The study listed may include approved and non-approved uses, formulations, or treatment regimens. The results reported in any single study may not reflect the overall profile of a product. Before prescribing any product mentioned in this registry, healthcare professionals should consult local prescribing information for the product approved in their country.

Results presented here may include different data points from those required on http://clinicaltrials.gov/.

PROTOCOL TITLE/NO.: A Phase III, Multicenter, Double-Blind, Randomized Study to Evaluate the Safety and Efficacy of the Addition of Sitagliptin Compared with the Addition of Glimepiride in Patients with Type 2 Diabetes Mellitus with Inadequate Glycemic Control on Metformin (Protocol: MK-0431-803)

PROTOCOL AMENDMENTS: MK-0431-803-01 (20-Dec-2007), MK-0431-803-02 (07-Feb-2008)

UNIQUE IDENTIFIER: NCT00701090

SPONSOR: Merck & Co., Inc.

STUDY CENTER(S): One hundred nine (109) sites received study drug worldwide.

PUBLICATION(S): NA

PRIMARY THERAPY PERIOD: 03-Jun-2008 through 27-Oct-2009	**CLINICAL PHASE:** III

DURATION OF TREATMENT: 30-week study

OBJECTIVES: In patients with type 2 diabetes mellitus (T2DM) with inadequate glycemic control on metformin: **Primary:** (1) After 30 weeks, to assess the effect of the addition of sitagliptin compared with glimepiride on hemoglobin A_{1c} (A1C); (2) To assess the safety and the tolerability of sitagliptin compared with glimepiride. **Secondary:** After 30 weeks, to assess the effect of the addition of sitagliptin compared with glimepiride on: (1) The incidence of hypoglycemic events; (2) Body weight; (3) Fasting plasma glucose (FPG); (4) Proportion of patients achieving goal A1C (<6.5%, <7.0%).

HYPOTHESES: In patients with T2DM with inadequate glycemic control on metformin: **Primary:** (1) After 30 weeks of treatment, the mean change from baseline in A1C in patients treated with sitagliptin is non-inferior compared with that in patients treated with glimepiride; (2) Sitagliptin is well tolerated. **Secondary:** (1) The addition of treatment with sitagliptin compared with glimepiride leads to a lower incidence of hypoglycemic events; (2) The addition of treatment with sitagliptin compared with glimepiride leads to less gain in body weight from baseline.

STUDY DESIGN: This was a multinational, double-blind, randomized, parallel-group study. Patients with T2DM who had inadequate glycemic control (i.e., A1C of ≥6.5 and ≤9.0%) on metformin monotherapy (≥1500 mg/day) were eligible. The duration of the study was up to 34 weeks for each patient, including a screening period of up to 2 weeks [Visits 1 to 2], a 2-week placebo run-in period [Visits 2 to 3], and a 30-week double-blind treatment period [Visits 3 to 8]. During the entire study period (run-in period through the completion of the double-blind treatment period), the patient was required to maintain the same regimen of metformin that was administered during the 12-week dose stable period prior to study entry. Patients meeting all enrollment criteria were randomized at Visit 3/Day 1 to treatment with either sitagliptin or glimepiride in a 1:1 ratio. Blinding was maintained using a double dummy approach, i.e., patients in the sitagliptin treatment group received placebo tablets matching the 1-mg and/or 2-mg glimepiride tablet; patients in the glimepiride treatment group received a placebo tablet matching the sitagliptin 100-mg tablet. The dose of sitagliptin was 100 mg once daily (q.d.) during the entire 30-week study treatment period. Based upon the results of the patient's self-blood glucose monitoring (SBGM) over the initial 18-week double-blind treatment period, glimepiride (or its matching placebo) was up-titrated starting from 1 mg q.d. to a maximum dose of 6 mg/day. After the initial 18 weeks of the double-blind treatment period, up-titration of glimepiride was not allowed; however, down-titration was allowed to avoid or control hypoglycemia.

SUBJECT/PATIENT DISPOSITION:

	Sitagliptin 100 mg	Glimepiride	Total
SCREENING FAILURES:			590
RANDOMIZED:	516	519	1035
Male (age range)	284 (32-83)	279 (29-78)	563 (29-83)
Female (age range)	232 (24-79)	240 (25-80)	472 (24-80)
COMPLETED:	468	468	936
DISCONTINUED:	48	51	99
Adverse Event	11	3	14
Lack of Efficacy	5	4	9
Lost to Follow-up	9	9	18
Other Protocol Specified Criteria	7	12	19
Physician Decision	3	4	7
Protocol Violation	2	3	5
Withdrawal by Subject	11	16	27

DOSAGE: Sitagliptin was administered using a 100-mg tablet. For patients in the sitagliptin group, the dose of sitagliptin was 100 mg q.d. during the entire 30-week study treatment period. For patients in the glimepiride treatment group, glimepiride was administered as either 1-mg or 2-mg tablets or both. Background medication (metformin) was to be sourced locally.

