Sulfonylurea Add-on Study in Patients With Type 2 Diabetes Mellitus (0431-035)

This study has been completed.

Sponsor:
Merck Sharp & Dohme Corp.

Information provided by (Responsible Party):
Merck Sharp & Dohme Corp.

ClinicalTrials.gov Identifier:
NCT00106704

First received: March 29, 2005
Last updated: June 4, 2015
Last verified: June 2015
History of Changes

Purpose

The purpose of this clinical study is to determine the safety and efficacy of an investigational drug in patients with Type 2 diabetes mellitus.

Condition	Intervention	Phase
Diabetes Mellitus, Type 2	Drug: Comparator: Sitagliptin Drug: Comparator: Placebo Drug: Comparator: Pioglitazone	Phase 3

Study Type: Interventional
Study Design: Allocation: Randomized
Endpoint Classification: Safety/Efficacy Study
Intervention Model: Crossover Assignment
Masking: Double Blind (Subject, Investigator)
Primary Purpose: Treatment

Official Title: A Multicenter, Randomized, Double Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of the Addition of MK0431 to Patients With Type 2 Diabetes Mellitus Who Have Inadequate Glycemic Control on Glimepiride Alone or in Combination With Metformin

Resource links provided by NLM:

MedlinePlus related topics: Diabetes Type 2

Drug Information available for: Pioglitazone Pioglitazone hydrochloride Sitagliptin Sitagliptin phosphate

U.S. FDA Resources

Further study details as provided by Merck Sharp & Dohme Corp.:

Primary Outcome Measures:

- Change From Baseline in A1C at Week 24 [Time Frame: Baseline and 24 Weeks] [Designated as safety issue: No]

  Hemoglobin A1C (A1C) is measured as percent. Thus this change from baseline reflects the Week 24 A1C percent minus the Week 0 A1C percent.

Secondary Outcome Measures:

- Change From Baseline in FPG at Week 24 [Time Frame: Baseline and 24 Weeks] [Designated as safety issue: No]

  The change from baseline is the Week 24 Fasting Plasma Glucose (FPG) minus the Week 0 FPG.

Enrollment:	441
Study Start Date:	March 2005
Study Completion Date:	January 2007
Primary Completion Date:	June 2006 (Final data collection date for primary outcome measure)

Arms	Assigned Interventions
Experimental: Sitagliptin Sitagliptin 10 mg tablet daily for 54 weeks	Drug: Comparator: Sitagliptin sitagliptin 10 mg tablet, once daily for 54 weeks
Placebo Comparator: Placebo/ Pioglitazone Placebo tablet daily for 24 weeks followed by Pioglitazone tablet daily for 30 weeks	Drug: Comparator: Placebo Placebo oral tablet once daily for 24 weeks Drug: Comparator: Pioglitazone Pioglitazone 30 mg tablet once daily for 30 weeks

Eligibility

Ages Eligible for Study:	18 Years to 75 Years
Genders Eligible for Study:	Both
Accepts Healthy Volunteers:	No

Criteria

Inclusion Criteria:

- Patients with Type 2 Diabetes Mellitus with inadequate glycemic control

Exclusion Criteria:

- Patients with Type 1 Diabetes Mellitus

Contacts and Locations

Choosing to participate in a study is an important personal decision. Talk with your doctor and family members or friends about deciding to join a study. To learn more about this study, you or your doctor may contact the study research staff using the Contacts provided below. For general information, see Learn About Clinical Studies.

Please refer to this study by its ClinicalTrials.gov identifier: NCT00106704

Sponsors and Collaborators

Merck Sharp & Dohme Corp.

Investigators

Study Director: Medical Monitor Merck Sharp & Dohme Corp.

More Information

Additional Information:

MedWatch - FDA maintained medical product safety Information

Merck: Patient & Caregiver U.S. Product Web Site

Publications:

Hermansen K, Kipnes M, Luo E, Fanurik D, Khatami H, Stein P; Sitagliptin Study 035 Group. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor, sitagliptin, in patients with type 2 diabetes mellitus inadequately controlled on glimepiride alone or on glimepiride and metformin. Diabetes Obes Metab. 2007 Sep;9(5):733-45. Epub 2007 Jun 26.

