National PBM Drug Monograph
Sitagliptin (Januvia™)
VHA Pharmacy Benefits Management Strategic Healthcare Group and Medical Advisory Panel

The purpose of VACO PBM-SHG drug monographs is to provide a comprehensive drug review for making formulary decisions. These documents will be updated when new data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.

EXECUTIVE SUMMARY

- Sitagliptin is a selective inhibitor of the enzyme dipeptidyl peptidase-4 (DPP-4), which metabolizes the naturally occurring incretins glucagon-like peptide-1(GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) resulting in enhanced glucose-dependent insulin secretion from the pancreas and decreased hepatic glucose production.

- Monotherapy with sitagliptin 100mg daily decreases mean HbA1c by 0.6-0.79% (mean difference from placebo). When used in combination with metformin or pioglitazone, the mean reduction is HbA1c is 0.7% and 0.9% respectively.

- The incidence of hypoglycemia with sitagliptin monotherapy was not significantly different than placebo. The addition of sitagliptin to metformin or pioglitazone did not significantly increase the incidence of hypoglycemia compared to monotherapy with metformin or pioglitazone. There was significantly less hypoglycemia with sitagliptin + metformin compared to glipizide + metformin (4.9% vs. 32%).

- Sitagliptin is considered to be weight neutral.

- Sitagliptin is considered to be lipid neutral.

- Pooled data from 2 monotherapy and 2 combination trials show that the incidence of hypoglycemia was 1.2% and 0.9% for sitagliptin 100mg and placebo respectively.

- Sitagliptin does not inhibit CYP3A4, 2C8, 2C9, 2D6, 1A2, 2C19, or 2B6 isoenzymes nor is it an inducer of CYP3A4. Sitagliptin is 38% bound to albumin so it is unlikely to result in interactions that involve protein binding displacement. Sitagliptin is a p-glycoprotein substrate; however, other drugs using this transport mechanism, such as digoxin, was not affected by sitagliptin.

- Sitagliptin is administered as 100mg once daily either as monotherapy or in combination with metformin or TZDs. It may be taken with or without food. Dosage adjustment in patients with moderate-severe renal insufficiency and ESRD is required.

- There are no studies beyond 52-weeks or long-term outcome studies at this time.

INTRODUCTION

Sitagliptin was FDA approved in October 2006 and is a member of a new class of agents used to treat diabetes known as the DPP-4 inhibitors. A second agent in this class, vildagliptin, will be reviewed by the FDA in February 2007. Sitalgliptin is approved for use in patients with type 2 diabetes either as monotherapy or in combination with metformin or thiazolidinediones (TZDs). Combination studies with sulfonylureas are ongoing.

PHARMACOLOGY

Incretins such as GLP-1 and GIP are naturally occurring hormones released from the GI tract in response to the ingestion of food. Meal-stimulated circulating levels of GLP-1 are reduced in type 2 diabetes whereas the insulinotropic effect of GIP is impaired. GLP-1 and GIP enhance glucose-dependent insulin secretion from the pancreas. Also, GLP-1 suppresses inappropriately elevated glucagon secretion from pancreatic α-cells ultimately

leading to decreased hepatic glucose production. Incretins do not suppress normal counter-regulatory increase in glucagon secretion during hypoglycemia.

Other potential effects of incretins include, preservation of β-cell function and increase in β-cell mass. Studies used to assess β-cell function include the Homeostasis Model Assessment-β (HOMA- β) and the pro-insulin/ insulin ratio. Three monotherapy and 2 combination trials, which are presented later, found that HOMA- β was significantly increased and the pro-insulin/insulin ratio decreased indicating improved β-cell function.

GLP-1 has a short plasma half-life; therefore, its utility as a pharmacologic agent is limited. Dipeptidyl peptase-4 is the enzyme responsible for metabolizing GLP-1 and GIP. Inhibition of DPP-4 activity results in meal-based enhancement of GLP-1 and GIP.

Sitagliptin is a selective inhibitor of DPP-4 and does not inhibit DPP-8 and DPP-9 enzymes. The later 2 enzymes have been shown to alter immune function in vitro and have been associated with toxicity in preclinical animal models.

PHARMACOKINETICS

Table 1: Pharmacokinetics

Bioavailability	87%
Cmax *	950nM
Tmax*	1-4 hours
AUC *	8.52μM·hr (AUC increased by ~ 14% at steady state)
Renal clearance*	350mL/min
Half-life*	~12.4 hours
Volume of distribution ^	198L
Protein binding	38%
Metabolism	undergoes limited metabolism via CYP3A4 and CYP2C8
Elimination	• 87 % (79% unchanged) in urine mainly via active tubular secretion • 13% feces

Information obtained from product package insert
*calculated following a single 100mg oral dose
^ calculated following a single 100mg IV dose

Moderate renal insufficiency resulted in approximately a 2-fold increase in plasma AUC of sitagliptin. Severe renal insufficiency and endstage renal disease resulted in a 4-fold increase AUC of sitagliptin. See DOSAGE AND ADMINISTRATION for recommended dosage adjustment.

The AUC and Cmax of sitagliptin was increased by 21% and 13% respectively in patients with moderate hepatic impairment (Child-Pugh score 7-9). No dosage adjustment is required. There is no experience using sitagliptin in patients with severe hepatic impairment.

EFFICACY

Monotherapy trials(See Appendix 1 for details)

There are 3 randomized, double-blind trials comparing monotherapy with sitagliptin to placebo. For all 3 studies, the primary outcome was change in HbA1c from baseline. Secondary and other endpoints for efficacy varied from study to study; however all 3 studies did evaluate FPG, proportion of patients achieving HbA1c < 7%, 2-hour postprandial glucose, change in HbA1c stratified by baseline HbA1c, and HOMA-β.