DIAGNOSIS/INCLUSION CRITERIA: Diagnosis – Patients with T2DM. Patients who are ≥18 years of age on a stable dose of metformin (at least 1500 mg per day) with inadequate glycemic control (i.e., A1C ≥6.5% and ≤9.0%).

EVALUATION CRITERIA:

EFFICACY MEASUREMENTS: Primary Endpoint: A1C. Secondary and Other Endpoints: FPG; lipid panel, and patient-reported outcomes (EuroQol questionnaire [EQ-5D]).

SAFETY MEASUREMENTS: Safety endpoints supporting the secondary hypothesis: assessment of hypoglycemia and body weight. Other safety endpoints: collection of adverse experiences, laboratory safety parameters, and vital signs. Laboratory safety studies included blood chemistry (including alanine aminotransferase [ALT], aspartate aminotransferase [AST], total bilirubin, alkaline phosphatase, gamma-glutamyl transferase [GGT]), hematology (including complete blood count [CBC], differential, and absolute neutrophil count), and urinalysis.

STATISTICAL PLANNING AND ANALYSIS:

EFFICACY: The primary efficacy objective of this study was to show that sitagliptin has similar glucose lowering efficacy compared with glimepiride in patients with T2DM with inadequate glycemic control while on a stable dose of metformin. The primary analysis was based on the change from baseline in A1C at Week 30. Similarity between sitagliptin and glimepiride was assessed by a non-inferiority analysis. The primary population for the non-inferiority analysis was the Per-Protocol (PP) population. The PP population consisted of all patients randomized who had a baseline measurement, a measurement at Week 30, and did not have any major protocol violations. An analysis of covariance (ANCOVA) was used to compare the treatment groups for A1C. The analysis adjusted for country and baseline A1C. The criterion for declaring sitagliptin non-inferior to glimepiride in terms of change from baseline in A1C was an upper boundary of the two-sided 95% confidence interval (CI) for the mean difference between sitagliptin and glimepiride less than the non-inferiority margin, δ=0.4%.

Approximately 1050 patients were planned to be randomized in a 1:1 ratio to the sitagliptin or glimepiride group. Assuming about 15% to 20% of randomized patients would drop out or be protocol violators during the 30 weeks of the double-blind treatment period, roughly 425 patients per group would be available for the PP analysis. Using a standard deviation of 0.9% for the A1C change from baseline at Week 30, a sample size of 425 PP-patients per group had at least 90% power to declare non-inferiority at Week 30 assuming that the true mean difference in A1C-lowering between sitagliptin and glimepiride at Week 30 was at most 0.2%.

In addition, the proportion of patients meeting A1C goals at Week 30 (<6.5% and <7%) was summarized.

SAFETY: Safety and tolerability were assessed by a review of all safety parameters including adverse experiences, laboratory safety parameters, body weight, and vital signs. The analyses of safety parameters followed a multi-tiered approach. To evaluate the secondary hypotheses, the between-treatment difference for the incidence of hypoglycemia was tested using the Cochran Mantel Haenszel-test and the between-treatment difference in change of body weight was tested using the ANCOVA model adjusting for baseline body weight and country as covariates. The testing procedure for the 2 secondary hypotheses was prioritized in the order of hypoglycemia then body weight. The overall Type I error rate for the testing of the secondary hypotheses was controlled at the two-sided 0.05 (or 0.025) level.

For other adverse experiences and predefined limits of change in laboratory variables, only summary tabulations and/or 95% CIs for between-group differences were provided.

RESULTS:

EFFICACY: Similar reductions in A1C at Week 30 were observed in both treatment groups. The criterion for declaring sitagliptin non-inferior to glimepiride in the test of the primary hypothesis was met: the upper limit of the two-sided 95% CI for the mean difference between sitagliptin and glimepiride was less than the pre-specified non-inferiority margin of 0.4%.

Analysis of Change from Baseline in A1C (%) at Week 30
(PP)

		Baseline	Week 30	Change from Baseline at Week 30	
Treatment	N	Mean (SD)	Mean (SD)	Mean (SD)	LS Mean (95% CI) [†]
Sitagliptin 100 mg	443	7.48 (0.68)	7.04 (0.83)	-0.44 (0.71)	-0.47 (-0.55, -0.39)
Glimepiride	436	7.49 (0.74)	6.98 (0.89)	-0.51 (0.80)	-0.54 (-0.62, -0.45)
Estimated Difference				Difference in LS Means (95% CI)	
Sitagliptin 100 mg vs. Glimepiride				0.07 (-0.03, 0.16)	
p-Values for ANCOVA effects					
Baseline A1C					<0.001
Country					<0.001
Root Mean Square Error of Change =0.70					

SD= standard deviation; LS = least-squares
[†] Based on an ANCOVA model controlling for treatment, country and baseline A1C.