Responsible Party:	Merck Sharp & Dohme Corp.
ClinicalTrials.gov Identifier:	NCT00106704 History of Changes
Other Study ID Numbers:	0431-035 2005_009
Study First Received:	March 29, 2005
Results First Received:	November 19, 2010
Last Updated:	June 4, 2015
Health Authority:	United States: Food and Drug Administration

Additional relevant MeSH terms:

Diabetes Mellitus	Hormones
Diabetes Mellitus, Type 2	Hormones, Hormone Substitutes, and Hormone Antagonists
Endocrine System Diseases	Hypoglycemic Agents
Glucose Metabolism Disorders	Incretins
Metabolic Diseases	Molecular Mechanisms of Pharmacological Action
Pioglitazone	Pharmacologic Actions
Sitagliptin	Physiological Effects of Drugs
Dipeptidyl-Peptidase IV Inhibitors	Protease Inhibitors
Enzyme Inhibitors	

ClinicalTrials.gov processed this record on April 13, 2016

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Results First Received: November 19, 2010

Study Type:	Interventional
Study Design:	Allocation: Randomized; Endpoint Classification: Safety/Efficacy Study; Intervention Model: Crossover Assignment; Masking: Double Blind (Subject, Investigator); Primary Purpose: Treatment
Condition:	Diabetes Mellitus, Type 2
Interventions:	Drug: Comparator: Sitagliptin Drug: Comparator: Placebo Drug: Comparator: Pioglitazone

Participant Flow

Hide Participant Flow

Recruitment Details

Key information relevant to the recruitment process for the overall study, such as dates of the recruitment period and locations

First Patient In: 27-Apr-2005. Last Patient Last Visit: 09-Jan-2007. 27 medical clinics in the United States (US), 25 in 11 countries in Europe, and 22 in 11 countries in the rest of the world.

Pre-Assignment Details

Significant events and approaches for the overall study following participant enrollment, but prior to group assignment

Patients 18-75 years of age with type 2 diabetes mellitus (T2DM) with inadequate glycemic control (hemoglobin A1c [A1C] ≥7.5% and ≤10.5%) at screening or after treatment with glimepiride (≥4 mg) alone or in combination with metformin (≥1500 mg) for a dose stable period of up to 10 weeks were eligible to participate.

Reporting Groups

	Description
Sitagliptin	The Sitagliptin group includes data from patients randomized to receive treatment with oral tablets of sitagliptin 100 mg q.d. (once daily) with glimepiride (≥4 mg/day) alone or in combination with metformin (≥1500 mg/day).
Placebo/ Pioglitazone	The Placebo group includes data from patients randomized to receive treatment with placebo to sitagliptin oral tablets q.d. with glimepiride (≥4 mg/day) alone or in combination with metformin (≥1500 mg/day).

Participant Flow: Overall Study

	Sitagliptin	Placebo/ Pioglitazone
STARTED	222	219
COMPLETED	91	68
NOT COMPLETED	131	151
Adverse Event	10	7
Death	2	1
Lack of Efficacy	67	69
Lost to Follow-up	7	3
Pregnancy	1	0
Protocol Violation	4	7
Withdrawal by Subject	14	21
Patient moved	1	0
Site terminated	0	1
Planned major surgery	1	0
Patient Received Glycemic Medication	22	41
Unable to re-enter US	1	0
Laboratory test	1	1

Baseline Characteristics

Hide Baseline Characteristics

Population Description

Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.
No text entered.

Reporting Groups

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Sitagliptin	The Sitagliptin group includes data from patients randomized to receive treatment with oral tablets of sitagliptin 100 mg q.d. (once daily) with glimepiride (≥4 mg/day) alone or in combination with metformin (≥1500 mg/day).
Placebo/ Pioglitazone	The Placebo group includes data from patients randomized to receive treatment with placebo to sitagliptin oral tablets q.d. with glimepiride (≥4 mg/day) alone or in combination with metformin (≥1500 mg/day).