Nonaka conducted a 12-week study using sitagliptin 100mg daily in Japanese patients. The mean baseline HbA1c and BMI was 7.6% and 25.2kg/m^2 respectively. The studies by Raz and Aschner evaluated both the 100mg and 200mg doses. Baseline HbA1c for both of these studies was approximately 8%. In Raz and Aschner, patients who were unable to achieve their glycemic goal received rescue treatment with metformin. These patients were

included in the primary efficacy and safety analysis up to the period of when rescue was initiated; however, data for the entire treatment time were included in the secondary safety analysis.

Not surprisingly, monotherapy with sitagliptin was found to be superior to placebo. As typically seen with other diabetes treatments, patients with higher baseline HbA1c values had a greater reduction in HbA1c at end of the treatment phase. Please see appendix 1 for other efficacy results.

Table 2: Change in HbA1c from monotherapy trials

	Duration	Sitagliptin 100mg (diff from placebo)	Sitagliptin 200mg (diff from placebo)	% pts. achieving HbA1c < 7% (100mg/200mg/placebo)
Nonaka	12-weeks	-1.05%	N/A	58.1%/ 14.5%
Raz	18-weeks	-0.6%	-0.48%	35.8%/ 28.6%/ 15.5%
Aschner	24-weeks	-0.79%	-0.94%	40.6%/ 45.4%/ 16.8%

Combination trials (See Appendix 2 for details)

There are 3 randomized double-blind trials comparing the addition of sitagliptin to other oral agents. For all 3 studies, the primary outcome was change in HbA1c from baseline. Secondary and other endpoints for efficacy varied from study to study; however all 3 studies did evaluate lipid panel, FPG, and proportion of patients achieving HbA1c < 7%, and change in HbA1c stratified by baseline HbA1c.

Charbonnel compared the addition of sitagliptin 100mg to metformin ≥ 1500mg daily versus metformin alone. Patients not on prior OHAs, on OHA monotherapy, or on combination of metformin + another OHA underwent a dose stabilization period with metformin monotherapy. Those with inadequate control on metformin ≥ 1500mg daily were randomized to the addition of sitagliptin or placebo for 24-weeks. During this 24-week period, patients who did not achieve their glycemic goal were to receive rescue therapy with pioglitazone. Mean baseline HbA1c of the study population was 8.0%.

Rosenstock compared the addition of sitagliptin 100mg daily to pioglitazone 30-45mg versus pioglitazone alone using a design similar to the one described above. During the 24-week treatment period, patients who did not achieve glycemic goal received rescue therapy with metformin. Those patients receiving rescue metformin were included in the primary efficacy and safety analysis up to the period of when rescue was initiated; however, data for the entire treatment time were included in the secondary safety analysis. Mean baseline HbA1c of the study population was 8.0%.

In a 52-week non-inferiority trial, Stein compared the addition of sitagliptin or glipizide to metformin. Patients who had an HbA1c of 6.5-10% while receiving any monotherapy or dual therapy that included metformin were eligible. Patients underwent a 2-week run-in period with metformin monotherapy at doses ≥ 1500mg/day. After the run-in patients were randomized to receive sitagliptin 100mg daily or glipizide 5mg daily (dose to be increased to 10mg b.i.d. unless FPG < 110mg/dL or patient experienced hypoglycemia). The primary efficacy analysis used the per-protocol population defined as completing 52-weeks with a measurement of HbA1c and no protocol violations. Mean baseline HbA1c of the study population was 7.5%. This trial will continue to obtain 104-weeks of data.

The combination of sitagliptin with metformin or pioglitazone was superior to using metformin or pioglitazone alone. The change in HbA1c using sitagliptin + metformin was found to be non-inferior to glipizide + metformin. Patients with higher baseline HbA1c values had a greater reduction in HbA1c at end of the treatment phase. Please see appendix 2 for other efficacy results.

Table 3: Change in HbA1c from comparator trials

	Duration	Treatment arms	Sitagliptin 100mg	Comparator	% achieving HbA1c < 7% (SIT vs. comparator)
Charbonnel	24-weeks	SIT + MET vs. MET	-0.7%	-0%	47%/ 18.3%
Rosenstock	24-weeks	SIT + PIO vs. PIO	-0.9%	-0.2%	45.4%/ 23%
Stein	52-weeks	SIT + MET vs. GLIP + MET	-0.67%	-0.67%	63%/59%

Abbreviations: GLIP=glipizide; MET=metformin; PIO=pioglitazone; SIT=sitagliptin

Ongoing studies
There is a 24-week randomized double-blind study (n=441) evaluating the addition of sitagliptin 100mg daily or placebo in patients with inadequate glycemic control receiving glimepiride ≥ 4mg/day ± metformin ≥ 1500mg/day. Results are currently being analyzed.

In another 24-week double-blind study (n=1091), patients were randomized into one of the following 6 treatment groups:

1. Sitagliptin 50mg b.i.d. + metformin 1000mg b.i.d.
2. Sitagliptin 50mg b.i.d. + metformin 500mg b.i.d.
3. Metformin 1000mg b.i.d.
4. Metformin 500mg b.i.d.
5. Sitagliptin 100mg once daily
6. Placebo

Preliminary results show that the reduction in HbA1c was greater with the sitagliptin and metformin combination treatments than either treatment alone (-2.07% and -1.57% for groups 1 and 2 respectively). The proportion of patients achieving an HbA1c < 7% was 66.3%, 43.2%, 38.4%, 23%, 20%, 9.1 for groups 1 through 6 respectively.

