Metformin HCl

Table 7: Effect of Metformin HCl on Systemic Exposure of Coadministered Drugs

Coadministered Drug	Dose of Coadministered Drug*	Dose of Metformin HCl*	Geometric Mean Ratio (ratio with/without metformin) No Effect = 1.00		
				AUC†	C_{max}
Cimetidine	400 mg	850 mg	Cimetidine	0.95‡	1.01
Glyburide	5 mg	500 mg§	Glyburide	0.78¶	0.63¶
Furosemide	40 mg	850 mg	Furosemide	0.87¶	0.69¶
Nifedipine	10 mg	850 mg	Nifedipine	1.10‡	1.08
Propranolol	40 mg	850 mg	Propranolol	1.01‡	0.94
Ibuprofen	400 mg	850 mg	Ibuprofen	0.97#	1.01#

* All doses administered as single dose unless otherwise specified.
† AUC is reported as $AUC_{0-\infty}$ unless otherwise specified.
‡ AUC_{0-24hr}.
§ GLUMETZA (metformin HCl extended-release tablets) 500 mg.
¶ Ratio of arithmetic means, p value of difference <0.05.
# Ratio of arithmetic means.

Table 8: Effect of Coadministered Drugs on Systemic Exposure of Metformin HCl

Coadministered Drug	Dose of Coadministered Drug*	Dose of Metformin HCl*	Geometric Mean Ratio (ratio with/without coadministered drug) No Effect = 1.00		
				AUC†	C_{max}
Glyburide	5 mg	500 mg‡	Metformin‡	0.98§	0.99§
Furosemide	40 mg	850 mg	Metformin	1.09§	1.22§
Nifedipine	10 mg	850 mg	Metformin	1.16	1.21
Propranolol	40 mg	850 mg	Metformin	0.90	0.94
Ibuprofen	400 mg	850 mg	Metformin	1.05§	1.07§
Drugs that are eliminated by renal tubular secretion may increase the accumulation of metformin. ***[See Warnings and Precautions (5.1) and Drug Interactions (7).]***					
Cimetidine	400 mg	850 mg	Metformin	1.40	1.61
Carbonic anhydrase inhibitors may cause metabolic acidosis. ***[See Warnings and Precautions (5.1) and Drug Interactions (7).]***					
Topiramate	100 mg¶	500 mg¶	Metformin	1.25¶	1.17

* All doses administered as single dose unless otherwise specified.
† AUC is reported as $AUC_{0-\infty}$ unless otherwise specified.
‡ GLUMETZA (metformin HCl extended-release tablets) 500 mg.
§ Ratio of arithmetic means.
¶ Steady state 100 mg Topiramate every 12 hr + metformin HCl 500 mg every 12 hr AUC = AUC_{0-12hr}.

13 NONCLINICAL TOXICOLOGY

• 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

JANUMET

No animal studies have been conducted with the combined products in JANUMET to evaluate carcinogenesis, mutagenesis or impairment of fertility. The following data are based on the findings in studies with sitagliptin and metformin individually.

Sitagliptin

A two-year carcinogenicity study was conducted in male and female rats given oral doses of sitagliptin of 50, 150, and 500 mg/kg/day. There was an increased incidence of combined liver adenoma/carcinoma in males and females and of liver carcinoma in females at 500 mg/kg. This dose results in exposures approximately 60 times the human exposure at the maximum recommended daily adult human dose (MRHD) of 100 mg/day based on AUC comparisons. Liver tumors were not observed at 150 mg/kg, approximately 20 times the human exposure at the MRHD. A two-year carcinogenicity study was conducted in male and female mice given oral doses of sitagliptin of 50, 125, 250, and 500 mg/kg/day. There was no increase in the incidence of tumors in any organ up to 500 mg/kg, approximately 70 times human exposure at the MRHD. Sitagliptin was not mutagenic or clastogenic with or without metabolic activation in the Ames

bacterial mutagenicity assay, a Chinese hamster ovary (CHO) chromosome aberration assay, an *in vitro* cytogenetics assay in CHO, an *in vitro* rat hepatocyte DNA alkaline elution assay, and an *in vivo* micronucleus assay.