Tables below show results for the analysis of the proportion of patients with an A1C value below 7.0% and 6.5% in the PP population at Week 30, respectively. The odds of achieving a Week 30 A1C level <7.0% and 6.5% were lower in the sitagliptin group than in the glimepiride group; for both endpoints, the 95% CI of the odds ratio excluded 1. Results based on the difference in percentage and relative risk were consistent with the results based on the adjusted odds ratio.

Analysis of Percentage of Patients with A1C Value < 7.0% at Week 30
(PP)

Treatment	N	n (%)
Sitagliptin 100 mg	443	232 (52.4)
Glimepiride	436	260 (59.6)

Estimated Difference	Difference in Percent (%) (95% CI)[†]	Relative Risk (95% CI)[‡]	Odds-Ratio (95% CI)[§]
Sitagliptin 100 mg vs. Glimepiride	-7.5 (-13.8, -1.1)	0.88 (0.78, 0.98)	0.65 (0.47, 0.90)

[†] Based on the method of Miettinen and Nurminen with country as a stratification factor.
[‡] Based on Cochran-Mantel-Haenszel (CMH) test with country as a CMH stratification factor.
[§] Based on a logistic regression model controlling for treatment, country and baseline A1C.

Analysis of Percentage of Patients with A1C Value < 6.5% at Week 30
(PP)

Treatment	N	n (%)
Sitagliptin 100 mg	443	94 (21.2)
Glimepiride	436	120 (27.5)

Estimated Difference	Difference in Percent (%) (95% CI)[†]	Relative Risk (95% CI)[‡]	Odds-Ratio (95% CI)[§]
Sitagliptin 100 mg vs. Glimepiride	-6.7 (-12.3, -1.1)	0.76 (0.60, 0.96)	0.67 (0.47, 0.95)

[†] Based on the method of Miettinen and Nurminen with country as a stratification factor.
[‡] Based on Cochran-Mantel-Haenszel (CMH) test with country as a CMH stratification factor.
[§] Based on a logistic regression model controlling for treatment, country and baseline A1C.

The analysis result for the change from baseline in FPG in the PP population at Week 30 is provided in the table below. Similar reductions in FPG at Week 30 were observed in both treatment groups.

Analysis of Change from Baseline in FPG (mg/dL) at Week 30
(PP)

Treatment	N	Baseline Mean (SD)	Week 30 Mean (SD)	Change from Baseline at Week 30	
				Mean (SD)	LS Mean (95% CI) †
Sitagliptin 100 mg	446	143.0 (32.5)	130.3 (31.5)	-12.7 (32.8)	-14.6 (-17.9, -11.2)
Glimepiride	444	145.9 (33.8)	128.7 (32.8)	-17.3 (37.0)	-17.5 (-20.8, -14.1)
Pairwise Comparison				Difference in LS Means (95% CI)	p-Value
Sitagliptin 100 mg vs. Glimepiride				2.9 (-0.9, 6.7)	0.136
p-Values for ANCOVA effects					
Baseline FPG					<0.001
Country					0.028
Root Mean Square Error of Change =28.8					
† Based on an ANCOVA model controlling for treatment, country and baseline FPG.					

SAFETY: Sitagliptin and glimepiride were generally well-tolerated. Over the 30-week treatment period, a higher incidence of adverse experiences was observed for the glimepiride group compared with the sitagliptin group. In addition, a higher incidence of drug-related adverse experiences occurred in the glimepiride group compared with the sitagliptin group. The higher incidences for overall adverse experiences and drug-related adverse experiences in the glimepiride group were mostly due to the higher incidence of hypoglycemia. Higher incidences of discontinuations due to an adverse experience and discontinuations due to a serious adverse experience were observed in the sitagliptin group compared with the glimepiride group. The higher incidences for these measures in the sitagliptin group were due to small differences for a range of specific adverse experiences without a discernible pattern. None of the patients in the sitagliptin group and 1 patient in the glimepiride treatment group died (hemorrhagic stroke). One serious adverse experience which was considered drug-related by the investigator was reported in the study; a 61 year old female in the sitagliptin group experienced a serious, drug-related adverse experience of thrombocytopenia on Day 109. The event resulted in hospitalization and was associated with a platelet count of 12,000/µL (normal range 150,000 to 400,000/µL). Hemoglobin and white blood cell counts were within the normal range and a bone marrow biopsy did not show clinically meaningful abnormalities. The patient was treated with prednisone and platelet counts returned to the normal range. The investigator reported the event as related to study drug, but also reported 2 other suspect therapies: pentoxifylline (started on Day 60 for dizziness) and amoxicillin + clavulanate potassium (from Day 92 to Day 106 for nasal sinusitis).