A post-marketing study evaluating the safety and efficacy of sitagliptin as add-on therapy to insulin is expected to begin in June 2007.

Effect on lipids
The addition of sitagliptin 100mg to metformin or pioglitazone did not significantly affect lipid parameters.

Table 4: Lipid parameters

	Charbonnel		Rosenstock	
	Sitagliptin + metformin (week 0/ week 24)	**Metformin (week 0/ week 24)**	**Sitagliptin + pioglitazone (week 0/ week 24)**	**Pioglitazone (week 0/ week 24)**
TC (mg/dL)	176.7 ± 35.6/ 178.6 ± 37.5	181 ± 37.9/ 186.4 ± 37.9	198 ± 47 / 199.7± 43.1	194.3 ± 45.8/ 197 ± 43.2
LDL-C (mg/dL)	97.8 ± 30.5/ ± 99.8 ± 32.7	101.3 ± 31.3/ 103.2 ± 32.5	117.4 ± 41.3/ 118.6 ± 32.8	112.9 ± 38.1 / 114.5 ± 36.5
HDL-C (mg/dL)	45.2 ± 10.8/ 46.4 ± 11.2	44.5 ± 10.8/ 45.2 ± 11.6	49.6 ± 12.9 / 49.7 ± 12.8	50.4 ± 13.5/ 49.8 ± 12.4
TG (mg/dL)	174.5 ± 100.1/ 167.4 ± 96.5	186 ± 127.5/ 205.5 ± 164.7	156.8 ± 84.6/ 155.7 ± 104	157.4 ± 81.7 / 169.5 ± 112

Mean ± SD

SAFETY
As of October 2006, approximately 4700 patients with Type 2 diabetes have received sitagliptin, of which approximately 1100 have been treated for more than a year.

In the 3 monotherapy trials, the incidence of drug-related adverse events with sitagliptin was similar to that of placebo (21.2% versus 26.2%). Among these, only 2 cases from each group were considered to be serious. Treatment was discontinued in both patients receiving placebo and in neither patient receiving sitagliptin. (Refer to appendix 3 for further detail)

In general the incidence of adverse events was similar between sitagliptin + metformin compared to metformin alone. However, more patients discontinued treatment due to serious adverse events (1.1% vs. 0.4%). Similarly, the incidence of adverse events was similar between sitagliptin + pioglitazone versus pioglitazone alone. Discontinuation of treatment due to an adverse event was greater in the combination group (5.7% vs. 1.1%).

In the comparator trial, there were more drug-related adverse events with glipizide + metformin than with sitagliptin and metformin (30.3% vs. 14.5%). Slightly more patients in the glipizide group had to discontinue treatment due to adverse events. (Refer to appendix 3 for further detail)

Pooled safety data from the monotherapy trials by Raz and Aschner and the combination trials by Charbonnel and Rosenstock are shown where the incidence of the adverse event was ≥ 3% and higher in the sitagliptin group.

Table 5: Adverse events occurring with greater frequency with sitagliptin and ≥ 3%

	Sitagliptin 100mg* (n=1082)	Sitagliptin 200mg* (n=456)	Placebo^ (n=778)
Upper respiratory tract infection	6.8%	6.1%	6.7%
Headache	3.6%	3.9%	3.6%
Nasopharyngitis	4.5%	4.4%	3.3%
Diarrhea	3%	2.6%	2.3%
Arthralgia	2.1%	3.3%	1.8%
Urinary Tract Infection	1.7%	3.1%	1.7%

*represents data using sitagliptin alone or in combination with metformin or pioglitazone
^represents data using placebo alone or monotherapy with metformin or pioglitazone

Using pooled data from the same 4 trials, adverse events of interest regardless of frequency are shown in table 5. When looking specifically at the Charbonnel study, addition of sitagliptin to metformin did not increase the incidence of adverse events compared to that of metformin alone.

Table 6: Adverse events of interest regardless of frequency

	Sitagliptin 100mg* (n=1082)	Sitagliptin 200mg* (n=456)	Placebo^ (n=778)
Hypoglycemia	1.2%	0.9%	0.9%
Abdominal Pain	2.3%	1.3%	2.1%
Nausea	1.4%	2.9%	0.6%
Vomiting	0.8%	0.7%	0.9%
Diarrhea	3.0%	2.6%	2.3%

*represents data using sitagliptin alone or in combination with metformin or pioglitazone
^represents data using placebo alone or monotherapy with metformin or pioglitazone

In the study by Rosenstock, the incidence of peripheral edema was 4% in the sitagliptin + pioglitazone group compared to 3.4% with pioglitazone monotherapy.

Hypoglycemia

In the monotherapy trials by Raz and Aschner, the incidence of hypoglycemia was not significantly different than that seen in the placebo group (numbers were not shown). Hypoglycemia was not observed in any patient in the study by Nonaka. Overall, the incidence of hypoglycemia in the combination trials was low. In a pooled analysis of the studies by Raz, Aschner, Charbonnel, and Rosenstock, the incidence of hypoglycemia was 1.2% with sitagliptin 100mg, 0.9% with sitagliptin 200mg, and 0.9% with placebo. The incidence of hypoglycemia reported in the combination studies is shown in table 6. Hypoglycemic events were characterized as mild.

