have reduced concentrations of intact GLP-1
- Weight loss has been noted with other GLP-1 based therapies. As improved glycemic control may lead to weight gain, the minimal body weight changes associated with sitagliptin could suggest that there is a tendency for weight reduction with sitagliptin counterbalanced by the tendency of improved glycemic control to increase weight.

	Sitagliptin (Januvia)
FDA Indication	Monotherapy: Adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus Combination Therapy: In patients with type 2 diabetes mellitus to improve glycemic control in combination with metformin or a thiazolidinedione when the single agent alone, with diet and exercise, does not provide adequate glycemic control
Mechanism of Action	Orally active inhibitor of the dipeptidyl peptidase-4 enzyme (DPP-4). Acts in patients with type 2 diabetes to slow the inactivation of incretin hormones thus increasing insulin release and decreasing glucose production in a glucose-dependent manner
Dose	Recommended dose is 100 mg once daily as monotherapy or as combination therapy
Dosage Forms and Strengths	Tablets in 100mg, 50 mg, and 25 mg
Contraindications	None
Pregnancy category	B
Nursing	Not known whether secreted in human milk, exercise caution. Rats milk:plasma ratio 4
Pediatrics	Safety and effectiveness has not been established in patients < 18 years old
Geriatrics	No overall differences observed in patients 65 years and older as compared to younger patients. Especially important to assess renal function
Volume of Distribution	198 liter
Protein Binding	38%
T _{1/2}	12.4 hours
Bioavailability	87%, administered with or without food
AUC 100 mg per day	8.52 micromole-hour
Metabolism	79% excreted unchanged in the urine (active tubular secretion), limited metabolism (CYP3A4 and CYP2C8)
Elimination	Primarily Renal 79% excreted unchanged in urine
Renal Insufficiency	Dosage adjustment necessary
Hepatic Insufficiency	No dosage adjustment necessary in moderate hepatic insufficiency, no data available in severe hepatic insufficiency (Child-Pugh score > 9)

Studies from package insert

Four double-blind, placebo controlled clinical safety and efficacy studies conducted to evaluate the effects of sitagliptin on glycemic control with a total of 2316 patients with type 2 diabetes. The mean age of these patients was 54.8 years. 62% were white, 18% were Hispanic, 6% were Black, 9% were Asian and 4% were of other racial groups.

Januvia Monotherapy Study

Total of 1262 patients with type 2 diabetes divided in two double-blind, placebo controlled studies, one of 18-week duration and another of 24-week duration. In the 18-week study, 521 patients were randomized to placebo, Januvia 100 mg, or Januvia 200 mg daily. In the 24-week study 741 patients were randomized to placebo, Januvia 100 mg, or Januvia 200 mg daily. Treatment with Januvia at 100 mg daily provided significant improvements in A1C, fasting plasma glucose (FPG), and 2-hour post-prandial glucose (PPG). Metformin was used as rescue therapy in patients who were not achieving desired goals during studies and was added on to either placebo or Januvia. Data compiled based on last observation before addition of metformin as rescue therapy. Januvia 200 mg daily dose did not provide any greater efficacy than the 100 mg daily dose. Rescue therapy required in 9% of Januvia and 17-21% of placebo patients.

Table 2
Glycemic Parameters in 18- and 24-Week Placebo-Controlled Studies of JANUVIA in Patients with Type 2 Diabetes[†]

	18-Week Study		24-Week Study	
	JANUVIA 100 mg	Placebo	JANUVIA 100 mg	Placebo
A1C (%)	N = 193	N = 103	N = 229	N = 244
Baseline (mean)	8.0	8.1	8.0	8.0
Change from baseline (adjusted mean [‡])	-0.5	0.1	-0.6	0.2
Difference from placebo (adjusted mean [‡]) (95% CI)	-0.6 [§] (-0.8, -0.4)		-0.8 [§] (-1.0, -0.6)	
Patients (%) achieving A1C <7%	69 (36%)	16 (16%)	93 (41%)	41 (17%)
FPG (mg/dL)	N = 201	N = 107	N = 234	N = 247
Baseline (mean)	180	184	170	176
Change from baseline (adjusted mean [‡])	-13	7	-12	5
Difference from placebo (adjusted mean [‡]) (95% CI)	-20 [§] (-31, -9)		-17 [§] (-24, -10)	
2-hour PPG (mg/dL)	 	 	N = 201	N = 204
Baseline (mean)			257	271
Change from baseline (adjusted mean [‡])			-49	-2
Difference from placebo (adjusted mean [‡]) (95% CI)			-47 [§] (-59, -34)	

[†] Intent to Treat Population using last observation on study prior to metformin rescue therapy.

[‡] Least squares means adjusted for prior antihyperglycemic therapy status and baseline value.

[§] p<0.001 compared to placebo.

^{||} Data not available.

Combination Therapy with Metformin Study

A total of 701 patients with type 2 diabetes in a 24-week, randomized, double-blind, placebo-controlled study to assess efficacy of Januvia in combination with metformin. Patients were randomized to either addition of 100 mg of Januvia or addition of placebo to at least a 1500 mg daily dose of metformin. Patients who failed to meet desired goals were treated with pioglitazone rescue. In combination with metformin, Januvia provided significant improvements in A1C, FPG, and 2-hour PPG compared to placebo with metformin. Rescue therapy required in 5% of Januvia and 14% of placebo patients.

Table 3
Glycemic Parameters at Final Visit (24-Week Study)
for JANUVIA in Combination with Metformin[†]

	JANUVIA 100 mg + Metformin	Placebo + Metformin
A1C (%)	N = 453	N = 224
Baseline (mean)	8.0	8.0
Change from baseline (adjusted mean [‡])	-0.7	-0.0
Difference from placebo + metformin (adjusted mean [‡]) (95% CI)	-0.7 [§] (-0.8, -0.5)	
Patients (%) achieving A1C <7%	213 (47%)	41 (18%)
FPG (mg/dL)	N = 454	N = 226
Baseline (mean)	170	174
Change from baseline (adjusted mean [‡])	-17	9
Difference from placebo + metformin (adjusted mean [‡]) (95% CI)	-25 [§] (-31, -20)	
2-hour PPG (mg/dL)	N = 387	N = 182
Baseline (mean)	275	272
Change from baseline (adjusted mean [‡])	-62	-11
Difference from placebo + metformin (adjusted mean [‡]) (95% CI)	-51 [§] (-61, -41)	

[†] Intent to Treat Population using last observation on study prior to pioglitazone rescue therapy.

[‡] Least squares means adjusted for prior antihyperglycemic therapy and baseline value.

[§] p<0.001 compared to placebo + metformin.

Combination Therapy with Pioglitazone Study

A total of 353 patients with type 2 diabetes in a 24-week, randomized, double-blind, placebo-controlled study to assess Januvia in combination with pioglitazone. All patients completed a run-in period of about 12 weeks of receiving 30-45 mg per day of pioglitazone and then were randomized to either add 100 mg of Januvia daily or placebo daily. Patients who failed to meet specific goals were treated with metformin as rescue therapy. In combination with pioglitazone, Januvia provided significant improvements in patients A1C and FPG compared to placebo with pioglitazone. Rescue therapy was required in 7% of Januvia and 14% of placebo patients.

Table 4
Glycemic Parameters at Final Visit (24-Week Study)
for JANUVIA in Combination with Pioglitazone[†]

	JANUVIA 100 mg + Pioglitazone	Placebo + Pioglitazone
A1C (%)	N = 163	N = 174
Baseline (mean)	8.1	8.0
Change from baseline (adjusted mean [‡])	-0.9	-0.2
Difference from placebo + pioglitazone (adjusted mean [‡]) (95% CI)	-0.7 [§] (-0.9, -0.5)	
Patients (%) achieving A1C <7%	74 (45%)	40 (23%)
FPG (mg/dL)	N = 163	N = 174
Baseline (mean)	168	166
Change from baseline (adjusted mean [‡])	-17	1
Difference from placebo + pioglitazone (adjusted mean [‡]) (95% CI)	-18 [§] (-24, -11)	

[†] Intent to Treat Population using last observation on study prior to metformin rescue therapy.

[‡] Least squares means adjusted for prior antihyperglycemic therapy status and baseline value.

[§] p<0.001 compared to placebo + pioglitazone.

Literature Review

Clin Ther. 2006 Oct;28(10):1556-68.

Efficacy and safety of the dipeptidyl peptidase-4 inhibitor sitagliptin added to ongoing pioglitazone therapy in patients with type 2 diabetes: a 24-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group study.

Rosenstock J, Brazg R, Andryuk PJ, Lu K, Stein P; Sitagliptin Study 019 Group.

Dallas Diabetes and Endocrine Center, Dallas, Texas, USA.