In rat fertility studies with oral gavage doses of 125, 250, and 1000 mg/kg, males were treated for 4 weeks prior to mating, during mating, up to scheduled termination (approximately 8 weeks total), and females were treated 2 weeks prior to mating through gestation day 7. No adverse effect on fertility was observed at 125 mg/kg (approximately 12 times human exposure at the MRHD of 100 mg/day based on AUC comparisons). At higher doses, nondose-related increased resorptions in females were observed (approximately 25 and 100 times human exposure at the MRHD based on AUC comparison).

Metformin

Long-term carcinogenicity studies have been performed in rats (dosing duration of 104 weeks) and mice (dosing duration of 91 weeks) at doses up to and including 900 mg/kg/day and 1500 mg/kg/day, respectively. These doses are both approximately four times the maximum recommended human daily dose of 2000 mg based on body surface area comparisons. No evidence of carcinogenicity with metformin was found in either male or female mice. Similarly, there was no tumorigenic potential observed with metformin in male rats. There was, however, an increased incidence of benign stromal uterine polyps in female rats treated with 900 mg/kg/day.

There was no evidence of a mutagenic potential of metformin in the following *in vitro* tests: Ames test (*S. typhimurium*), gene mutation test (mouse lymphoma cells), or chromosomal aberrations test (human lymphocytes). Results in the *in vivo* mouse micronucleus test were also negative. Fertility of male or female rats was unaffected by metformin when administered at doses as high as 600 mg/kg/day, which is approximately three times the maximum recommended human daily dose based on body surface area comparisons.

14 CLINICAL STUDIES

The coadministration of sitagliptin and metformin has been studied in patients with type 2 diabetes inadequately controlled on diet and exercise and in combination with other antihyperglycemic agents.

None of the clinical efficacy studies described below was conducted with JANUMET; however, bioequivalence of JANUMET with coadministered sitagliptin and metformin HCl tablets was demonstrated.

- **Sitagliptin and Metformin Coadministration in Patients with Type 2 Diabetes Inadequately Controlled on Diet and Exercise**

A total of 1091 patients with type 2 diabetes and inadequate glycemic control on diet and exercise participated in a 24-week, randomized, double-blind, placebo-controlled factorial study designed to assess the efficacy of sitagliptin and metformin coadministration. Patients on an antihyperglycemic agent (N=541) underwent a diet, exercise, and drug washout period of up to 12 weeks duration. After the washout period, patients with inadequate glycemic control (A1C 7.5% to 11%) were randomized after completing a 2-week single-blind placebo run-in period. Patients not on antihyperglycemic agents at study entry (N=550) with inadequate glycemic control (A1C 7.5% to 11%) immediately entered the 2-week single-blind placebo run-in period and then were randomized. Approximately equal numbers of patients were randomized to receive placebo, 100 mg of sitagliptin once daily, 500 mg or 1000 mg of metformin HCl twice daily, or 50 mg of sitagliptin twice daily in combination with 500 mg or 1000 mg of metformin HCl twice daily. Patients who failed to meet specific glycemic goals during the study were treated with glyburide (glibenclamide) rescue.

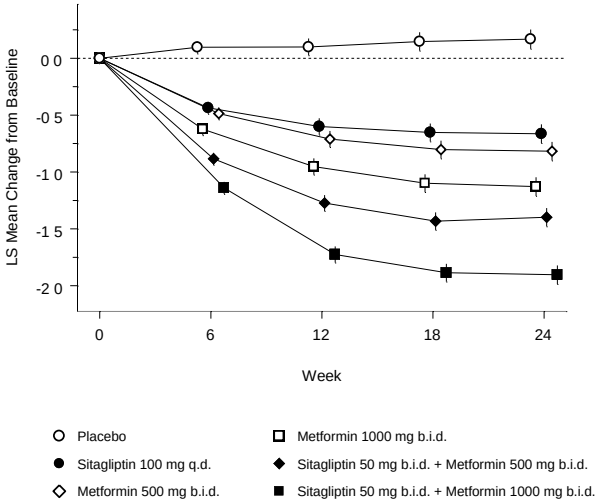
Sitagliptin and metformin coadministration provided significant improvements in A1C, FPG, and 2-hour PPG compared to placebo, to metformin alone, and to sitagliptin alone (Table 9, Figure 1). Mean reductions from baseline in A1C were generally greater for patients with higher baseline A1C values. For patients not on an antihyperglycemic agent at study entry, mean reductions from baseline in A1C were: sitagliptin 100 mg once daily, -1.1%; metformin HCl 500 mg bid, -1.1%; metformin HCl 1000 mg bid, -1.2%; sitagliptin 50 mg bid with metformin HCl 500 mg bid, -1.6%; sitagliptin 50 mg bid with metformin HCl 1000 mg bid, -1.9%; and for patients receiving placebo, -0.2%. Lipid effects were generally neutral. The decrease in body weight in the groups given sitagliptin in combination with metformin was similar to that in the groups given metformin alone or placebo.