Table 7: Incidence of Hypoglycemia in Combination Studies

	Treatments	Sitagliptin	Comparator
Charbonnel	Sitagliptin + metformin vs. metformin	1.3%	2.1%
Rosenstock	Sitagliptin + pioglitazone vs. pioglitazone	1.1%	0
Stein	Sitagliptin + metformin vs. Glipizide + metformin	4.9%	32%

Change in Weight

When sitagliptin is used as monotherapy or in combination with metformin, a modest decrease in weight is seen. When combined with pioglitazone, a drug known to cause weight gain, the mean weight gain was 0.3kg greater than that of pioglitazone alone. In general, the DPP-4 inhibitors have been considered as weight neutral.

Table 8: Change in Weight

	Treatments	Sitagliptin	Comparator
Nonaka	Sitagliptin vs. placebo	-0.1kg (100mg)	-0.7kg
Raz	Sitagliptin vs. placebo	-0.6kg (100mg) -0.2kg (200mg)	-0.7kg
Aschner	Sitagliptin vs. placebo	-0.2kg (100mg) -0.1kg (200mg)	-1.1kg
Charbonnel	Sitagliptin + metformin vs. metformin	-0.7kg	-0.6kg
Rosenstock	Sitagliptin + pioglitazone vs. pioglitazone	1.8kg	1.5kg
Stein	Sitagliptin + metformin vs. Glipizide + metformin	-1.3kg	1.2kg

DRUG INTERACTIONS

Sitagliptin does not inhibit CYP3A4, 2C8, 2C9, 2D6, 1A2, 2C19, or 2B6 isoenzymes nor is it an inducer of CYP3A4. Sitagliptin is 38% bound to albumin so it is unlikely to result in interactions that involve protein binding displacement. Sitagliptin is a p-glycoprotein substrate; however, other drugs using this transport mechanism, such as digoxin, was not clinically significantly affected by sitagliptin.

Table 9: Drug Interactions

n	subjects	Sitagliptin	Co-administered Drug	Results
12	healthy subjects	Sitagliptin 200mg once daily x 5 days	Single-dose rosiglitazone 4mg on day 5 of sitagliptin	Sitagliptin does not significantly alter the PK of rosiglitazone
8	healthy subjects	Sitagliptin 200mg once daily x 6 days	Single dose glyburide 1.25mg on day 5 of sitagliptin	Sitagliptin does not significantly alter the PK of glyburide
12	healthy subjects	Sitagliptin 200mg once daily x 11 days	Single-dose warfarin 30mg on day 5 of sitagliptin	Sitagliptin does not significantly alter the PK/PD of warfarin
12	healthy subjects	Sitagliptin 200mg once daily x 5 days	Single-dose simvastatin 20mg on day 5	Sitagliptin does not significantly alter the PK of simvastatin
32	healthy subjects	Sitagliptin 100mg once daily x 10 days	Digoxin 0.25mg or placebo once daily x 10 days	Sitagliptin 100mg increased digoxin AUC and Cmax by 11% and 18% respectively compared with digoxin alone; unlikely to be clinically meaningful
8	healthy subjects	Sitagliptin 100mg single dose	Single dose cyclosporine A 600mg	Sitagliptin AUC and Cmax were increased by 24% and 68% respectively. This increase is unlikely to be clinically meaningful

Data obtained from AMCP dossier for sitagliptin October 2006

DOSAGE AND ADMINISTRATION

Sitagliptin is administered as 100mg once daily either as monotherapy or in combination with metformin or TZDs. It may be taken with or without food.

Dosage adjustment is recommended for patients with moderate-severe renal insufficiency and endstage renal disease (ESRD).

- 50mg once daily for patients with moderate renal impairment (CrCl ≥ 30 to <50mL/min or SCr >1.7- ≤ 3.0mg/dl for males >1.5- ≤ 2.5mg/dl females)
- 25mg once daily for patients with severe renal impairment (CrCl < 30mL/min or SCr > 3.0mg/dl for males or > 2.5mg/dl for females) and for ESRD requiring dialysis. Sitagliptin may be administered without regard to time of dialysis.

No dosage adjustment is necessary for patients with mild-moderate hepatic insufficiency. There is no experience in patients with severe hepatic insufficiency (Child-Pugh score > 9)

No dosage adjustment is needed based on body mass index, gender, age, or race.

LOOK-ALIKE/SOUND-ALIKE

The VA PBM and Center for Medication Safety is conducting a pilot program which queries a multi-attribute drug product search engine for similar sounding and appearing drug names based on orthographic and phonologic similarities, as well as similarities in dosage form, strength and route of administration. Based on similarity scores as well as clinical judgment, the following drug names may be potential sources of drug name confusion:

Generic name sitagliptin: sumatriptan 100mg tablets, simvastatin 10mg tablets, Symlin injection
Brand name Januvia: Enjuvia 0.3mg tablets, Avandia 2mg tablets

COST
The 25mg, 50mg and 100mg tablets of sitagliptin are flat-priced at $3.60 per tablet (FSS price).

Table 10: VA Acquisition Cost

	Usual daily dose	Cost/day	Cost/month
Sitagliptin	100mg	$3.60	$108.20
Rosiglitazone	4mg	$1.09- $1.18*	$32.80 - $35.53*
Rosiglitazone	8mg	$1.95 - $2.11*	$58.46 - $63.34*
Pioglitazone	30mg	$2.93	$87.90
Pioglitazone	45mg	$3.23	$96.90

*Range of cost based on market share (tiers 3-5)
Does not take into account tablet splitting of rosiglitazone 8mg

SUMMARY
The mean decrease in HbA1c with sitagliptin is < 1%. Sitagliptin has a low incidence of hypoglycemia, is weight neutral, does not appreciably affect lipids, has a low likelihood for drug-interactions, and is administered once daily. There are no long-term safety and efficacy data at this time.