There were 36 (7.0%) patients in the sitagliptin treatment group who reported 73 episodes of hypoglycemia compared with 114 patients (22.0%) in the glimepiride group who reported 460 episodes of hypoglycemia ($p<0.001$ for difference in proportion of patients with at least one episode). In the sitagliptin treatment group, 1 (0.2%) patient required non-medical assistance but did not exhibit marked severity and 1 (0.2%) patient experienced an episode with marked severity (depressed level of consciousness). In the glimepiride treatment group, 8 (1.5%) patients had episodes of hypoglycemia which required non-medical assistance did not exhibit marked severity and 3 (0.6%) patients experienced at least 1 episode with marked severity (1 of these 3 patients had 2 episodes which resulted in a seizure) (see Table below). A decrease from baseline in body weight of 0.8 kg was observed in the sitagliptin treatment group while an increase in body weight of 1.2 kg was observed in the glimepiride treatment group. At Week 30, a significant between-group difference of 2.0 kg ($p<0.001$) was observed (see Table below). No meaningful differences in laboratory measurements, predefined limits of change for laboratory safety measurements, and vital signs were observed.

Adverse Event Summary
(All Patients as Treated [APaT])

	Sitagliptin 100 mg		Glimepiride	
	n	(%)	n	(%)
Patients in population	516		518	
with one or more adverse events	244	(47.3)	291	(56.2)
with no adverse event	272	(52.7)	227	(43.8)
with drug-related[†] adverse events	47	(9.1)	116	(22.4)
with serious adverse events	16	(3.1)	11	(2.1)
with serious drug-related adverse events	1	(0.2)	0	(0.0)
who died	0	(0.0)	1	(0.2)
discontinued[‡] due to an adverse event	10	(1.9)	2	(0.4)
discontinued due to a drug-related adverse event	2	(0.4)	2	(0.4)
discontinued due to a serious adverse event	5	(1.0)	0	(0.0)
discontinued due to a serious drug-related adverse event	1	(0.2)	0	(0.0)

[†] Determined by the investigator to be related to the drug.
[‡] Study medication withdrawn.

Analysis of Clinical Assessment of Hypoglycemia
(APaT)

Treatment	Patients With at Least One Episode		
	n/N (%)	Difference in % vs. Comparator (95% CI)	p-Value[†]
Episodes of Any Type			
Sitagliptin 100 mg	36/516 (7.0)	-15.0 (-19.3, -10.9)	<0.001
Glimepiride	114/518 (22.0)		
Episodes Requiring Non-Medical Assistance and Not Exhibiting Marked Severity			
Sitagliptin 100 mg	1/516 (0.2)	-1.4 (-2.9, -0.3)	0.019
Glimepiride	8/518 (1.5)		
Episodes Requiring Medical Assistance or Exhibiting Marked Severity			
Sitagliptin 100 mg	1/516 (0.2)	-0.4 (-1.5, 0.6)	0.318
Glimepiride	3/518 (0.6)		

[†] Based on Miettinen & Nurminen method.

Estimated differences, confidence intervals and p-values are provided in accordance with the statistical analysis plan.

Every patient is counted a single time for each applicable specific episode category.

Analysis of Change from Baseline in Body Weight (kg) at Week 30
(APaT)

Treatment	N	Baseline Mean (SD)	Week 30 Mean (SD)	Change from Baseline at Week 30	
				Mean (SD)	LS Mean (95% CI) [†]
Sitagliptin 100 mg	465	80.6 (15.2)	79.8 (15.5)	-0.8 (3.0)	-0.8 (-1.1, -0.5)
Glimepiride	461	82.2 (16.8)	83.3 (17.1)	1.2 (2.8)	1.2 (0.9, 1.5)
Pairwise Comparison				Difference in LS Means (95% CI)	p-Value
Sitagliptin 100 mg vs. Glimepiride				-2.0 (-2.3, -1.6)	<0.001
p-Values for ANCOVA effects					
Baseline Body Weight					0.489
Country					0.446
Root Mean Square Error of Change =2.9					
[†] Based on an ANCOVA model controlling for treatment, country and baseline Body Weight.					

CONCLUSIONS: In patients with T2DM and inadequate glycemic control on metformin at a dose of at least 1500 mg/day:

(1) Sitagliptin treatment provides glycemic control that is non-inferior to that of treatment with glimepiride.

(2) Sitagliptin treatment is associated with a lower incidence of hypoglycemia compared to treatment with glimepiride.

(3) Sitagliptin treatment leads to a reduction in body weight while treatment with glimepiride leads to weight gain.

(4) Sitagliptin treatment is generally well-tolerated.

DATE OF THE REPORT: 11-Aug-2010