Table 9: Glycemic Parameters at Final Visit (24-Week Study) for Sitagliptin and Metformin, Alone and in Combination in Patients with Type 2 Diabetes Inadequately Controlled on Diet and Exercise*

	Placebo	Sitagliptin 100 mg once daily	Metformin HCl 500 mg twice daily	Metformin HCl 1000 mg twice daily	Sitagliptin 50 mg twice daily + Metformin HCl 500 mg twice daily	Sitagliptin 50 mg twice daily + Metformin HCl 1000 mg twice daily
A1C (%)	**N = 165**	**N = 175**	**N = 178**	**N = 177**	**N = 183**	**N = 178**
Baseline (mean)	8.7	8.9	8.9	8.7	8.8	8.8
Change from baseline (adjusted mean†)	0.2	-0.7	-0.8	-1.1	-1.4	-1.9
Difference from placebo (adjusted mean†) (95% CI)		-0.8‡ (-1.1, -0.6)	-1.0‡ (-1.2, -0.8)	-1.3‡ (-1.5, -1.1)	-1.6‡ (-1.8, -1.3)	-2.1‡ (-2.3, -1.8)
Patients (%) achieving A1C <7%	15 (9%)	35 (20%)	41 (23%)	68 (38%)	79 (43%)	118 (66%)
% Patients receiving rescue medication	32	21	17	12	8	2
FPG (mg/dL)	**N = 169**	**N = 178**	**N = 179**	**N = 179**	**N = 183**	**N = 180**
Baseline (mean)	196	201	205	197	204	197
Change from baseline (adjusted mean†)	6	-17	-27	-29	-47	-64
Difference from placebo (adjusted mean†) (95% CI)		-23‡ (-33, -14)	-33‡ (-43, -24)	-35‡ (-45, -26)	-53‡ (-62, -43)	-70‡ (-79, -60)
2-hour PPG (mg/dL)	**N = 129**	**N = 136**	**N = 141**	**N = 138**	**N = 147**	**N = 152**
Baseline (mean)	277	285	293	283	292	287
Change from baseline (adjusted mean†)	0	-52	-53	-78	-93	-117
Difference from placebo (adjusted mean†) (95% CI)		-52‡ (-67, -37)	-54‡ (-69, -39)	-78‡ (-93, -63)	-93‡ (-107, -78)	-117‡ (-131, -102)

* Intent-to-treat population using last observation on study prior to glyburide (glibenclamide) rescue therapy.
† Least squares means adjusted for prior antihyperglycemic therapy status and baseline value.
‡ p<0.001 compared to placebo.

Figure 1: Mean Change from Baseline for A1C (%) over 24 Weeks with Sitagliptin and Metformin, Alone and in Combination in Patients with Type 2 Diabetes Inadequately Controlled with Diet and Exercise*



* All Patients Treated Population: least squares means adjusted for prior antihyperglycemic therapy and baseline value.

Initial combination therapy or maintenance of combination therapy should be individualized and are left to the discretion of the health care provider.

- **Sitagliptin Add-on Therapy in Patients with Type 2 Diabetes Inadequately Controlled on Metformin Alone**

A total of 701 patients with type 2 diabetes participated in a 24-week, randomized, double-blind, placebo-controlled study designed to assess the efficacy of sitagliptin in combination with metformin. Patients already on metformin (N=431) at a dose of at least 1500 mg per day were randomized after completing a 2-week, single-blind placebo run-in period. Patients on metformin and another antihyperglycemic agent (N=229) and patients not on any antihyperglycemic agents (off therapy for at least 8 weeks, N=41) were randomized after a run-in period of approximately 10 weeks on metformin HCl (at a dose of at least 1500 mg per day) in monotherapy. Patients were randomized to the addition of either 100 mg of sitagliptin or placebo, administered once daily. Patients who failed to meet specific glycemic goals during the studies were treated with pioglitazone rescue.