REFERENCES
Raz I, Hanefeld M, Xu C, et al. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor sitagliptin as monotherapy in patients with Type 2 diabetes mellitus. Diabetologia 2006; 49:2564-71.

Aschner P, Kipnes MS, Lunceford JK, et al. Effect of the dipeptidyl peptidase-4 inhibitor sitagliptin as monotherapy on glycemic control in patients with type 2 diabetes. Diabetes Care 2006; 29: 2632-2637.

Charbonnel B, Karasik A, Liu J, et al. 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. Diabetes Care 2006; 29: 2638-2643.

Rosenstock J, Brazg R, Andryuk PJ, et al. 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. Clin Ther 2006; 28: 1556-1568.

Formulary Dossier for Januvia. October 2006

Prepared by Debbie Khachikian, Pharm. D
November 2006

Appendix 1: Monotherapy Studies

<table>
<tr><th>Study</th><th>Inclusion/Exclusion</th><th>Dosage</th><th>Demographics/Baseline values</th><th>Results</th></tr>
<tr>
<td>Nonaka (Study 201)
R, DB, PC, PR
n=151
12-weeks

Modified ITT
(LOCF)</td>
<td>Type 2 DM
Japanese
27-69 years old
HbA1c 6.5-10% after 8-week diet and exercise run-in

<u>Exclusions:</u>
Type 1 DM, 2° DM, IGT, gestational DM, fasting C-peptide ≤ 0.7ng.mL, combination antihyperglycemic tx within 8 weeks of visit 1</td>
<td>8-week diet and exercise run-in

Sitagliptin 100mg once daily (n=75)
Placebo (n=76)</td>
<td>Age: 55.3 (range 27-69)
Gender: 62.9% male
Race: 100% Japanese
HbA1c: 7.6%
BMI: 25.2kg/m^2(range 18.5 – 37.9)
FPG: 163.5mg/dL

Mean values</td>
<td>
<table>
<tr><th></th><th>Sitagliptin</th><th>Placebo</th></tr>
<tr><td>Drop-outs</td><td>0.4%</td><td>11.8%</td></tr>
<tr><td>HbA1c</td><td>-0.65%</td><td>+0.41%</td></tr>
<tr><td>FPG (mg/dL)</td><td>-22.5</td><td>+9.4</td></tr>
<tr><td>% achieving HbA1c < 7%</td><td>58.1%</td><td>14.5%</td></tr>
<tr><td>2-h PPG (mg/dL) §</td><td>-69.2*</td><td>+11.7</td></tr>
<tr><td>Plasma insulin levels</td><td colspan="2">Significantly increased vs. placebo (data not shown)*</td></tr>
<tr><td>Weight</td><td>-0.1kg</td><td>-0.7kg^</td></tr>
<tr><td>HOMA-β</td><td>9.5*</td><td>-3.1</td></tr>
<tr><td>HOMA-IR</td><td>-0.15</td><td>0.09</td></tr>
<tr><td>Hypoglycemia</td><td colspan="2">Not observed in either group</td></tr>
</table>
§ Determined after a meal tolerance test in a subset of patients
*Significant vs. placebo
^Significant vs. sitagliptin
</td>
</tr>
<tr>
<td>Raz (Study 023)
R, DB, PC
n=521
18-weeks

<u>ITT (LOCF)</u>
n=193 (S100mg)
n=199 (S200mg)
n=103 (placebo)</td>
<td>Type 2 DM
18-75 years old
Not on an OHA or on 1-2 OHAs who could be taken off their OHA during the run-in period
HbA1c 7-10% after prior OHA washout period

<u>Exclusions:</u>
Type 1 DM, insulin therapy; significant hepatic or renal disease; hepatic transaminase or creatinine phosphokinase ≥ 2x ULN; FPG > 270mg/dL; BMI < 20 or > 43kg/m^2</td>
<td>Drug washout period for those on prior OHAs, diet/exercise run-in for up to 12 weeks
2-week SB placebo run-in
2:2:1 randomization

Sitagliptin 100mg once daily
Sitagliptin 200mg once daily
Placebo

Rescue therapy with metformin was allowed for patients not meeting glycemic goals. These patients were included in the primary efficacy and safety analysis up to the period of when rescue was initiated; however, data for the entire treatment time were included in the secondary safety analysis.</td>
<td>Age: 55.1 (range 27-76)
Gender: 54.3% male
Race: 68.3% White, 18.8% Hispanic, 7.5% Black, 3.8% Asian
Duration of DM: 4.5 years (range 0-30 years)
HbA1c: 8.1% (6.2- 10.5%)
Weight: 90.3kg (range 47.5 -148kg)
BMI: 32kg/m^2(range 18.9 – 43.6)
FPG: 182.2mg/dL