OBJECTIVE: The efficacy and tolerability of the dipeptidyl peptidase-4 inhibitor sitagliptin added to ongoing pioglitazone therapy were assessed in patients with type 2 diabetes and inadequate glycemic control (glycosylated hemoglobin [HbA(1c)] $> \text{or} = 7\%$ and $< \text{or} = 10\%$) while receiving a stable dose of pioglitazone. **METHODS:** This was a 24-week, multicenter, randomized, double-blind, placebo-controlled, parallel group study in patients aged $> \text{or} = 18$ years (ClinicalTrials.gov NCT00086502). At screening, all patients began a diet/exercise program that continued throughout the study period. Patients taking antihyperglycemic therapy other than pioglitazone underwent a washout of this therapy and entered an 8- to 14-week open-label pioglitazone dose-titration/stabilization period. Patients with an HbA(1c) $> \text{or} = 7\%$ and $< \text{or} = 10\%$ at the end of this period entered a 2-week, single-blind, placebo run-in period (total duration of run-in period, up to 21 weeks). Patients who had been receiving pioglitazone monotherapy (30 or 45 mg/d) and had an HbA(1c) $> \text{or} = 7\%$ and $< \text{or} = 10\%$ entered the 2-week, single-blind, placebo run-in period directly. Thus, at the time of randomization, all patients were receiving ongoing pioglitazone (30 or 45 mg/d). Patients were randomized in a 1:1 ratio to receive sitagliptin 100 mg once daily or placebo for 24 weeks. During this period, patients not meeting specific progressive glycemic goals (fasting plasma glucose > 270 mg/dL between randomization and week 6; FPG > 240 mg/dL after week 6 through week 12; or FPG > 200 mg/dL after week 12 through week 24) were given rescue therapy (metformin) through the end of the study. To avoid the confounding influence of use of rescue therapy on efficacy comparisons in this 24-week study, data were treated as missing after the initiation of metformin rescue therapy in the efficacy analyses. Missing data were input using the last-observation-carried-forward method. The primary efficacy end point was the change from baseline in HbA(1c) at week 24. Secondary efficacy end points included the change from baseline in fasting plasma glucose (FPG), insulin, and proinsulin; the Homeostasis Model Assessment beta-cell function and insulin-resistance indexes; the proinsulin/insulin ratio; the Quantitative Insulin Sensitivity Check Index; the percent changes from baseline in selected lipid parameters; the proportion of patients meeting the American Diabetes Association HbA(1c), goal of $< 7.0\%$; the proportion of patients requiring metformin rescue therapy; and the time to the initiation of rescue therapy. **RESULTS:** One hundred seventy-five patients were randomized to receive sitagliptin, and 178 were randomized to receive placebo. The mean (SD) baseline HbA1c value was 8.1% (0.8) in the sitagliptin group and 8.0% (0.8) in the placebo group. After 24 weeks, sitagliptin added to pioglitazone therapy was associated with significant reductions compared with placebo in HbA(1c) (between-treatment difference in least squares [LS] mean change from baseline, -0.70% ; 95% CI, -0.85 to -0.54 ; $P < 0.001$) and FPG (-17.7 mg/dL; 95% CI, -24.3 to -11.0 ; $P < 0.001$). Mean HbA(1c) values at end point were 7.2% (0.9) and 7.8% (1.1) in the respective treatment groups, and the proportions of patients reaching a target HbA(1c) of $< 7.0\%$ were 45.4% and 23.0% ($P < 0.001$). There was a continuous reduction in HbA(1c) throughout the 24-week treatment period, with the maximum reduction observed at week 24. A smaller proportion of patients in the sitagliptin group required metformin rescue therapy during the 24-week study compared with patients in the placebo group (6.9% vs 14.0%, respectively; $P < 0.05$). The time to initiation of rescue therapy was significantly longer in the sitagliptin group compared with the placebo group ($P < 0.05$). Significant reductions in fasting serum proinsulin levels and the proinsulin/insulin ratio were seen with sitagliptin treatment compared with placebo (both, $P < 0.01$) suggesting potential to improve beta-cell function. Also significant reductions in Triglycerides with sitagliptin compared with placebo. Sitagliptin was generally well tolerated, with no increased risk of hypoglycemia compared with placebo (2 vs 0 patients, respectively). The number of patients discontinuing the study due to clinical adverse experiences (5.7% vs 1.1%) and the incidence of abdominal pain (3.4% vs 0%) were significantly greater in the sitagliptin group compared with the placebo group (both, $P < 0.05$). The LS mean change in body weight from baseline did not differ significantly between sitagliptin or placebo added to pioglitazone therapy (between-treatment difference in LS mean change from baseline: 0.2 kg; 95% CI, -0.5 to 1.0).

PMID: 17157112 [PubMed - in process]

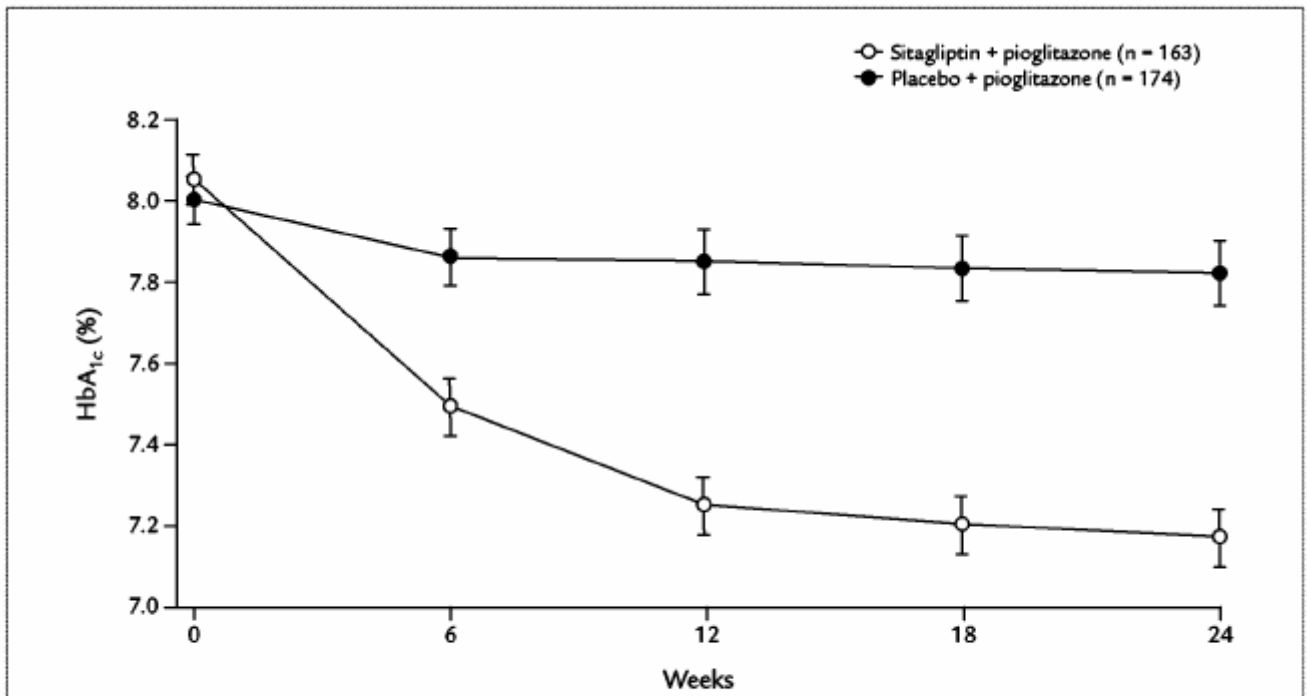


Figure 2. Changes in mean (SE) glycosylated hemoglobin (HbA_{1c}) over time with sitagliptin 100 mg once daily or placebo added to ongoing pioglitazone therapy in patients with type 2 diabetes who had not achieved adequate glycemic control with pioglitazone alone.

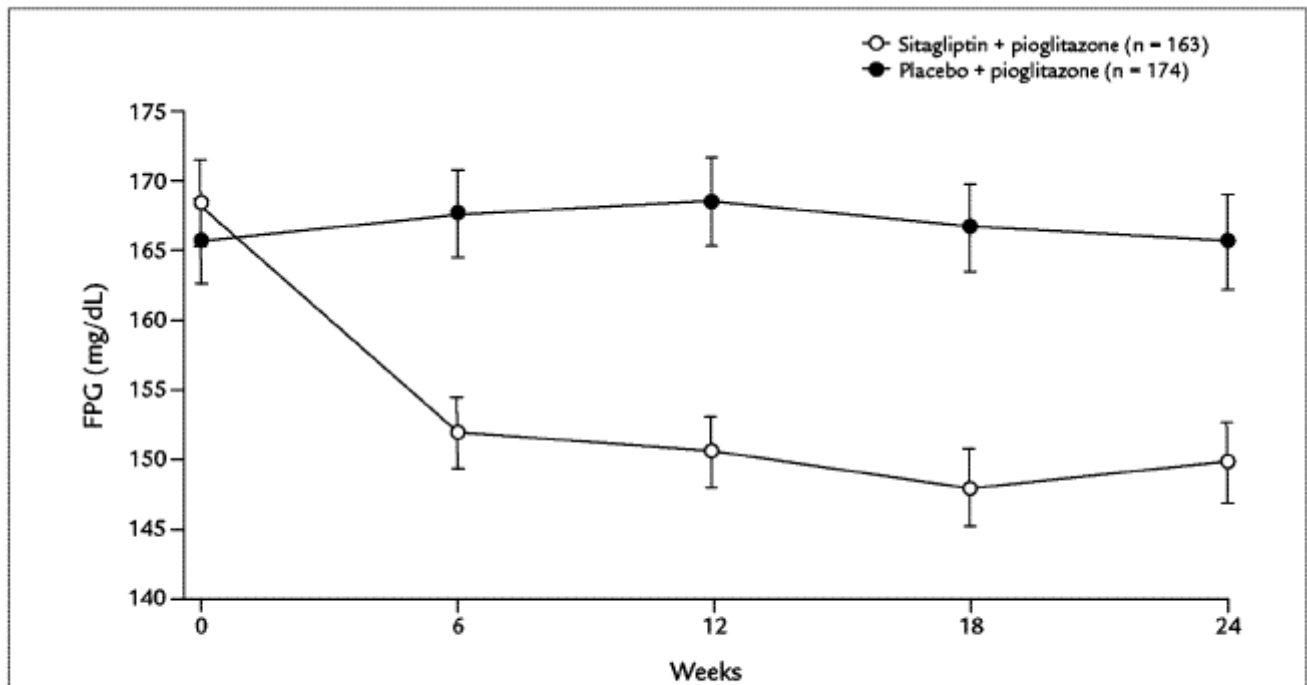


Figure 3. Changes in mean (SE) fasting plasma glucose (FPG) over time with sitagliptin 100 mg once daily or placebo added to ongoing pioglitazone therapy in patients with type 2 diabetes who had not achieved adequate glycemic control with pioglitazone alone.

Int J Clin Pract. 2006 Dec 5;

Efficacy and tolerability of the dipeptidyl peptidase-4 inhibitor sitagliptin as monotherapy over 12 weeks in patients with type 2 diabetes.

Scott R, Wu M, Sanchez M, Stein P.

Christchurch School of Medicine, Christchurch, New Zealand.