Total	Total of all reporting groups

Baseline Measures

	Sitagliptin	Placebo/ Pioglitazone	Total
Number of Participants [units: participants]	222	219	441
Age [units: years] Mean (Standard Deviation)	55.6 (9.6)	56.5 (9.6)	56.0 (9.6)
Gender [units: participants]			
Female	105	102	207
Male	117	117	234
Race/Ethnicity, Customized [units: participants]			
White	136	140	276
Black	10	12	22
Hispanic	39	32	71
Asian	22	25	47
Other	15	10	25
Fasting Plasma Glucose (FPG) [units: mg/dL] Mean (Standard Deviation)	180.9 (37.7)	181.6 (42.5)	181.2 (40.1)
Hemoglobin A1C (A1C) [units: Percent] Mean (Standard Deviation)	8.34 (0.76)	8.34 (0.74)	8.34 (0.75)

Outcome Measures

Hide All Outcome Measures

1. Primary: Change From Baseline in A1C at Week 24 [Time Frame: Baseline and 24 Weeks]

Measure Type	Primary
Measure Title	Change From Baseline in A1C at Week 24
Measure Description	Hemoglobin A1C (A1C) is measured as percent. Thus this change from baseline reflects the Week 24 A1C percent minus the Week 0 A1C percent.
Time Frame	Baseline and 24 Weeks
Safety Issue	No

Population Description

Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.
All Patients Treated included patients who received at least 1 dose of study therapy, and had a baseline value and ≥1 post-baseline value for

this outcome. The last post-baseline observed measurement was carried forward to Week 24 for patients with no data at Week 24. Data obtained after glycemic rescue were considered missing.

Reporting Groups

	Description
Sitagliptin	The Sitagliptin group includes data from patients randomized to receive treatment with oral tablets of sitagliptin 100 mg q.d. (once daily) with glimepiride (≥4 mg/day) alone or in combination with metformin (≥1500 mg/day).
Placebo/ Pioglitazone	The Placebo group includes data from patients randomized to receive treatment with placebo to sitagliptin oral tablets q.d. with glimepiride (≥4 mg/day) alone or in combination with metformin (≥1500 mg/day).

Measured Values

	Sitagliptin	Placebo/ Pioglitazone
Number of Participants Analyzed [units: participants]	**217**	**208**
Change From Baseline in A1C at Week 24 [units: Percent] Least Squares Mean (95% Confidence Interval)	**-0.45 (-0.57 to -0.34)**	**0.28 (0.17 to 0.40)**

Statistical Analysis 1 for Change From Baseline in A1C at Week 24

Groups [1]	All groups
Method [2]	ANCOVA
P Value [3]	<0.001
Mean Difference (Net) [4]	-0.74
Standard Error of the mean	(0.08)
95% Confidence Interval	-90.0 to -0.57

[1]	Additional details about the analysis, such as null hypothesis and power calculation:
	No text entered.
[2]	Other relevant method information, such as adjustments or degrees of freedom:
	Model terms: treatment, stratum (on metformin or not), baseline A1C
[3]	Additional information, such as whether or not the p-value is adjusted for multiple comparisons and the a priori threshold for statistical significance:
	No text entered.
[4]	Other relevant estimation information:
	No text entered.

2. Secondary: Change From Baseline in FPG at Week 24 [Time Frame: Baseline and 24 Weeks]

Measure Type	Secondary
Measure Title	Change From Baseline in FPG at Week 24

Measure Description	The change from baseline is the Week 24 Fasting Plasma Glucose (FPG) minus the Week 0 FPG.
Time Frame	Baseline and 24 Weeks
Safety Issue	No

Population Description

Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.
All Patients Treated included patients who received at least 1 dose of study therapy, and had a baseline value and ≥1 post-baseline value for this outcome. The last post-baseline observed measurement was carried forward to Week 24 for patients with no data at Week 24. Data after rescue were considered missing.

Reporting Groups

	Description
Sitagliptin	The Sitagliptin group includes data from patients randomized to receive treatment with oral tablets of sitagliptin 100 mg q.d. (once daily) with glimepiride (≥4 mg/day) alone or in combination with metformin (≥1500 mg/day).
Placebo/ Pioglitazone	The Placebo group includes data from patients randomized to receive treatment with placebo to sitagliptin oral tablets q.d. with glimepiride (≥4 mg/day) alone or in combination with metformin (≥1500 mg/day).