Mean values</td>
<td>
<table>
<tr><th></th><th>Sitagliptin 100mg</th><th>Sitagliptin 200mg</th><th>Placebo</th></tr>
<tr><td>Drop-outs</td><td>8.3%</td><td>10.7%</td><td>17.3%</td></tr>
<tr><td>HbA1c</td><td>-0.48%</td><td>-0.36%</td><td>+0.12%</td></tr>
<tr><td>HbA1c (diff from placebo)</td><td>-0.6%*</td><td>-0.48%*</td><td></td></tr>
<tr><td>Stratified by baseline A1c ≥9%/ 8-8.9%/ < 8% (diff from placebo)</td><td>-1.2%/ -0.61%/ -0.44%</td><td>-1.04%/ -0.39%/ -0.33%</td><td>N/A</td></tr>
<tr><td>% achieving HbA1c < 7%</td><td>35.8%*</td><td>28.6%*</td><td>15.5%</td></tr>
<tr><td>FPG (mg/dL)</td><td>-12.7*</td><td>-9.9*</td><td>+7.0</td></tr>
<tr><td>Required rescue metformin</td><td>8.8%</td><td>11.7%</td><td>17.3%</td></tr>
<tr><td>2-h PPG (mg/dL) §</td><td>-41.4*</td><td>-47.8*</td><td>+4.9</td></tr>
<tr><td>HOMA-β, Proinsulin: insulin</td><td colspan="3">Significantly improved vs. placebo</td></tr>
<tr><td>Weight</td><td>-0.6kg</td><td>-0.2kg</td><td>-0.7kg</td></tr>
<tr><td>Hypoglycemia</td><td>3 (1.5%)</td><td>2 (1.0%)</td><td>0</td></tr>
</table>
*Significant vs. placebo
§Determined after a meal tolerance test (n=150)
</td>
</tr>
</table>

<table>
<tr>
<td>Aschner (Study 021)
R, DB, PC
n=741
24-weeks
ITT

Diabetes Care (in press)</td>
<td>Type 2 DM
18-75 years old
HbA1c 7-10% (off OHA therapy)

<u>Exclusions:</u>
Required insulin within the prior 8 weeks; CrCl < 50mL/min; SCr > 1.8mg/dL (male and ≤ 65 y/o) SCr > 1.6mg/dL/dL (male and > 65 y/o OR female and ≤ 65y/o) SCr > 1.3mg/dL (female and > 65y/o); >0.5mg albumin /mg creatinine in urine</td>
<td>Drug washout period for those on prior OHAs, diet/exercise run-in for up to 15 weeks
2-week SB placebo run-in
1:1:1 randomization

Sitagliptin 100mg once daily
Sitagliptin 200mg once daily
Placebo

Rescue therapy with metformin was allowed for patients not meeting glycemic goals. These patients were included in the primary efficacy and safety analysis up to the period of when rescue was initiated; however, data for the entire treatment time were included in the secondary safety analysis.</td>
<td>Age: 54.2 (range 18-75)
Gender: 51.7% male
Race: 51.4% White, 23.6% Hispanic, 5.1% Black, 13.9% Asian
Duration of DM: 4.4 years (range 0-38 years)
HbA1c: 8%
Weight: 86.4kg (range 44.5 - 145.5kg)
BMI: 30.5kg/m^2(range 19.1 - 44.7)
FPG: 173.7mg/dL

Mean values</td>
<td>
<table>
<tr><th></th><th>Sitagliptin 100mg</th><th>Sitagliptin 200mg</th><th>Placebo</th></tr>
<tr><td>Drop-outs</td><td>12.2%</td><td>14.4%</td><td>14.6%</td></tr>
<tr><td>HbA1c (diff from placebo)</td><td>-0.79%*</td><td>-0.94%*</td><td></td></tr>
<tr><td>Stratified by baseline A1c ≥9%/ 8-8.9%/ < 8% (diff from placebo)</td><td>-1.52%/ -0.8%/ -0.57%*</td><td>-1.51%/ -1.13%/ -0.65%*</td><td>N/A</td></tr>
<tr><td>% achieving HbA1c < 7%</td><td>40.6%*</td><td>45.4%*</td><td>16.8%</td></tr>
<tr><td>FPG (mg/dL)</td><td>-12.4*</td><td>-16.6*</td><td>+4.7</td></tr>
<tr><td>2-h PPG (mg/dL) §</td><td>-48.9</td><td>-56.3</td><td>-2.2</td></tr>
<tr><td>Required rescue OHA</td><td>8.8%</td><td>4.8%</td><td>20.6%</td></tr>
<tr><td>HOMA-β, fructosamine, proinsulin/insulin ratio</td><td colspan="3">Significantly improved vs. placebo (values not shown)*</td></tr>
<tr><td>Weight</td><td>-0.2kg</td><td>-0.1kg</td><td>-1.1kg^</td></tr>
<tr><td>Hypoglycemia</td><td colspan="3">No significant difference between groups</td></tr>
</table>
§Determined after a meal tolerance test
*Significant vs. placebo
^ Significant vs. sitagliptin
No significant differences between the 2 sitagliptin doses for A1c, FPG, 2-h PPG</td>
</tr>
</table>

Abbreviations: BMI=body mass index; CrCl= creatinine clearance; DB= double-blind; DM=diabetes mellitus; FPG=fasting plasma glucose; HOMA-β= Homeostasis Model Assessment- β; IGT=impaired glucose tolerance; ITT=intent-to-treat; LOCF=last observation carried forward; N/A=not applicable; OHA=oral hypoglycemic agent; PC=placebo-controlled; PPG=postprandial glucose; PR=parallel; R=randomized; SB=single-blind; SCr=serum creatinine

Appendix 2: Combination Studies

<table>
<tr><th>Study</th><th>Inclusion/Exclusion</th><th>Dosage</th><th>Demographics/Baseline values</th><th>Results</th></tr>
<tr>
<td>Charbonnel
(Study020)
R, DB, PC, PR
n=701
24-weeks (DB period)

Primary analysis-ITT (n=677)

Diabetes Care (in press)</td>
<td>Type 2 DM
18-78 years old
No OHA or mono or dual tx with OHA
HbA1c 7-10% after metformin dose stabilization