The aim of this study was to assess the efficacy and tolerability of the dipeptidyl peptidase-4 inhibitor, sitagliptin, in patients with type 2 diabetes who have inadequate glycaemic control on diet and exercise. In a randomised, double-blind, placebo- and active-controlled study, 743 patients with type 2 diabetes and a mean baseline HbA(1c) of 7.9% were randomised to receive one of six treatments for 12 weeks: placebo, sitagliptin 5, 12.5, 25 or 50 mg b.i.d., or glipizide 5 mg/day (electively titrated up to 20 mg/day). At week 12, treatment with sitagliptin at all doses tested led to a significant ($p < 0.001$) reduction in HbA(1c) relative to placebo, with the largest reductions occurring in the 50-mg b.i.d. group. The placebo-subtracted differences in HbA(1c) for the sitagliptin dose groups ranged from -0.38% to -0.77% in a dose-dependent manner, and -1.00% in the glipizide group. Sitagliptin also produced significant reductions in fasting plasma glucose and mean daily glucose across the dose range studied. Relative to placebo, small, inconsistent increases in fasting insulin were observed across the sitagliptin treatment groups. Fasting insulin was increased in the glipizide group. HOMA-B was numerically increased across the sitagliptin dose groups and significantly increased relative to placebo in the sitagliptin 50-mg bid group. HOMA-B also increased in the glipizide group. Changes in QUICKI and HOMA-IR were not significantly different from placebo in the sitagliptin groups. Treatment with sitagliptin produced small but statistically significant decreases in triglycerides and increases in HDL relative to placebo. Sitagliptin treatment was well tolerated and resulted in no significant weight change relative to placebo. There was a modest weight gain observed with glipizide treatment relative to placebo. No increase in the incidence of gastrointestinal adverse experiences was observed with sitagliptin compared with placebo or glipizide. This may be due to the more moderate elevations in GLP-1 as opposed to the pharmacological doses of GLP-1 achieved with incretin mimetics. Hypoglycemia adverse experiences were reported with the highest incidence in the glipizide group (17%) compared with the placebo (2%) or sitagliptin groups (0-4%, not dose-dependent). In summary, in this study sitagliptin improved glycaemic control, with 50 mg b.i.d. being the most effective dose, and was generally well-tolerated in patients with type 2 diabetes.

PMID: 17156104 [PubMed - as supplied by publisher]

Diabetes Care. 2006 Dec;29(12):2638-43.

Efficacy and safety of the dipeptidyl peptidase-4 inhibitor sitagliptin added to ongoing metformin therapy in patients with type 2 diabetes inadequately controlled with metformin alone.

Charbonnel B, Karasik A, Liu J, Wu M, Meininger G; Sitagliptin Study 020 Group.

Center Hospitalier Universitaire de Nantes, France.

OBJECTIVE: The efficacy and safety of the dipeptidyl peptidase-4 inhibitor, sitagliptin, added to ongoing metformin therapy, were assessed in patients with type 2 diabetes who had inadequate glycemic control (HbA(1c) [A1C] $>or=7$ and $<or=10\%$) with metformin alone. **RESEARCH DESIGN AND METHODS:** After a screening diet/exercise run-in period, a metformin dose titration/stabilization period, and a 2-week, single-blind, placebo run-in period, 701 patients, aged 19-78 years, with mild to moderate hyperglycemia (mean A1C 8.0%) receiving ongoing metformin ($>or=1,500$ mg/day) were randomly assigned to receive the addition of placebo or sitagliptin 100 mg once-daily in a 1:2 ratio for 24 weeks. Patients exceeding specific glycemic limits were provided rescue therapy (pioglitazone) until the end of the study. The efficacy analyses were based on an all-patients-treated population using an ANCOVA and excluded data obtained after glycemic rescue. **RESULTS:** At week 24, sitagliptin treatment led to significant reductions compared with placebo in A1C (-0.65%), fasting plasma glucose, and 2-h postmeal glucose. A1C decreased in the sitagliptin group relative to the placebo group during the first 12 weeks of treatment and then remained generally stable, with a slight trend toward further reduction, over the subsequent double-blind treatment period. Fasting insulin, fasting C-peptide, fasting proinsulin-to-insulin ratio, postmeal insulin and C-peptide areas under the curve (AUCs), postmeal insulin AUC-to-glucose AUC ratio, homeostasis model assessment of beta-cell function, and quantitative insulin sensitivity check index were significantly improved with sitagliptin relative to placebo. A significantly greater proportion of patients achieved an A1C $<7\%$ with sitagliptin (47.0%) than with placebo (18.3%). A significantly smaller proportion of patients in the sitagliptin group required glycemic rescue therapy during the 24-week study compared with the placebo group (4.5% vs 13.5%). Additionally the time to initiation of rescue therapy was significantly ($P < 0.001$) later in the sitagliptin group than in the placebo group. Treatment with sitagliptin 100 mg led to statistically significant but small decreases in total cholesterol and triglycerides as well as a small but statistically significant increase in HDL. There was no significant between-group difference in LDL. There was no increased risk of

hypoglycemia or gastrointestinal adverse experiences with sitagliptin compared with placebo. Body weight decreased similarly with sitagliptin and placebo. CONCLUSIONS: Sitagliptin 100 mg once-daily added to ongoing metformin therapy was efficacious and well tolerated in patients with type 2 diabetes who had inadequate glycemic control with metformin alone.

Publication Types:

- Research Support, Non-U.S. Gov't

PMID: 17130197 [PubMed - in process]

Diabetes Care. 2006 Dec;29(12):2632-7.

Effect of the dipeptidyl peptidase-4 inhibitor sitagliptin as monotherapy on glycemic control in patients with type 2 diabetes.

Aschner P, Kipnes MS, Lunceford JK, Sanchez M, Mickel C, Williams-Herman DE; Sitagliptin Study 021 Group.

Colombian Diabetes Association, Bogota, Colombia.

OBJECTIVE: To examine the efficacy and safety of once-daily oral sitagliptin as monotherapy in patients with type 2 diabetes. RESEARCH DESIGN AND METHODS: In a randomized, double-blind, placebo-controlled study, 741 patients (baseline HbA(1c) [A1C] 8.0%) were randomized to sitagliptin 100 or 200 mg or placebo for 24 weeks. During the study, patients not meeting progressively stricter glycemic goals were provided rescue therapy with metformin until study completion. Missing data were handled using the last observation carried forward method. To avoid the confounding influence of rescue therapy on efficacy comparisons data collected after initiation of rescue therapy were treated as missing. RESULTS: Sitagliptin 100 and 200 mg produced significant ($P < 0.001$) placebo-subtracted reductions in A1C (-0.79 and -0.94%, respectively) and fasting plasma glucose (-1.0 mmol/l [-17.1 mg/dl] and -1.2 mmol/l [-21.3 mg/dl], respectively). Patients with baseline A1C $\geq 9\%$ had greater reductions in placebo-subtracted A1C with sitagliptin 100 and 200 mg (-1.52 and -1.50%, respectively) than those with baseline A1C $< 8\%$ (-0.57 and -0.65%) or ≥ 8 to $< 9.0\%$ (-0.80 and -1.13%, respectively). The effects on FPG were maintained over 24 weeks with a slight upward trend starting at week 12. In a meal tolerance test, sitagliptin 100 and 200 mg significantly decreased 2-h postprandial glucose (PPG) (placebo-subtracted PPG - 2.6 mmol/l [-46.7 mg/dl] and -3.0 mmol/l [-54.1 mg/dl], respectively). Results for the above key efficacy parameters were not significantly different between sitagliptin doses. Homeostasis model assessment of beta-cell function and proinsulin-to-insulin ratio improved with sitagliptin suggesting improved beta-cell function. Sitagliptin had no effect on indexes of insulin resistance and sensitivity (HOMA-IR and QUICKI). Sitagliptin had no significant effects on fasting lipids. The incidence of hypoglycemia was similar between the groups. Slightly higher, but not statistically significant, incidences of gastrointestinal adverse effects were reported with sitagliptin. No meaningful body weight changes from baseline were observed with sitagliptin 100 (-0.2 kg) or 200 mg (-0.1 kg). The body weight change with placebo (-1.1 kg) was significantly ($P < 0.01$) different from that observed with sitagliptin. There were no meaningful differences between groups in incidences of overall clinical adverse experiences or of those assessed as serious, drug-related, or leading to discontinuation. CONCLUSIONS: In this 24-week study, once-daily sitagliptin monotherapy improved glycemic control in the fasting and postprandial states, improved measures of beta-cell function, and was well tolerated in patients with type 2 diabetes.

Publication Types:

- Research Support, Non-U.S. Gov't

PMID: 17130196 [PubMed - in process]

Lancet. 2006 Nov 11;368(9548):1696-705.

The incretin system: glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in type 2 diabetes.

Drucker DJ, Nauck MA.

Samuel Lunenfeld Research Institute, Mount Sinai Hospital, University of Toronto, Toronto, Ontario, Canada.
d.drucker@utoronto.ca

Glucagon-like peptide 1 (GLP-1) is a gut-derived incretin hormone that stimulates insulin and suppresses glucagon secretion, inhibits gastric emptying, and reduces appetite and food intake. Therapeutic approaches for enhancing incretin action include degradation-resistant GLP-1 receptor agonists (incretin mimetics), and inhibitors of dipeptidyl peptidase-4 (DPP-4) activity (incretin enhancers). Clinical trials with the incretin mimetic exenatide (two injections per day or long-acting release form once weekly) and liraglutide (one injection per day) show reductions in fasting and postprandial glucose concentrations, and haemoglobin A1c (HbA1c) (1-2%), associated with weight loss (2-5 kg). The most common adverse event associated with GLP-1 receptor agonists is mild nausea, which lessens over time. Orally administered DPP-4 inhibitors, such as sitagliptin and vildagliptin, reduce HbA1c by 0.5-1.0%, with few adverse events and no weight gain. These new classes of antidiabetic agents, and incretin mimetics and enhancers, also expand beta-cell mass in preclinical studies. However, long-term clinical studies are needed to determine the benefits of targeting the incretin axis for the treatment of type 2 diabetes.