In combination with metformin, sitagliptin provided significant improvements in A1C, FPG, and 2-hour PPG compared to placebo with metformin (Table 10). Rescue glycemic therapy was used in 5% of patients treated with sitagliptin 100 mg and 14% of patients treated with placebo. A similar decrease in body weight was observed for both treatment groups.

Table 10: Glycemic Parameters at Final Visit (24-Week Study) of Sitagliptin as Add-on Combination Therapy with Metformin*

	Sitagliptin 100 mg once daily + 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.

- **Sitagliptin Add-on Therapy in Patients with Type 2 Diabetes Inadequately Controlled on the Combination of Metformin and Glimepiride**

A total of 441 patients with type 2 diabetes participated in a 24-week, randomized, double-blind, placebo-controlled study designed to assess the efficacy of sitagliptin in combination with glimepiride, with or without metformin. Patients entered a run-in treatment period on glimepiride (≥4 mg per day) alone or glimepiride in combination with metformin HCl (≥1500 mg per day). After a dose-titration and dose-stable run-in period of up to 16 weeks and a 2-week placebo run-in period, patients with inadequate glycemic control (A1C 7.5% to 10.5%) were randomized to the addition of either 100 mg of sitagliptin or placebo, administered once daily. Patients who failed to meet specific glycemic goals during the studies were treated with pioglitazone rescue.

Patients receiving sitagliptin with metformin and glimepiride had significant improvements in A1C and FPG compared to patients receiving placebo with metformin and glimepiride (Table 11), with mean reductions from baseline relative to placebo in A1C of -0.9% and in FPG of -21 mg/dL. Rescue therapy was used in 8% of patients treated with add-on sitagliptin 100 mg and 29% of patients treated with add-on placebo. The patients treated with add-on sitagliptin had a mean increase in body weight of 1.1 kg vs. add-on placebo (+0.4 kg vs. -0.7 kg). In addition, add-on sitagliptin resulted in an increased rate of hypoglycemia compared to add-on placebo. *[See Warnings and Precautions (5.6); Adverse Reactions (6.1).]*

Table 11: Glycemic Parameters at Final Visit (24-Week Study) for Sitagliptin in Combination with Metformin and Glimepiride*

	Sitagliptin 100 mg + Metformin and Glimepiride	Placebo + Metformin and Glimepiride
A1C (%)	**N = 115**	**N = 105**
Baseline (mean)	8.3	8.3
Change from baseline (adjusted mean†)	-0.6	0.3
Difference from placebo (adjusted mean†) (95% CI)	-0.9‡ (-1.1, -0.7)	
Patients (%) achieving A1C <7%	26 (23%)	1 (1%)
FPG (mg/dL)	**N = 115**	**N = 109**
Baseline (mean)	179	179
Change from baseline (adjusted mean†)	-8	13
Difference from placebo (adjusted mean†) (95% CI)	-21‡ (-32, -10)	

* Intent-to-treat population using last observation on study prior to pioglitazone rescue therapy.
† Least squares means adjusted for prior antihyperglycemic therapy status and baseline value.
‡ p<0.001 compared to placebo.

Sitagliptin Add-on Therapy in Patients with Type 2 Diabetes Inadequately Controlled on the Combination of Metformin and Rosiglitazone

A total of 278 patients with type 2 diabetes participated in a 54-week, randomized, double-blind, placebo-controlled study designed to assess the efficacy of sitagliptin in combination with metformin and rosiglitazone. Patients on dual therapy with metformin HCl ≥1500 mg/day and rosiglitazone ≥4 mg/day or with metformin HCl ≥1500 mg/day and pioglitazone ≥30 mg/day (switched to rosiglitazone ≥4 mg/day) entered a dose-stable run-in period of 6 weeks. Patients on other dual therapy were switched to metformin HCl ≥1500 mg/day and rosiglitazone ≥4 mg/day in a dose titration/stabilization run-in period of up to 20 weeks in duration. After the run-in period, patients with inadequate glycemic control (A1C 7.5% to 11%) were randomized 2:1 to the addition of either 100 mg of sitagliptin or placebo, administered once daily. Patients who failed to meet specific glycemic goals during the studies were treated with glipizide (or other sulfonylurea) rescue. The primary time point for evaluation of glycemic parameters was Week 18.