<u>Exclusions:</u>
Required insulin within the prior 8 weeks; SCr ≥ 1.4mg dL (males) SCr ≥ 1.3mg/dL (females) or CrCl < 60mL/min; > 0.5mg albumin /mg of creatinine in urine</td>
<td>Metformin titration/stabilization period for up to 19 weeks

Eligible if inadequate control on metformin monotherapy ≥ 1500mg/d

2-week SB placebo run-in
2:1 randomization

Sitagliptin 100mg once daily + prior metformin
Placebo + prior metformin

Rescue tx with pioglitazone if:
FPG > 270mg/dLfrom baseline to week 6, if FPG > 240mg/dL week 6-12, FPG > 200mg/dL after week 12</td>
<td>Age: 54.5 (range 19-78)
Gender: 57.1% male
Race: 64.5% White, 14.3% Hispanic, 6.5% Black, 10.7% Asian
Duration of DM: 6.2 years (range 0.1-34 years)
HbA1c: 8%
Weight: 87.7kg (range 49, 161.5kg)
BMI: 31.2kg/m^2(range 19.6, 43.9)
FPG: 171.5mg/dL
2-h PPG: 275mg/dL

Mean values</td>
<td>
<table>
<tr><th></th><th>Sitagliptin + metformin</th><th>Placebo + metformin</th></tr>
<tr><td>Drop-outs</td><td>10.3%</td><td>19%</td></tr>
<tr><td>HbA1c</td><td>-0.7%*</td><td>-0%</td></tr>
<tr><td>Stratified by baseline A1c > 9%/ 8-8.9%/ < 8%</td><td>-0.91/ -0.82/ -0.53</td><td></td></tr>
<tr><td>% achieving HbA1c < 7%</td><td>47%*</td><td>18.3%</td></tr>
<tr><td>FPG (mg/dL)</td><td>-16.9*
[95%CI -21.5, -12.3]</td><td>8.5 [95%CI 2.9, 14.1]</td></tr>
<tr><td>2-h PPG (mg/dL)</td><td>-62*
[95%CI -70.2, -53.8]</td><td>-11.4
[95%CI -21.7, -1.0]</td></tr>
<tr><td>Weight (kg)</td><td>-0.7</td><td>-0.6</td></tr>
<tr><td>Hypoglycemia (all)</td><td>1.3%</td><td>2.1%</td></tr>
<tr><td>Proinsulin/insulin ratio</td><td colspan="2">Significantly decreased vs. placebo (values not shown)*</td></tr>
<tr><td>HOMA-β</td><td colspan="2">Significantly increased vs. placebo (values not shown)*</td></tr>
<tr><td>insulin, C-peptide (fasting, post-meal, AUC)</td><td colspan="2">Significantly increased vs. placebo (values not shown)*</td></tr>
<tr><td>Required PIO rescue</td><td>4.8%</td><td>13.5%</td></tr>
</table>
*Significant vs. placebo
</td>
</tr>
<tr>
<td>Rosenstock
(Study 019)
R, DB, PC
n=353
24-weeks (DB period)

<u>ITT (LOCF)</u>
n=163 (sitagliptin)
n=174 (placebo)</td>
<td>Type 2 DM
≥ 18 years old
No OHA or mono tx or dual tx with TZD + other OHA
HbA1c 7-10% after PIO dose stabilization

<u>Exclusions:</u>
Type 1 DM, required insulin within the prior 8 weeks; CrCl < 45mL/min; SCr > 2.0mg/ dL (male and ≤ 65 y/o) SCr > 1.7mg/dL/dL (male and > 65 y/o OR female and ≤ 65y/o) SCr > 1.4mg/dL (female and > 65y/o); intolerant to TZDs</td>
<td>Diet/exercise run-in
8-14 week dose stable period on PIO
Eligible if inadequate control on pioglitazone 30 or 45mg

2-week SB placebo run-in
1:1 randomization

Sitagliptin 100mg once daily + prior pioglitazone
Placebo + prior pioglitazone

Rescue therapy with metformin was allowed for patients not meeting glycemic goals. These patients were included in the primary efficacy and safety analysis up to the period of when rescue was initiated; however, data for the entire treatment time were included in the secondary safety analysis.</td>
<td>Age: 56 years old (24-87)
Gender: 55% male
Race: 72.5% White, 12.2% Hispanic, 6.5% Black, 4.2% Asian
Weight: 88.7kg (range 50, 135.2)
BMI: 31.5kg/m^2 (range 20.1, 44.2)
HbA1c: 8.0% (range 6.4-10.4)
HbA1c < 8%/ 8-9%/ > 9%: 52.4%/ 30.9%/ 16.4%
FPG: 167mg/dl (range 94-315)
DM duration: 6.1 years (range 0-38)
No OHA: 9.6%
Monotherapy: 60%
Dual tx with a TZD: 30%
On a TZD: 49%