Publication Types:

- [Research Support, Non-U.S. Gov't](#)
- [Review](#)

PMID: 17098089 [PubMed - indexed for MEDLINE]

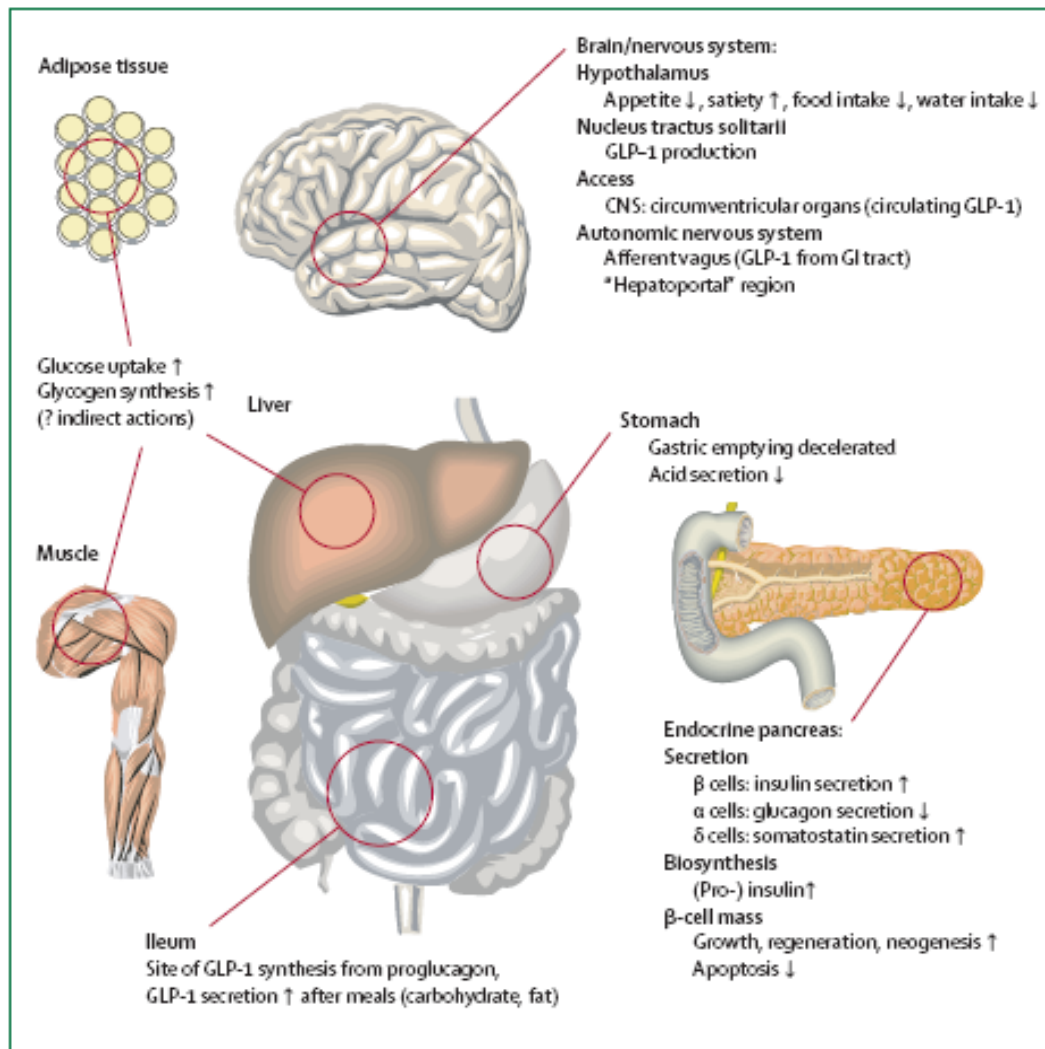


Figure 1: Physiology of GLP-1 secretion and action on GLP-1 receptors in different organs and tissues

DPP-4 inhibitors and their potential role in the management of type 2 diabetes.

Barnett A.

Department of Medicine, University of Birmingham and Heart of England National Health Service Foundation Trust (Teaching), Birmingham, UK. anthony.barnett@heartofengland.nhs.uk

The dipeptidyl peptidase 4 (DPP-4) inhibitors enhance the body's own ability to control blood glucose by increasing the active levels of incretin hormones in the body. Their mechanism of action is distinct from any existing class of oral glucose-lowering agents. They control elevated blood glucose by triggering pancreatic insulin secretion, suppressing pancreatic glucagon secretion, and signalling the liver to reduce glucose production. The leading DPP-4 inhibitors have shown clinically significant HbA1c reductions up to 1 year of treatment and offer many potential advantages over existing diabetes therapies including a low risk of hypoglycaemia, no effect on body weight, and the potential, based on animal and in vitro studies, for the regeneration and differentiation of pancreatic beta-cells. They are efficacious as monotherapy and also in combination with commonly prescribed antidiabetic agents and are suitable for once-daily oral dosing. Consequently, many DPP-4 inhibitors such as vildagliptin (Galvus; LAF-237), sitagliptin (Januvia; MK-0431), and saxagliptin (BMS-477118) have advanced into late-stage human clinical trials. Search strategy and selection criteria This review was built on a systematic MEDLINE search for publications on the subject with the key words: DPP-4 inhibitor; vildagliptin (LAF-237); sitagliptin (MK-0431); saxagliptin (BMS-477118); and type 2 diabetes; up to August 2006. Meeting abstracts were also searched, as much of the data currently only exists in abstract form. Take home message for clinician The DPP-4 inhibitors appear to have great potential for the treatment of type 2 diabetes, but time will tell if this will be realized. While they do not lower glucose to a greater extent than existing therapies, they offer many potential advantages, including the ability to achieve sustainable reductions in HbA1c with a well-tolerated agent that has a low risk of hypoglycaemia and no weight gain, and which can be administered as a once-daily oral dose.

PMID: 17073841 [PubMed - in process]

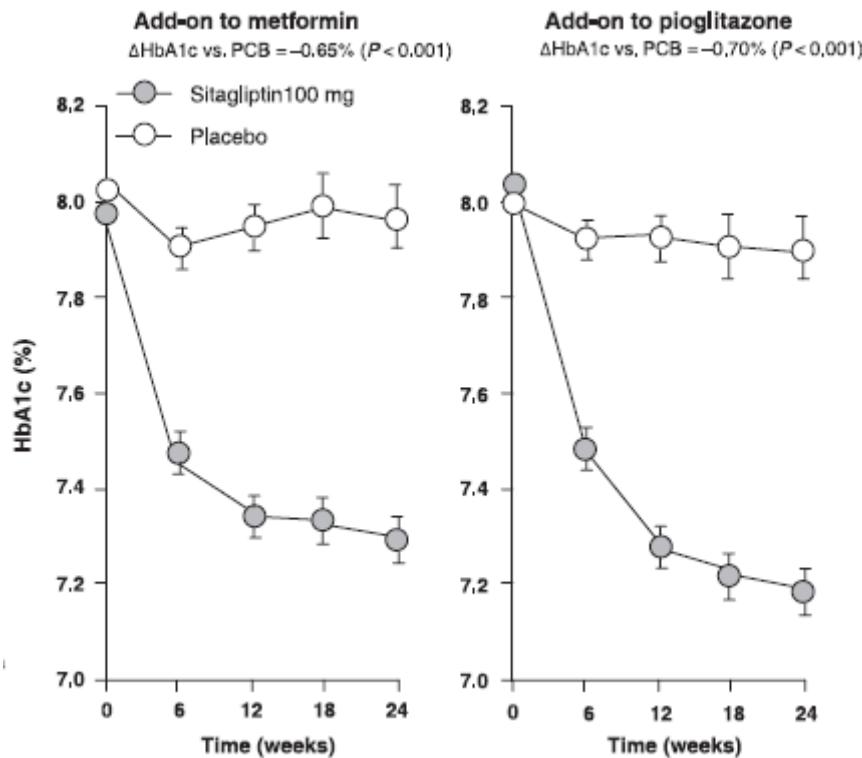


Figure 6 Placebo-subtracted difference in mean change from baseline HbA1c for sitagliptin as add-on to metformin or as add-on to pioglitazone therapy vs. placebo (46,50)

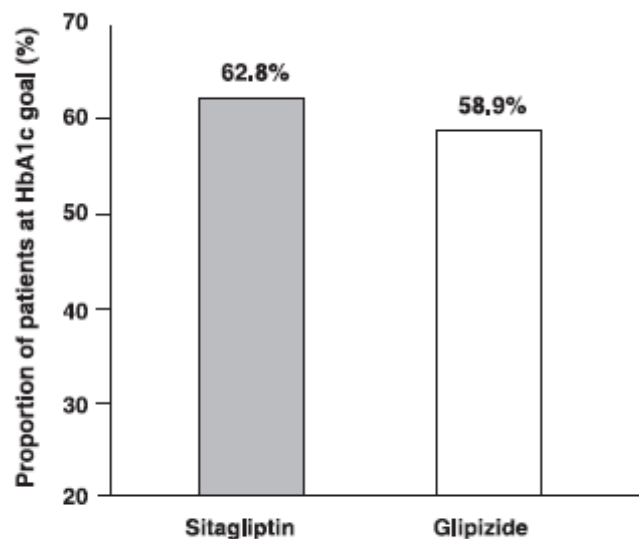


Figure 7 Proportion of patients achieving American Diabetes Association HbA1c goal of <7% with sitagliptin vs. glipizide as add-on to metformin therapy at 52 weeks (63)

Curr Med Res Opin. 2006 Oct;22(10):1939-47.

Tolerability and pharmacokinetics of metformin and the dipeptidyl peptidase-4 inhibitor sitagliptin when co-administered in patients with type 2 diabetes.

Herman GA, Bergman A, Yi B, Kipnes M: The Sitagliptin Study 012 Group.