In combination with metformin and rosiglitazone, sitagliptin provided significant improvements in A1C, FPG, and 2-hour PPG compared to placebo with metformin and rosiglitazone (Table 12) at Week 18. At Week 54, mean reduction in A1C was -1.0% for patients treated with sitagliptin and -0.3% for patients treated with placebo in an analysis based on the intent-to-treat population. Rescue therapy was used in 18% of patients treated with sitagliptin 100 mg and 40% of patients treated with placebo. There was no significant difference between sitagliptin and placebo in body weight change.

Table 12: Glycemic Parameters at Week 18 for Sitagliptin in Add-on Combination Therapy with Metformin and Rosiglitazone*

	Week 18	
	Sitagliptin 100 mg + Metformin + Rosiglitazone	**Placebo + Metformin + Rosiglitazone**
A1C (%)	**N = 176**	**N = 93**
Baseline (mean)	8.8	8.7
Change from baseline (adjusted mean†)	-1.0	-0.4
Difference from placebo + rosiglitazone + metformin (adjusted mean†) (95% CI)	-0.7‡ (-0.9,-0.4)	
Patients (%) achieving A1C <7%	39 (22%)	9 (10%)
FPG (mg/dL)	**N = 179**	**N = 94**
Baseline (mean)	181	182
Change from baseline (adjusted mean†)	-30	-11
Difference from placebo + rosiglitazone + metformin (adjusted mean†) (95% CI)	-18‡ (-26, -10)	
2-hour PPG (mg/dL)	**N = 152**	**N = 80**
Baseline (mean)	256	248
Change from baseline (adjusted mean†)	-59	-21
Difference from placebo + rosiglitazone + metformin (adjusted mean†) (95% CI)	-39‡ (-51, -26)	

* Intent-to-treat population using last observation on study prior to glipizide (or other sulfonylurea) rescue therapy.
† Least squares means adjusted for prior antihyperglycemic therapy status and baseline value.
‡ p<0.001 compared to placebo + metformin + rosiglitazone.

Sitagliptin Add-on Therapy in Patients with Type 2 Diabetes Inadequately Controlled on the Combination of Metformin and Insulin

A total of 641 patients with type 2 diabetes participated in a 24-week, randomized, double-blind, placebo-controlled study designed to assess the efficacy of sitagliptin as add-on to insulin therapy. Approximately 75% of patients were also taking metformin. Patients entered a 2-week, single-blind run-in treatment period on pre-mixed, long-acting, or intermediate-acting insulin, with or without metformin HCl (≥1500 mg per day). Patients using short-acting insulins were excluded unless the short-acting insulin was administered as part of a pre-mixed insulin. After the run-in period, patients with inadequate glycemic control (A1C 7.5% to 11%) were randomized to the addition of either 100 mg of sitagliptin (N=229) or placebo (N=233), administered once daily. Patients were on a stable dose of insulin prior to enrollment with no changes in insulin dose permitted during the run-in period. Patients who failed to meet specific glycemic goals during the double-blind treatment period were to have uptitration of the background insulin dose as rescue therapy.

Among patients also receiving metformin, the median daily insulin (pre-mixed, intermediate or long acting) dose at baseline was 40 units in the sitagliptin-treated patients and 42 units in the placebo-treated patients. The median change from baseline in daily dose of insulin was zero for both groups at the end of the study. Patients receiving sitagliptin with metformin and insulin had significant improvements in A1C, FPG and 2-hour PPG compared to patients receiving placebo with metformin and insulin (Table 13). The adjusted mean change from baseline in body weight was -0.3 kg in patients receiving sitagliptin with metformin and insulin and -0.2 kg in patients receiving placebo with metformin and insulin. There was an increased rate of hypoglycemia in patients treated with sitagliptin. *[See Warnings and Precautions (5.6); Adverse Reactions (6.1).]*

Table 13: Glycemic Parameters at Final Visit (24-Week Study) for Sitagliptin as Add-on Combination Therapy with Metformin and Insulin*