Mean values</td>
<td>
<table>
<tr><th></th><th>Sitagliptin + PIO</th><th>Placebo + PIO</th></tr>
<tr><td>Drop-outs</td><td>14.8%</td><td>11.2%</td></tr>
<tr><td>HbA1c</td><td>-0.85%*
[95%CI -0.98, -0.72]</td><td>-0.15%
[95%CI -0.28, -0.03]</td></tr>
<tr><td>Stratified by baseline A1c ≥ 8.5%/ < 8.5%</td><td>-1.17/ -0.73</td><td>Not shown</td></tr>
<tr><td>% achieving HbA1c < 7%</td><td>45.4%*</td><td>23%</td></tr>
<tr><td>FPG (mg/dL)</td><td>-16.7*
[95%CI -22.4, -11]</td><td>1.0
[95%CI -4.3, 6.3]</td></tr>
<tr><td>Proinsulin/insulin ratio</td><td>-0.08*</td><td>0</td></tr>
<tr><td>HOMA-β index</td><td>11.5%</td><td>5.8%</td></tr>
<tr><td>Weight (kg)</td><td>1.8</td><td>1.5</td></tr>
<tr><td>Hypoglycemia</td><td>2 (1.1%)</td><td>0</td></tr>
<tr><td>Required metformin rescue</td><td>6.9%</td><td>14%</td></tr>
<tr><td>Peripheral edema</td><td>7 (4%)</td><td>6 (3.4%)</td></tr>
</table>
*Significant vs. placebo
</td>
</tr>
</table>

Stein R, DB, active-control Non-inferiority design n=1172 52-weeks Primary analysis – per protocol pop. Defined as completing 52-weeks with a measurement of A1c and nor protocol violations (n=793)	Type 2 DM 18-78 years old HbA1c 6.5-10% Inadequate control on metformin alone or in combination with another agent	2-week metformin monotherapy run-in Eligible if inadequate control on ≥ 1500mg of metformin Sitagliptin 100mg once daily + metformin Glipizide up to 10mg BID + metformin	**Gender:** 60% male **Age:** 57 years **Duration of DM:** 6 years **HbA1c:** 7.5% Mean values	

	Sitagliptin + metformin	**Glipizide + metformin**
HbA1c	-0.67%	-0.67%
Stratified by baseline A1c ≥ 9%/ 8-<9%/ 7-<8%/ <7%	-1.68/ -1.13/ -0.53/ -0.26	-1.76/ -1.11/ -0.59/ -0.14
% achieving HbA1c < 7%	63%	59%
Weight	-1.3kg	+1.2kg*
≥ 1 hypoglycemic episode	4.9%	32%*

*Significant vs. sitagliptin + metformin

Abbreviations: BMI=body mass index; CrCl= creatinine clearance; DB= double-blind; DM=diabetes mellitus; FPG=fasting plasma glucose; HOMA-β= Homeostasis Model Assessment- β; ITT=intent-to-treat; LOCF=last observation carried forward; OHA=oral hypoglycemic agent; PC=placebo-controlled; PIO=pioglitazone; PPG=postprandial glucose; PR=parallel; R=randomized; SB=single-blind; SCr=serum creatinine; TZD=thiazolidinedione

Appendix 3: Adverse Events and Study Discontinuation

	Nonaka		**Raz**			**Aschner**			**Charbonnel**		**Rosenstock**		**Stein**	
	SIT 100mg	**Placebo**	**SIT 100mg**	**SIT 200mg**	**Placebo**	**SIT 100mg**	**SIT 200mg**	**Placebo**	**SIT + MET**	**MET**	**SIT + PIO**	**PIO**	**SIT + MET**	**GLIP + MET**
Randomized	75	76	205	206	110	238	250	253	464	237	175	178	588	584
≥ 1 clinical AE	44 (58.7%)	49 (64.5%)	99 (48.3%)	88 (42.7%)	55 (50%)	155 (65.1%)	159 (63.6%)	160 (63.2%)	258 (55.6%)	126 (53.2%)	83 (47.4%)	91 (51.1%)	419 (71.3%)	444 (76%)
Drug-related AE	2 (2.7%)	3 (3.9%)	21 (10.2%)	16 (7.8%)	19 (17.3%)	83 (34.9%)	91 (36.4%)	93 (36.8%)	43 (9.3%)	24 (10.1%)	16 (9.1%)	16 (9%)	85 (14.5%)	177 (30.3%)
Serious AE	1 (1.3%)	3 (3.9%)	7 (3.4%)	3 (1.5%)	3 (2.7%)	11 (4.6%)	12 (4.8%)	8 (3.2%)	12 (2.6%)	7 (3%)	5 (2.9%)	7 (3.9%)	43 (7.3%)	44 (7.5%)
Serious drug - related AE	0	1 (1.3%)	0	0	0	2 (0.8%)	0	1 (0.4%)	0	0	1 (0.6%)	0	0	2 (0.3%)
Died	0	0	0	0	0	0	0	0	0	0	0	0	1 (0.2%)	2 (0.3%)
D/C due to AE	0	2 (2.6%)	4 (2%)	0	3 (2.7%)	5 (2.1%)	4 (1.6%)	4 (1.6%)	9 (1.9%)	6 (2.5%)	10 (5.7%)	2 (1.1%)	16 (2.7%)	21 (3.6%)
D/C due to drug-related AE	0	2 (2.6%)	1 (0.5%)	0	3 (2.7%)	1 (0.4%)	0	2 (0.8%)	4 (0.9%)	0	1 (0.6%)	1 (0.6%)	8 (1.4%)	8 (1.4%)
D/C due to serious AE	0	1 (1.3%)	3 (1.5%)	0	0	3 (1.3%)	3 (1.2%)	3 (1.2%)	5 (1.1%)	1 (0.4%)	3 (1.7%)	1 (0.6%)	6 (1%)	7 (1.2%)
D/C due to serious drug -related AE	0	1 (1.3%)	0	0	0	0	0	1 (0.4%)	0	0	1 (0.6%)	0	0	0

Abbreviations: AE=adverse event; D/C=discontinued; GLIP=glipizide; MET=metformin; PIO=pioglitazone; SIT=sitagliptin