Measured Values

	Sitagliptin	**Placebo/ Pioglitazone**
Number of Participants Analyzed [units: participants]	**219**	**213**
Change From Baseline in FPG at Week 24 [units: mg/dL] Least Squares Mean (95% Confidence Interval)	**-4.4 (-10.2 to 1.4)**	**15.7 (9.8 to 21.6)**

Statistical Analysis 1 for Change From Baseline in FPG at Week 24

Groups [1]	All groups
Method [2]	ANCOVA
P Value [3]	<0.001
Mean Difference (Net) [4]	-20.1
Standard Error of the mean	(4.2)
95% Confidence Interval	-28.4 to -11.8

[1]	Additional details about the analysis, such as null hypothesis and power calculation:
	No text entered.
[2]	Other relevant method information, such as adjustments or degrees of freedom:
	Model terms: treatment, stratum (on metformin or not at Visit 3), baseline A1C
[3]	Additional information, such as whether or not the p-value is adjusted for multiple comparisons and the a priori threshold for statistical significance:
	No text entered.

[4]	Other relevant estimation information:
	No text entered.

Serious Adverse Events

Hide Serious Adverse Events

Time Frame	Weeks 0 to 54
Additional Description	Patients received glycemic rescue medication if they met specific glycemic goals. SAEs includes events that occurred either before or after receiving rescue medication. Other AEs only includes those AEs that occurred prior to a patient receiving rescue medication.

Reporting Groups

	Description
Sitagliptin	The Sitagliptin group includes data from patients randomized to receive treatment with oral tablets of sitagliptin 100 mg q.d. (once daily) with glimepiride (≥4 mg/day) alone or in combination with metformin (≥1500 mg/day).
Placebo/ Pioglitazone	The Placebo group includes data from patients randomized to receive treatment with placebo to sitagliptin oral tablets q.d. with glimepiride (≥4 mg/day) alone or in combination with metformin (≥1500 mg/day).

Serious Adverse Events

	Sitagliptin	Placebo/ Pioglitazone
Total, serious adverse events		
# participants affected / at risk	**17/222 (7.66%)**	**13/219 (5.94%)**
Cardiac disorders		
Angina Pectoris * 1		
# participants affected / at risk	**2/222 (0.90%)**	**0/219 (0.00%)**
Cardio-Respiratory Arrest * 1		
# participants affected / at risk	**0/222 (0.00%)**	**1/219 (0.46%)**
Coronary Artery Disease * 1		
# participants affected / at risk	**2/222 (0.90%)**	**1/219 (0.46%)**
Coronary Artery Occlusion * 1		
# participants affected / at risk	**1/222 (0.45%)**	**0/219 (0.00%)**
Ischaemic Cardiomyopathy * 1		
# participants affected / at risk	**1/222 (0.45%)**	**0/219 (0.00%)**
Myocardial Infarction * 1		
# participants affected / at risk	**0/222 (0.00%)**	**1/219 (0.46%)**
Myocardial Ischaemia * 1		
# participants affected / at risk	**0/222 (0.00%)**	**1/219 (0.46%)**
Gastrointestinal disorders		
Abdominal Pain * 1		
# participants affected / at risk	**0/222 (0.00%)**	**1/219 (0.46%)**