Merck Research Laboratories, Rahway, NJ 07065-0900, USA. gary_herman@merck.com

OBJECTIVE: As part of the clinical development of sitagliptin, a dipeptidyl peptidase-4 inhibitor, for the treatment of type 2 diabetes, the potential for pharmacokinetic interactions with other antihyperglycemic agents used in managing patients with type 2 diabetes are being carefully evaluated. The purposes of this study were to evaluate the tolerability of co-administered sitagliptin and metformin and effects of sitagliptin on metformin pharmacokinetics as well as metformin on sitagliptin pharmacokinetics under steady-state conditions. **METHODS:** This placebo-controlled, multiple-dose, crossover study in patients with type 2 diabetes assessed the tolerability of co-administered sitagliptin (50 mg b.i.d.) with metformin (1000 mg b.i.d.). Patients received, in a randomized crossover manner, three treatments (each of 7 days duration): 50 mg sitagliptin twice daily and placebo to metformin twice daily; 1000 mg of metformin twice daily and placebo to sitagliptin twice daily; concomitant administration of 50 mg of sitagliptin twice daily and 1000 mg of metformin twice daily. Following dosing on Day 7 of each treatment period, these pharmacokinetic parameters were determined for plasma sitagliptin and metformin: area under the plasma concentrations-time curve over the dosing interval (AUC(0-12h)), maximum observed plasma concentrations (C(max)), and time of occurrence of maximum observed plasma concentrations (T(max)). Renal clearance was also determined for sitagliptin. **RESULTS:** In this study, no adverse experiences were reported by 11 of 13 patients. Two patients had adverse experiences, which were not related to study drugs as determined by the investigators. The mean metformin plasma concentration-time profiles were nearly identical with or without sitagliptin co-administration [metformin AUC(0-12h) geometric mean ratio (GMR; [metformin + sitagliptin]/metformin)] was 1.02 (90% CI 0.95, 1.09). Similarly metformin administration did not alter the plasma sitagliptin pharmacokinetics [sitagliptin AUC(0-12 h) GMR ([sitagliptin + metformin]/sitagliptin)] was 1.02 (90% CI 0.97, 1.08) or renal clearance of sitagliptin. No efficacy measurements (glycosylated hemoglobin or fasting plasma glucose) were obtained during this study. Urinary pharmacokinetics for metformin were not determined due to the lack of effect of sitagliptin on plasma metformin pharmacokinetics. **CONCLUSIONS:** In this study, co-administration of sitagliptin and metformin was generally well tolerated in patients with type 2 diabetes and did not meaningfully alter the steady-state pharmacokinetics of either agent.

Publication Types:

- Randomized Controlled Trial
- Research Support, Non-U.S. Gov't

PMID: 17022853 [PubMed - indexed for MEDLINE]

Diabetologia. 2006 Nov;49(11):2564-71. Epub 2006 Sep 26.

Efficacy and safety of the dipeptidyl peptidase-4 inhibitor sitagliptin as monotherapy in patients with type 2 diabetes mellitus.

Raz I, Hanefeld M, Xu L, Caria C, Williams-Herman D, Khatami H; Sitagliptin Study 023 Group.

Diabetes Research Center, Hadassah University Hospital, Jerusalem, Israel.

AIMS/HYPOTHESIS: The aim of this study was to assess the efficacy and safety of sitagliptin (MK-0431) as monotherapy in patients with type 2 diabetes mellitus and inadequate glycaemic control (HbA(1c) $\geq 7\%$ and $\leq 10\%$) on exercise and diet. METHODS: A total of 521 patients aged 27-76 years with a mean baseline HbA(1c) of 8.1% were randomised in a 1:2:2 ratio to treatment with placebo, sitagliptin 100 mg once daily, or sitagliptin 200 mg once daily, for 18 weeks. The efficacy analysis was based on an all-patients-treated population using an analysis of covariance, excluding data obtained after glycaemic rescue of metformin. RESULTS: After 18 weeks, HbA(1c) was significantly reduced with sitagliptin 100 mg and 200 mg compared with placebo (placebo-subtracted HbA(1c) reduction: -0.60% and -0.48%, respectively). Sitagliptin also significantly decreased fasting plasma glucose relative to placebo showing persistence over the 18 weeks of treatment. Patients with higher baseline HbA(1c) ($\geq 9\%$) experienced greater placebo-subtracted HbA(1c) reductions with sitagliptin (-1.20% for 100 mg and -1.04% for 200 mg) than those with HbA(1c) $< 8\%$ (-0.44% and -0.33%, respectively) or $\geq 8\%$ to 8.9% (-0.61% and -0.39%, respectively); however, the treatment-by-subgroup interaction was not significant ($p=0.087$). After week 12 the mean change from baseline over time in HbA1C rose slightly in the sitagliptin 200 mg and placebo groups, while the mean change from baseline in HbA1C appeared stable after week 12 in the sitagliptin 100 mg group. HbA1C lowering effects of sitagliptin 100 and 200 mg at week 18 were consistent among subgroups. Patients with a baseline duration of diabetes at or below the median of less than or equal to 3 years, had a greater HbA1C reduction with sitagliptin than those with a duration greater than 3 years. Sitagliptin also significantly improved 2 and 3 hour postprandial glucose levels. Homeostasis model assessment beta cell function index and fasting proinsulin:insulin ratio, markers of insulin secretion and beta cell function, were significantly improved with sitagliptin. No significant treatment effects on HOMA-IR or lipid parameters. The incidence of hypoglycaemia or gastrointestinal adverse experiences was not significantly different between sitagliptin and placebo. Sitagliptin had a neutral effect on body weight. CONCLUSIONS/INTERPRETATION: Sitagliptin significantly improved glycaemic control and was well tolerated in patients with type 2 diabetes mellitus who had inadequate glycaemic control on exercise and diet.

PMID: 17001471 [PubMed - in process]

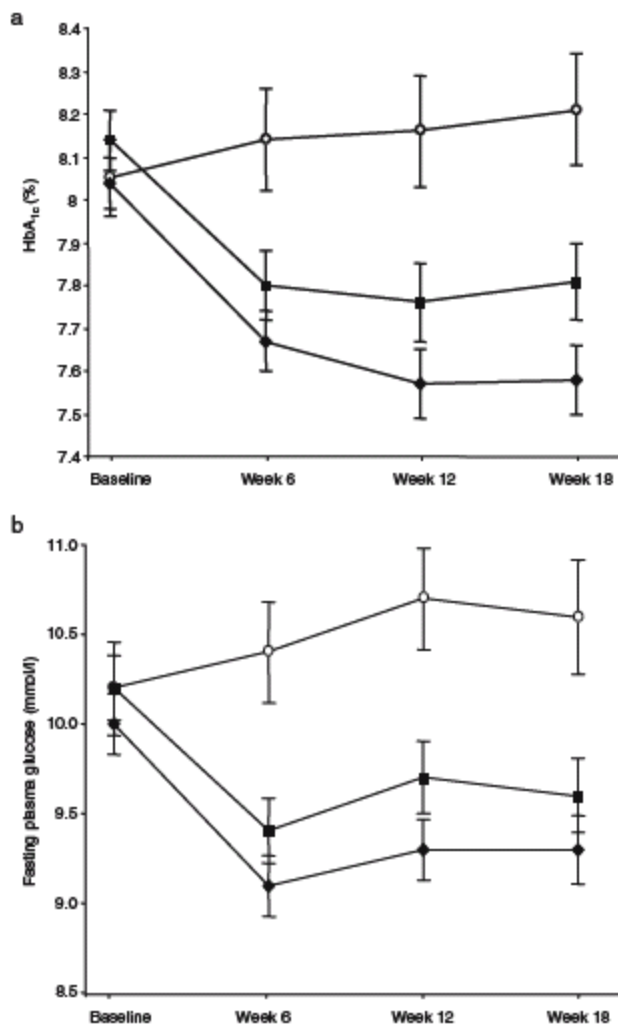


Fig. 1 Mean (±SEM) HbA_{1c} (a) and fasting plasma glucose (b) over time for placebo (open circles), once-daily sitagliptin 100 mg (filled diamonds) and once-daily sitagliptin 200 mg (filled squares) groups

Exp Biol Med (Maywood). 2006 Sep;231(8):1373-8.

Inhibition of dipeptidyl-peptidase IV does not increase circulating IGF-1 concentrations in growing pigs.

Faidley TD, Leiting B, Pryor KD, Lyons K, Hickey GJ, Thompson DR.

Department of Pharmacology, Merck Research Laboratories, Branchburg Farm, 203 River Road, Somerville, NJ 08876, USA. terry_faidley@merck.com

The enzyme dipeptidyl peptidase-IV (DPP-IV) inactivates a variety of bioactive peptides, including glucagon-like peptide-1 (GLP-1) and growth hormone releasing hormone (GHRH). Inhibiting DPP-IV in order to increase circulating GLP-1 is of interest as a treatment for Type II diabetes. Inactivation of DPP-IV may also increase circulating GHRH, potentially enhancing growth in domestic animals. To test the hypothesis that inhibition of DPP-IV activity will influence the growth hormone/IGF-1 axis, growing pigs (*Sus scrofa domestica*, 78 kg) were treated with a DPP-IV inhibitor (Compound 1, the 2,5-difluor-o-phenyl analog of the triazolopiperazine MK0431, sitagliptin), and plasma concentrations of IGF-1 were monitored. Pigs were administered either sterile saline (0.11 ml/kg followed by a continuous infusion at 2 ml/hr for 72 hrs, controls, n = 2), Compound 1 (2.78 mg/kg followed by a continuous infusion at 0.327 mg/kg x hr for 72 hrs, n = 4) or GHRH (0.11 ml/kg sterile saline, followed by a continuous infusion of GHRH at 2.5 microg/kg x hr for 48 hrs, n = 4). Plasma concentrations of Compound 1 were maintained at 1 microM, which resulted in a 90% inhibition of circulating DPP-IV activity. Relative to the predose 24-hr period, area under the IGF-1 concentration curve (AUC) tended to be lower (P = 0.062) with Compound 1 (79 ± 130 ng/ml x hr) than controls (543 ± 330 ng/ml x hr). GHRH treatment increased the IGF-1 AUC (1210 ± 160 ng/ml x hr, P = 0.049 vs. controls and P = 0.001 vs. Compound 1). We conclude that inhibition of DPP-IV does not alter the circulating levels of IGF-1 in the growing pig.

PMID: 16946406 [PubMed - indexed for MEDLINE]

J Clin Endocrinol Metab. 2006 Nov;91(11):4612-9. Epub 2006 Aug 15.

Effect of single oral doses of sitagliptin, a dipeptidyl peptidase-4 inhibitor, on incretin and plasma glucose levels after an oral glucose tolerance test in patients with type 2 diabetes.

Herman GA, Bergman A, Stevens C, Kotey P, Yi B, Zhao P, Dietrich B, Golor G, Schrodter A, Keymeulen B, Lasseter KC, Kipnes MS, Snyder K, Hilliard D, Tanen M, Cilissen C, De Smet M, de Lepeleire I, Van Dyck K, Wang AQ, Zeng W, Davies MJ, Tanaka W, Holst JJ, Deacon CF, Gottesdiener KM, Wagner JA.