	Sitagliptin 100 mg + Metformin + Insulin	Placebo + Metformin + Insulin
A1C (%)	**N = 223**	**N = 229**
Baseline (mean)	8.7	8.6
Change from baseline (adjusted mean[†,‡])	-0.7	-0.1
Difference from placebo (adjusted mean[†]) (95% CI)	-0.5[§] (-0.7, -0.4)	
Patients (%) achieving A1C <7%	32 (14%)	12 (5%)
FPG (mg/dL)	**N = 225**	**N = 229**
Baseline (mean)	173	176
Change from baseline (adjusted mean[†])	-22	-4
Difference from placebo (adjusted mean[†]) (95% CI)	-18[§] (-28, -8.4)	
2-hour PPG (mg/dL)	**N = 182**	**N = 189**
Baseline (mean)	281	281
Change from baseline (adjusted mean[†])	-39	1
Difference from placebo (adjusted mean[†]) (95% CI)	-40[§] (-53, -28)	

* Intent-to-treat population using last observation on study prior to rescue therapy.
† Least squares means adjusted for insulin use at the screening visit, type of insulin used at the screening visit (pre-mixed vs. non pre-mixed [intermediate- or long-acting]), and baseline value.
‡ Treatment by insulin stratum interaction was not significant (p >0.10).
§ p<0.001 compared to placebo.

Maintenance of Sitagliptin During Initiation and Titration of Insulin Glargine

A total of 746 patients with type 2 diabetes (mean baseline HbA1C 8.8%, disease duration 10.8 years) participated in a 30-week, randomized, double-blind, placebo-controlled study to assess the efficacy and safety of continuing sitagliptin during the initiation and uptitration of insulin glargine. Patients who were on a stable dose of metformin HCl (≥1500 mg/day) in combination with a DPP-4 inhibitor and/or sulfonylurea but with inadequate glycemic control (A1C 7.5% to 11%) were enrolled in the study. Those on metformin and sitagliptin (100 mg/day) directly entered the double-blind treatment period; those on another DPP-4 inhibitor and/or on a sulfonylurea entered a 4-8 week run-in period in which they were maintained on metformin and switched to sitagliptin (100 mg); other DPP-4 inhibitors and sulfonylureas were discontinued. At randomization patients were randomized either to continue sitagliptin or to discontinue sitagliptin and switch to a matching placebo. On the day of randomization, insulin glargine was initiated at a dose of 10 units subcutaneously in the evening. Patients were instructed to uptitrate their insulin dose in the evening based on fasting blood glucose measurements to achieve a target of 72-100 mg/dL.

At 30 weeks, the mean reduction in A1C was greater in the sitagliptin group than in the placebo group (Table 14). At the end of the trial, 27.3% of patients in the sitagliptin group and 27.3% in the placebo group had a fasting plasma glucose (FPG) in the target range; there was no significant difference in insulin dose between arms.

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Table 14: Change from Baseline in A1C and FPG at Week 30 in the Maintenance of Sitagliptin During Initiation and Titration of Insulin Glargine Study

	Sitagliptin 100 mg +Metformin + Insulin Glargine	Placebo +Metformin + Insulin Glargine
A1C (%)	**N = 373**[†]	**N = 370**[†]
Baseline (mean)	8.8	8.8
Week 30 (mean)	6.9	7.3
Change from baseline (adjusted mean)*	-1.9	-1.4
Difference from placebo (adjusted mean) (95% CI)*	-0.4 (-0.6, -0.3)[‡]	
Patients (%) with A1C <7%	202 (54.2%)	131 (35.4%)
FPG (mg/dL)	**N = 373**[†]	**N = 370**[†]
Baseline (mean)	199	201
Week 30 (mean)	118	123
Change from baseline (adjusted mean)*	-81	-76

* Analysis of Covariance including all post-baseline data regardless of rescue or treatment discontinuation. Model estimates calculated using multiple imputation to model washout of the treatment effect using placebo data for all subjects having missing Week 30 data.

[†] N is the number of randomized and treated patients.

[‡] p<0.001 compared to placebo.