Merck Research Laboratories, Experimental Medicine, Rahway, New Jersey 07065, USA. gary_herman@merck.com

CONTEXT: In response to a meal, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP) are released and modulate glycemic control. Normally these incretins are rapidly degraded by dipeptidyl peptidase-4 (DPP-4). DPP-4 inhibitors are a novel class of oral antihyperglycemic agents in development for the treatment of type 2 diabetes. The degree of DPP-4 inhibition and the level of active incretin augmentation required for glucose lowering efficacy after an oral glucose tolerance test (OGTT) were evaluated. OBJECTIVE: The objective of the study was to examine the pharmacodynamics, pharmacokinetics, and tolerability of sitagliptin. DESIGN: This was a randomized, double-blind, placebo-controlled, three-period, single-dose crossover study. SETTING: The study was conducted at six investigational sites. PATIENTS: The study population consisted of 58 patients with type 2 diabetes who were not on antihyperglycemic agents. INTERVENTIONS: Interventions included sitagliptin 25 mg, sitagliptin 200 mg, or placebo. MAIN OUTCOME MEASURES: Measurements included plasma DPP-4 activity; post-OGTT glucose excursion; active and total incretin GIP levels; insulin, C-peptide, and glucagon concentrations; and sitagliptin pharmacokinetics. RESULTS: Sitagliptin dose-dependently inhibited plasma DPP-4 activity over 24 h, enhanced active GLP-1 and GIP levels, increased insulin/C-peptide, decreased glucagon, and reduced glycemic excursion after OGTTs administered at 2 and 24 h after single oral 25- or 200-mg doses of sitagliptin. Sitagliptin was generally well tolerated, with no hypoglycemic events. CONCLUSIONS: In this study in patients with type 2 diabetes, near maximal glucose-lowering efficacy of sitagliptin after single oral doses was associated with inhibition of plasma DPP-4 activity of 80% or greater, corresponding to a plasma sitagliptin concentration of 100 nm or greater, and an augmentation of active GLP-1 and GIP levels of 2-fold or higher after an OGTT.

Publication Types:

- Multicenter Study
- Randomized Controlled Trial
- Research Support, Non-U.S. Gov't

PMID: 16912128 [PubMed - in process]

Sitagliptin: a dipeptidyl peptidase IV inhibitor for the treatment of type 2 diabetes.

Miller S, St Onge EL.

Pharmacotherapy Faculty, Florida Hospital Family Practice Residency, Orlando, 32822, USA. Shannon.miller@flhosp.org

OBJECTIVE: To review the pharmacology, pharmacokinetics, safety, and efficacy of sitagliptin, a dipeptidyl peptidase IV (DPP-IV) inhibitor in the management of type 2 diabetes mellitus. **DATA SOURCES:** A MEDLINE search (1966-February 2006) was conducted for English-language articles using the terms dipeptidyl peptidase IV inhibitor, incretin, MK-0431, and sitagliptin. Abstracts from the American Diabetes Association annual meetings in 2004 and 2005 were included as sources of data. **STUDY SELECTION AND DATA EXTRACTION:** Articles pertaining to the pharmacology of sitagliptin, its pharmacokinetics, safety and efficacy were reviewed. **DATA SYNTHESIS:** Sitagliptin is a potent, competitive, reversible inhibitor of the DPP-IV enzyme. It is eliminated renally, with a terminal half-life of 11.8-14.4 hours. In Phase II clinical trials, sitagliptin was found to be superior to placebo for the treatment of type 2 diabetes mellitus. Results of a small trial comparing sitagliptin with glipizide indicate that both treatments are comparable. The efficacy of sitagliptin has also been demonstrated when used as adjunctive therapy with metformin. Few adverse effects have been reported. Weight gain and hypoglycemia have not been seen with sitagliptin therapy. **CONCLUSIONS:** Based on its unique mechanism of action, sitagliptin will provide practitioners with an additional tool in the treatment of diabetes. Review of the literature to date implies sitagliptin may be effective as monotherapy in type 2 diabetes. In addition, existing evidence supports the use of sitagliptin as adjunct therapy to sulfonylureas and metformin. Another advantage of sitagliptin use is that it appears to be free from the adverse effects of weight gain and hypoglycemia that are associated with currently available treatments.

PMID: 16868220 [PubMed - in process]

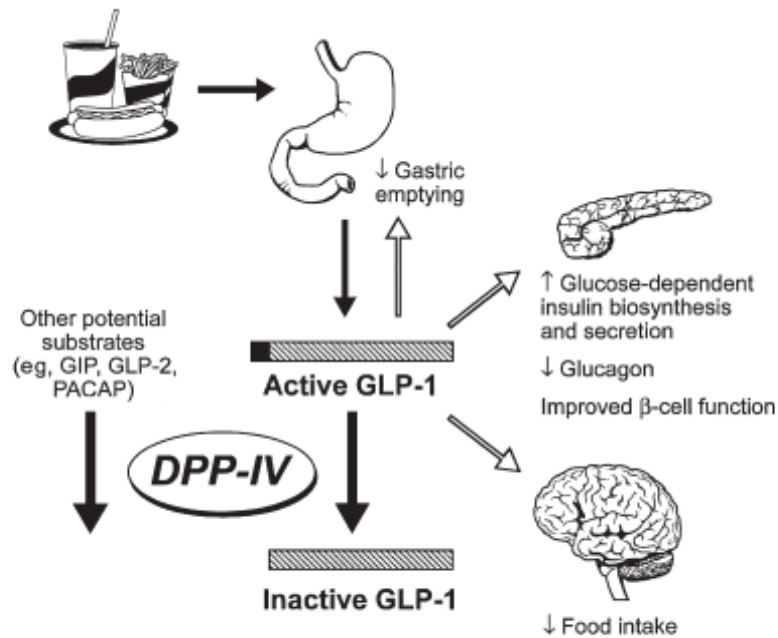


Figure 1. The role of GLP-1 in glucose homeostasis. DPP-IV = dipeptidyl peptidase IV; GIP = glucose-dependent insulinotropic polypeptide; GLP = glucagon-like peptide; PACAP = pituitary adenylate cyclase-activating polypeptide. Reprinted with permission from *Journal of Medicinal Chemistry*. Copyright 2004 American Chemical Society.

Table 1. Sitagliptin Clinical Trials							
Reference	Pts. ^a	Design/Aims	Treatment	Findings			
				Glucose	Hypoglycemia	ADEs	Other
Herman (2005) ¹⁸	N = 56 T2DM	R, PC, CO; efficacy, tolerability	single dose of sitagliptin 25 or 200 mg	↓ AUGC 22% and 26%	NR	NR	↑ plasma insulin and C peptide, ↓ plasma glucagon
Herman (2005) ¹⁹	N = 552 T2DM	R, DB, PC, ITT; efficacy, tolerability	1 of 5: placebo; sitagliptin 25, 50, 100 mg qd; sitagliptin 50 mg bid	↓ A1C 0.6–1.1 (sitagliptin 100 mg qd)	one event	NR	no weight gain
Scott (2005) ²⁰	N = 743	R, DB, PC, ITT; efficacy, tolerability	1 of 6: placebo; sitagliptin 5, 12.5, 25, 50 mg bid; or glip 5 mg bid	↓ A1C 0.4–0.8% (sitagliptin 50 mg bid); ↓ A1C 1% glip	4% sitagliptin; 17% glip	NR	↓ FPG, fructosamine, and mean daily glucose with both sitagliptin and glip; no weight gain with sitagliptin (↑ 1.1 kg glip)
Brazg (2005) ²¹	N = 28 T2DM	R, DB, PC, CO; efficacy, tolerability in combination with metformin	metformin plus placebo; metformin plus sitagliptin 50 mg bid	24 h weighted mean glucose ^b : metformin plus sitagliptin 125 mg/dL; metformin plus placebo 158 mg/dLs	NR	no ↑ of GI ADEs	no weight gain, fructosamine
Herman (2005) ¹⁴	N = 32	R, MC, PC; safety, tolerability, pharmacokinetics	200 mg bid or placebo for 28 days	↓ glucose AUC by 35%	NR	NA	steady-state in 2 days, ↑ GLP levels by 2.7 fold, ↓ post OGTT excursion
Herman (2005) ²²	T2DM	R, DB, CO; compare pharmacokinetics of metformin and sitagliptin alone vs combination	sitagliptin 50 mg bid plus metformin 1000 mg bid; sitagliptin 50 mg bid plus placebo; placebo plus metformin 1000 mg bid	NA	NR	NA	metformin pharmacokinetics not altered, sitagliptin plasma concentrations not altered with metformin
Bergman (2005) ¹³	N = 11	R, DB, PC; safety, tolerability, pharmacokinetics/ pharmacodynamics	escalating doses of sitagliptin 25–600 mg qd or 300 mg bid	NA	NR	NR	steady-state at day 3, terminal half-life 11.8–14.4 h, ↑ GLP levels consistent with daily dosing
Bergman (2005) ¹⁵	N = 38	PC; pharmacokinetics with age, gender, obesity, safety	in each panel, single dose of sitagliptin 50 mg or placebo	NA	NA	NA	modest difference seen in plasma pharmacokinetics, no dose adjustment for gender, age, obesity

ADEs = adverse drug events; AUGC = area under glucose curve; CO = crossover; DB = double-blind; FPG = fasting plasma glucose; GI = gastrointestinal; glip = glipizide; ITT = intent-to-treat; MC = multicenter; NA = not available; NR = none reported; PC = placebo-controlled; R = randomized; T2DM = type 2 diabetes mellitus.

^aEvaluable patients.

^bWeighted mean glucose is an average of 7 finger stick glucose determinations over a 24 hour period.

J Clin Pharmacol. 2006 Aug;46(8):876-86.

Pharmacokinetics and pharmacodynamic effects of the oral DPP-4 inhibitor sitagliptin in middle-aged obese subjects.

Herman GA, Bergman A, Liu F, Stevens C, Wang AQ, Zeng W, Chen L, Snyder K, Hilliard D, Tanen M, Tanaka W, Meehan AG, Lasseter K, Dilzer S, Blum R, Wagner JA.

Merck Research Laboratories, RY34-A536, 126 East Lincoln Avenue, Rahway, NJ 07065-0900, USA.
gary_herman@merck.com

Sitagliptin (MK-0431) is an oral, potent, and selective dipeptidyl peptidase-IV (DPP-4) inhibitor developed for the treatment

of type 2 diabetes. This multicenter, randomized, double-blind, placebo-controlled study examined the pharmacokinetic and pharmacodynamic effects of sitagliptin in obese subjects. Middle-aged (45-63 years), nondiabetic, obese (body mass index: 30-40 kg/m²) men and women were randomized to sitagliptin 200 mg bid (n = 24) or placebo (n = 8) for 28 days. Steady-state plasma concentrations of sitagliptin were achieved within 2 days of starting treatment, and >90% of the dose was excreted unchanged in urine. Sitagliptin treatment led to approximately 90% inhibition of plasma DPP-4 activity, increased active glucagon-like peptide-1 (GLP-1) levels by 2.7-fold (P < .001) as compared to placebo and to pretreatment baseline active GLP-1 levels. Similar increases in active GLP-1 levels also appeared to be present after overnight fasting, prior to administration of the oral glucose tolerance test. Decreased post-oral glucose tolerance test glucose excursion by 35% (P < .050) compared to placebo. In nondiabetic obese subjects, treatment with sitagliptin 200 mg bid was generally well tolerated without associated hypoglycemia and led to maximal inhibition of plasma DPP-4 activity, increased active GLP-1, and reduced glycemic excursion. Body weight changes were not significant in either group. No effect on total GLP-1 levels versus placebo or compared to pretreatment baseline levels. Growth hormone-releasing hormone (GHRH) has been proposed to be a potential substrate of DPP-4, but it is unknown whether this hormone is a physiologically relevant substrate of DPP-4 in vivo. If meaningful stabilization of GHRH were achieved by DPP-4 inhibition, one might expect to see increases in IGF-1 or IGF-bp3 levels. In this study, however, at dosages of sitagliptin that provided near-maximal inhibition of DPP-4, no increases in serum IGF-1 (insulin-like growth factor 1) and IGF-bp3 (insulin-like growth factor binding protein -3) levels compared to predose baseline levels were observed. Glucagon-like peptide-1 has been hypothesized to play a role in the regulation of appetite and satiety. Based on preclinical studies in DPP-4 deficient mice, and analogous to what is observed in clinical studies with other GLP-1 based therapies, little or no weight gain is expected with DPP-4 inhibitors, a potential advantage over currently available insulin secretagogues. Treatment with sitagliptin 200 mg bid exhibited plasma concentration-time profiles and principal pharmacokinetic parameters after 28 days of dosing that were similar to those observed on the first day of dosing and led to sustained inhibition of DPP-4 over a 24-hour dosing interval. Pre-clinical studies have shown that inhibiting 80% or more DPP-4 produces the maximal or near maximal lowering of glucose levels.

Publication Types:

- [Multicenter Study](#)
- [Randomized Controlled Trial](#)

PMID: 16855072 [PubMed - indexed for MEDLINE]

[Diabetes](#), 2006 Jun;55(6):1695-704.

Chronic Inhibition of Dipeptidyl Peptidase-4 With a Sitagliptin Analog Preserves Pancreatic {beta}-Cell Mass and Function in a Rodent Model of Type 2 Diabetes.

Mu J, Woods J, Zhou YP, Rov RS, Li Z, Zycband E, Feng Y, Zhu L, Li C, Howard AD, Moller DE, Thornberry NA, Zhang BB.

RY80W-180, Merck Research Laboratories, P.O. Box 2000, Rahway, NJ 07065. bei_zhang@merck.com.

Inhibitors of dipeptidyl peptidase-4 (DPP-4), a key regulator of the actions of incretin hormones, exert antihyperglycemic effects in type 2 diabetic patients. A major unanswered question concerns the potential ability of DPP-4 inhibition to have beneficial disease-modifying effects, specifically to attenuate loss of pancreatic beta-cell mass and function. Here, we investigated the effects of a potent and selective DPP-4 inhibitor, an analog of sitagliptin (des-fluoro-sitagliptin), on glycemic control and pancreatic beta-cell mass and function in a mouse model with defects in insulin sensitivity and secretion, namely high-fat diet (HFD) streptozotocin (STZ)-induced diabetic mice. Significant and dose-dependent correction of postprandial and fasting hyperglycemia, HbA(1c), and plasma triglyceride and free fatty acid levels were observed in HFD/STZ mice following 2-3 months of chronic therapy. Treatment with des-fluoro-sitagliptin dose dependently increased the number of insulin-positive beta-cells in islets, leading to the normalization of beta-cell mass and beta-cell-to-alpha-cell ratio. In addition, treatment of mice with des-fluoro-sitagliptin, but not glipizide, significantly increased islet insulin content and improved glucose-stimulated insulin secretion in isolated islets. These findings suggest that DPP-4 inhibitors may offer long-lasting efficacy in the treatment of type 2 diabetes by modifying the courses of the disease.

PMID: 16731832 [PubMed - in process]

Therapies for the treatment of type 2 diabetes mellitus based on incretin action.

Gallwitz B.

Department of Medicine IV, Eberhard-Karls-University, Tübingen, Germany. baptist.gallwitz@med.uni-tuebingen.de

Orally ingested glucose leads to a much higher insulin response than intravenous glucose leading to identical postprandial plasma glucose excursions. This phenomenon, termed "incretin effect" comprises up to 60% of the postprandial insulin secretion and is diminished in type 2 diabetes. The gastrointestinal hormones glucagon-like peptide-1 (GLP-1) and gastric inhibitory polypeptide (GIP) promote the incretin effect. Type 2 diabetes is characterized by an incretin defect: while GIP does not stimulate insulin secretion, GLP-1 action is still preserved under supraphysiological concentrations. GLP-1 stimulates insulin secretion only under hyperglycaemic conditions, therefore it does not cause hypoglycaemia. Furthermore, GLP-1 inhibits glucagon secretion and delays gastric emptying. In vitro and animal data demonstrated that GLP-1 increases beta cell mass by stimulating islet cell neogenesis and by inhibiting apoptosis of islets. The improvement of beta cell function can be indirectly observed from the increased insulin secretory capacity of humans receiving GLP-1. In contrast to GIP, GLP-1 may represent an attractive therapeutic method for type 2 diabetes due to its multiple effects also including the stimulation of satiety in the central nervous system by acting as transmitter or by crossing the blood brain barrier. Native GLP-1 is degraded rapidly upon intravenous or subcutaneous administration and is therefore not feasible for routine therapy. Long-acting GLP-1 analogs (e.g. Liraglutide) and exendin-4 (Exenatide, Byetta) that are resistant to degradation, called "incretin mimetics" are approved (Exenatide, Byetta) or in clinical trials. DPP-4-inhibitors (e.g. Vildagliptin), Sitagliptin and Saxagliptin) that inhibit the enzyme DPP-4 responsible for incretin degradation are also under study.

Publication Types:

- Review

PMID: 16682937 [PubMed - indexed for MEDLINE]

Pharmacokinetic and pharmacodynamic properties of multiple oral doses of sitagliptin, a dipeptidyl peptidase-IV inhibitor: a double-blind, randomized, placebo-controlled study in healthy male volunteers.

Bergman AJ, Stevens C, Zhou Y, Yi B, Laethem M, De Smet M, Snyder K, Hilliard D, Tanaka W, Zeng W, Tanen M, Wang AQ, Chen L, Winchell G, Davies MJ, Ramael S, Wagner JA, Herman GA.

Merck & Co., Inc., Whitehouse Station, New Jersey 07065-0900, USA.

BACKGROUND: Dipeptidyl peptidase-IV (DPP-IV) inhibitors represent a new class of oral antihyperglycemic agents. Sitagliptin is an orally active and selective DPP-IV inhibitor currently in Phase III development for the treatment of type 2 diabetes mellitus. **OBJECTIVE:** The aim of this study was to assess the pharmacokinetic and pharmacodynamic (PK/PD) properties and tolerability of multiple oral once-daily or twice-daily doses of sitagliptin. **METHODS:** This double-blind, randomized, placebo-controlled, incremental oral-dose study was conducted at SGS Biopharma, Antwerp, Belgium. Healthy, nonsmoking male volunteers aged 18 to 45 years with a creatinine clearance rate of >80 mL/min and normoglycemia and weighing within 15% of their ideal height/weight range were randomly assigned to 1 of 8 treatment groups: sitagliptin 25, 50, 100, 200, or 400 mg or placebo, QD for 10 days; a single dose of sitagliptin 800 mg administered on day 1 followed by 600 mg QD on days 3 to 10; or sitagliptin 300 mg BID for 10 days. For analysis of PK properties, plasma and urine samples were obtained before study drug administration on day 1 and at 0.5, 1, 2, 4, 6, 8, 10, 12, and 16 hours after study drug administration on day 1; before study drug administration on days 2 to 9; and every 24 hours for 96 hours after the last dose on day 10, and analyzed for sitagliptin concentrations. Assays were used to measure inhibition of plasma DPP-IV activity and plasma concentrations of active and total glucagon-like peptide-1 (GLP-1), glucose, and glucagon, and serum concentrations of insulin, C-peptide, insulin-like growth factor-1, and insulin like growth factor binding protein-3. Tolerability was assessed throughout the study using physical examination, including vital sign measurements; 12-lead electrocardiography; and laboratory analysis, including hematology, biochemistry (hepatic aminotransferase and creatine phosphokinase), and urinalysis. **RESULTS:** Seventy subjects were enrolled (mean age, 32.9 years [range, 18-45 years]; mean weight, 79.7 kg [range, 63.4-97.7 kg]; 8 patients per sitagliptin study group and 14 patients in the control group). In the sitagliptin groups, the plasma concentration-time profiles and principal PK parameters (T(max), C(max), and t((1/2))) were statistically similar at days 1 (single dose) and 10 (steady state). In the groups receiving sitagliptin QD doses, accumulation of sitagliptin was modest (AUC accumulation ratio [day 10/day 1] range, 1.05-1.29), and the apparent terminal elimination t((1/2)) was 11.8 to

14.4 hours. At steady state in the sitagliptin QD groups, the mean proportion of drug excreted unchanged in the urine was approximately 70.6%. Dose-dependent inhibition of plasma DPP-IV activity was apparent, and the pattern of inhibition at steady state (day 10) was statistically similar to that observed on day 1. Day-10 weighted mean inhibition of plasma DPP-IV activity over 24 hours was $\geq 80\%$ for doses of ≥ 50 mg QD. After a standard meal, active GLP-1 concentrations were significantly increased in the sitagliptin groups by approximately 2-fold compared with that in the control group, a finding consistent with near-maximal acute glucose lowering in preclinical studies. Across doses, no apparent adverse effects, including hypoglycemia, were found or reported. Neutral effect on weight gain. GIP was not measured in this study.