- **Sitagliptin Add-on Therapy vs. Glipizide Add-on Therapy in Patients with Type 2 Diabetes Inadequately Controlled on Metformin**

The efficacy of sitagliptin was evaluated in a 52-week, double-blind, glipizide-controlled noninferiority trial in patients with type 2 diabetes. Patients not on treatment or on other antihyperglycemic agents entered a run-in treatment period of up to 12 weeks duration with metformin monotherapy (dose of ≥1500 mg per day) which included washout of medications other than metformin, if applicable. After the run-in period, those with inadequate glycemic control (A1C 6.5% to 10%) were randomized 1:1 to the addition of sitagliptin 100 mg once daily or glipizide for 52 weeks. Patients receiving glipizide were given an initial dosage of 5 mg/day and then electively titrated over the next 18 weeks to a maximum dosage of 20 mg/day as needed to optimize glycemic control. Thereafter, the glipizide dose was to be kept constant, except for down-titration to prevent hypoglycemia. The mean dose of glipizide after the titration period was 10 mg.

After 52 weeks, sitagliptin and glipizide had similar mean reductions from baseline in A1C in the intent-to-treat analysis (Table 15). These results were consistent with the per protocol analysis (Figure 2). A conclusion in favor of the non-inferiority of sitagliptin to glipizide may be limited to patients with baseline A1C comparable to those included in the study (over 70% of patients had baseline A1C less than 8% and over 90% had A1C less than 9%).

Table 15: Glycemic Parameters in a 52-Week Study Comparing Sitagliptin to Glipizide as Add-On Therapy in Patients Inadequately Controlled on Metformin (Intent-to-Treat Population)*

	Sitagliptin 100 mg + Metformin	Glipizide + Metformin
A1C (%)	**N = 576**	**N = 559**
Baseline (mean)	7.7	7.6
Change from baseline (adjusted mean[†])	-0.5	-0.6
FPG (mg/dL)	**N = 583**	**N = 568**
Baseline (mean)	166	164
Change from baseline (adjusted mean[†])	-8	-8

* The intent-to-treat analysis used the patients' last observation in the study prior to discontinuation.

[†] Least squares means adjusted for prior antihyperglycemic therapy status and baseline A1C value.

Pancreatitis

Inform patients that acute pancreatitis has been reported during postmarketing use of JANUMET. Inform patients that persistent severe abdominal pain, sometimes radiating to the back, which may or may not be accompanied by vomiting, is the hallmark symptom of acute pancreatitis. Instruct patients to promptly discontinue JANUMET and contact their physician if persistent severe abdominal pain occurs *[see Warnings and Precautions (5.2)].*

Heart Failure

Inform patients of the signs and symptoms of heart failure. Before initiating JANUMET, ask patients about a history of heart failure or other risk factors for heart failure including moderate to severe renal impairment. Instruct patients to contact their health care provider as soon as possible if they experience symptoms of heart failure, including increasing shortness of breath, rapid increase in weight or swelling of the feet *[see Warnings and Precautions (5.3)].*

Vitamin B_{12} Deficiency

Inform patients about the importance of regular monitoring of hematological parameters while receiving JANUMET *[see Warnings and Precautions (5.5)].*

Hypoglycemia

Inform patients that the incidence of hypoglycemia is increased when JANUMET is added to an insulin secretagogue (e.g., sulfonylurea) or insulin therapy. Explain to patients receiving JANUMET in combination with these medications the risks of hypoglycemia, its symptoms and treatment, and conditions that predispose to its development *[see Warnings and Precautions (5.6)].*

Hypersensitivity Reactions

Inform patients that allergic reactions have been reported during postmarketing use of sitagliptin, one of the components of JANUMET. If symptoms of allergic reactions (including rash, hives, and swelling of the face, lips, tongue, and throat that may cause difficulty in breathing or swallowing) occur, patients must stop taking JANUMET and seek medical advice promptly.

Severe and Disabling Arthralgia

Inform patients that severe and disabling joint pain may occur with this class of drugs. The time to onset of symptoms can range from one day to years. Instruct patients to seek medical advice if severe joint pain occurs *[see Warnings and Precautions (5.8)].*

Bullous Pemphigoid

Inform patients that bullous pemphigoid may occur with this class of drugs. Instruct patients to seek medical advice if blisters or erosions occur *[see Warnings and Precautions (5.9)].*

Females of Reproductive Age:

Inform females that treatment with JANUMET may result in ovulation in some premenopausal anovulatory women which may lead to unintended pregnancy *[see Use in Specific Populations (8.3)].*

Administration Instructions

Inform patients that the tablets must never be split or divided before swallowing.

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For patent information: www.merck.com/product/patent/home.html

Ramesh Raghavachari

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