CONCLUSIONS: The results from this study in a select population of healthy male volunteers suggest that multiple oral doses of sitagliptin inhibited plasma DPP-IV activity and affected active GLP-1 concentrations in a dose-dependent manner, without producing hypoglycemia. Multiple dosing of sitagliptin exhibited a PK/PD profile consistent with that of a QD regimen and was well tolerated. Selective for DPP-4 and not DPP-8/9 which have been associated with multi-organ toxicity and attenuation of T-cell activation. Weighted average inhibition of DPP-4 with multiple doses of sitagliptin was 80% resulting in approximately 2-fold increase in GLP-1 concentrations over 24 hours for doses of or greater than 50 mg every day. Taken together with the observed PK properties of sitagliptin, these data are consistent with those of a QD dosing regimen for sitagliptin and suggest that doses greater than or equal to 100 mg every day of sitagliptin will result in sustained DPP-4 inhibition greater than or equal to 80% over a 24-hour dosing interval and might provide near-maximal glucose lowering. No apparent treatment-related effects of sitagliptin on fasting and postprandial levels of glucose, insulin, glucagons, or C-peptide in this select population of healthy men with normoglycemia.

Publication Types:

- Randomized Controlled Trial

PMID: 16490580 [PubMed - indexed for MEDLINE]

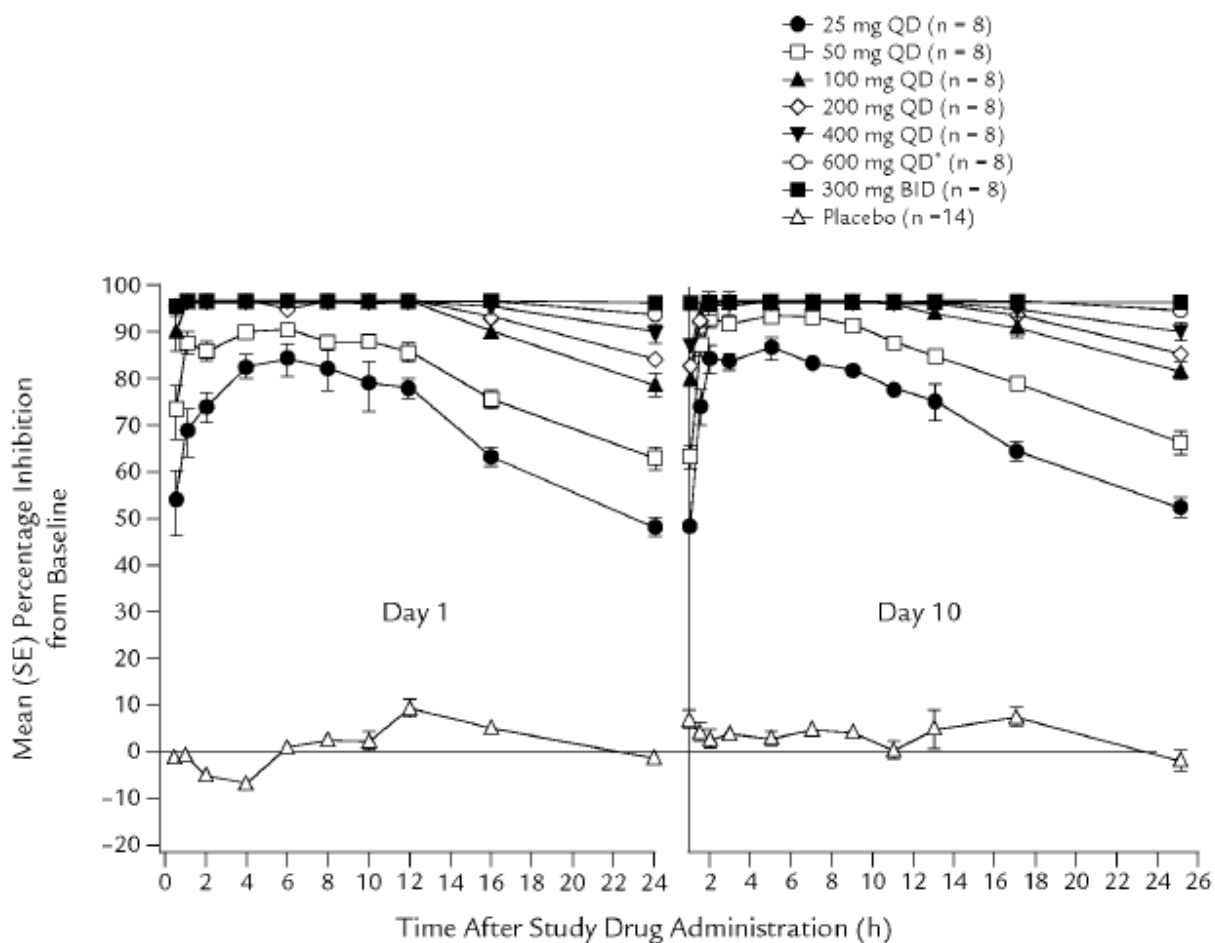


Figure 2. Percentage inhibition of dipeptidyl peptidase-IV activity of sitagliptin after single-dose administration (day 1) and at steady state (day 10) in healthy men. *These subjects received 800 mg on day 1 and 600 mg QD on days 3 to 10.

Clin Pharmacol Ther. 2005 Dec;78(6):675-88.

Pharmacokinetics and pharmacodynamics of sitagliptin, an inhibitor of dipeptidyl peptidase IV, in healthy subjects: results from two randomized, double-blind, placebo-controlled studies with single oral doses.

Herman GA, Stevens C, Van Dyck K, Bergman A, Yi B, De Smet M, Snyder K, Hilliard D, Tanen M, Tanaka W, Wang AQ, Zeng W, Musson D, Winchell G, Davies MJ, Ramael S, Gottesdiener KM, Wagner JA.

Merck & Co., Whitehouse Station, NJ 07065, USA. gary_herman@merck.com

BACKGROUND: Sitagliptin (MK-0431 [(2R)-4-oxo-4-(3-[trifluoromethyl]-5,6-dihydro[1,2,4]triazolo[4,3-a]pyrazin-7[8H]-yl)-1-(2,4,5-trifluorophenyl)butan-2-amine]) is an orally active, potent, and selective inhibitor of dipeptidyl peptidase IV (DPP-IV) currently in phase III development for the treatment of type 2 diabetes. METHODS: Two double-blind, randomized, placebo-controlled, alternating-panel studies evaluated the safety, tolerability, pharmacokinetics, and pharmacodynamics of single oral doses of sitagliptin (1.5-600 mg) in healthy male volunteers. RESULTS: Sitagliptin was well absorbed (approximately 80% excreted unchanged in the urine) with an apparent terminal half-life ranging from 8 to 14 hours. Renal clearance of sitagliptin averaged 388 mL/min and was largely uninfluenced by the dose administered. The area under the plasma concentration-time curve for sitagliptin increased in an approximately dose-dependent manner and was not meaningfully influenced by food. Single doses of sitagliptin markedly and dose-dependently inhibited plasma DPP-IV activity, with approximately 80% or greater inhibition of DPP-IV activity occurring at 50 mg or greater over a 12-hour period and at 100 mg or greater over a 24-hour period. Compared with placebo, sitagliptin produced an approximately 2-fold increase in postmeal active glucagon-like peptide 1 levels. Sitagliptin was well tolerated and was not associated with

hypoglycemia. CONCLUSIONS: This study provides proof of pharmacologic characteristics for sitagliptin in humans. By inhibiting plasma DPP-IV activity, sitagliptin increases the postprandial rise in active glucagon-like peptide 1 concentrations without causing hypoglycemia in normoglycemic healthy male volunteers. Sitagliptin possesses pharmacokinetic and pharmacodynamic characteristics that support a once-daily dosing regimen.

Publication Types:

- Randomized Controlled Trial

PMID: 16338283 [PubMed - indexed for MEDLINE]

Treat Endocrinol. 2005;4(6):361-70.

Glucagon-like peptide-1-based therapies for the treatment of type 2 diabetes mellitus.

Gallwitz B.

Department of Medicine, Eberhard-Karls-University, Tübingen, Germany. baptist.gallwitz@med.uni-tuebingen.de

The 'incretin effect' describes the phenomenon of an enhanced insulin response following oral ingestion of glucose compared with that after intravenous administration of glucose, leading to identical postprandial plasma glucose excursions. It accounts for up to 60% of the postprandial insulin secretion, but is diminished in patients with type 2 diabetes mellitus. Gastrointestinal hormones that promote the incretin effect are called incretins. Glucagon-like peptide-1 (GLP-1) is an important incretin. Under hyperglycemic conditions in humans, it stimulates insulin secretion and normalizes blood glucose levels. GLP-1 does not stimulate insulin secretion at normal glucose levels; therefore, it does not cause hypoglycemia. Furthermore, it inhibits glucagon secretion and delays gastric emptying. In vitro and animal data have demonstrated that GLP-1 increases beta-cell mass by stimulating islet cell neogenesis and by inhibiting the apoptosis of islet cells. The improvement of beta-cell function due to GLP-1 can be indirectly observed from the increased insulin secretory capacity of humans receiving such treatment. GLP-1 may represent an attractive therapeutic method for patients with type 2 diabetes because of its multiple effects, including the stimulation of satiety in the CNS by acting as a transmitter or by crossing the blood brain barrier. Native GLP-1 is degraded rapidly upon intravenous or subcutaneous administration and is therefore not feasible for routine therapy. Long-acting GLP-1 analogs (e.g. liraglutide) and exendin-4 (exenatide) that are resistant to degradation, called 'incretin mimetics', are being investigated in clinical trials. Dipeptidyl peptidase-IV inhibitors (e.g. vildagliptin, sitagliptin, and saxagliptin) that inhibit the enzyme responsible for incretin degradation are also being studied.

Publication Types:

- Review

PMID: 16318402 [PubMed - indexed for MEDLINE]