General disorders		
Drowning [*1]		
# participants affected / at risk	**1/222 (0.45%)**	**0/219 (0.00%)**
Multi-Organ Failure [*1]		
# participants affected / at risk	**0/222 (0.00%)**	**1/219 (0.46%)**
Non-Cardiac Chest Pain [*1]		
# participants affected / at risk	**1/222 (0.45%)**	**0/219 (0.00%)**
Immune system disorders		
Hypersensitivity [*1]		
# participants affected / at risk	**0/222 (0.00%)**	**1/219 (0.46%)**
Infections and infestations		
Diabetic Foot Infection [*1]		
# participants affected / at risk	**0/222 (0.00%)**	**1/219 (0.46%)**
Meningitis [*1]		
# participants affected / at risk	**0/222 (0.00%)**	**1/219 (0.46%)**
Pneumonia [*1]		
# participants affected / at risk	**0/222 (0.00%)**	**1/219 (0.46%)**
Sepsis [*1]		
# participants affected / at risk	**0/222 (0.00%)**	**1/219 (0.46%)**
Injury, poisoning and procedural complications		
Fall [*1]		
# participants affected / at risk	**1/222 (0.45%)**	**0/219 (0.00%)**
Polytraumatism [*1]		
# participants affected / at risk	**1/222 (0.45%)**	**0/219 (0.00%)**
Musculoskeletal and connective tissue disorders		
Lumbar Spinal Stenosis [*1]		
# participants affected / at risk	**0/222 (0.00%)**	**1/219 (0.46%)**
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		
Glioblastoma Multiforme [*1]		
# participants affected / at risk	**0/222 (0.00%)**	**1/219 (0.46%)**
Keratoacanthoma [*1]		
# participants affected / at risk	**1/222 (0.45%)**	**0/219 (0.00%)**
Small Cell Lung Cancer Stage Unspecified [*1]		
# participants affected / at risk	**1/222 (0.45%)**	**0/219 (0.00%)**
Squamous Cell Carcinoma Of Skin [*1]		
# participants affected / at risk	**1/222 (0.45%)**	**0/219 (0.00%)**
Nervous system disorders		
Cerebellar Infarction [*1]		
# participants affected / at risk	**1/222 (0.45%)**	**0/219 (0.00%)**
Cerebral Infarction [*1]		

# participants affected / at risk	1/222 (0.45%)	0/219 (0.00%)
Cerebrovascular Accident * 1		
# participants affected / at risk	0/222 (0.00%)	1/219 (0.46%)
Convulsion * 1		
# participants affected / at risk	1/222 (0.45%)	0/219 (0.00%)
Pregnancy, puerperium and perinatal conditions		
Abortion Spontaneous * 1		
# participants affected / at risk	1/222 (0.45%)	0/219 (0.00%)
Psychiatric disorders		
Completed Suicide * 1		
# participants affected / at risk	1/222 (0.45%)	1/219 (0.46%)
Renal and urinary disorders		
Nephrolithiasis * 1		
# participants affected / at risk	1/222 (0.45%)	0/219 (0.00%)
Reproductive system and breast disorders		
Endometriosis * 1		
# participants affected / at risk	0/222 (0.00%)	1/219 (0.46%)
Ovarian Cyst * 1		
# participants affected / at risk	1/222 (0.45%)	0/219 (0.00%)
Respiratory, thoracic and mediastinal disorders		
Interstitial Lung Disease * 1		
# participants affected / at risk	1/222 (0.45%)	0/219 (0.00%)
Pulmonary Embolism * 1		
# participants affected / at risk	0/222 (0.00%)	1/219 (0.46%)
Vascular disorders		
Deep Vein Thrombosis * 1		
# participants affected / at risk	0/222 (0.00%)	1/219 (0.46%)

* Events were collected by non-systematic assessment
1 Term from vocabulary, MedDRA (9.0)

Other Adverse Events

Hide Other Adverse Events

Time Frame	Weeks 0 to 54
Additional Description	Patients received glycemic rescue medication if they met specific glycemic goals. SAEs includes events that occurred either before or after receiving rescue medication. Other AEs only includes those AEs that occurred prior to a patient receiving rescue medication.

Frequency Threshold

Threshold above which other adverse events are reported	5%

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Other Adverse Events

	Sitagliptin	Placebo/ Pioglitazone
Total, other (not including serious) adverse events		
# participants affected / at risk	**66/222 (29.73%)**	**57/219 (26.03%)**
Infections and infestations		
Nasopharyngitis * 1		
# participants affected / at risk	**19/222 (8.56%)**	**12/219 (5.48%)**
Upper Respiratory Tract Infection * 1		
# participants affected / at risk	**17/222 (7.66%)**	**20/219 (9.13%)**
Urinary Tract Infection * 1		
# participants affected / at risk	**12/222 (5.41%)**	**6/219 (2.74%)**
Investigations		
Blood Glucose Increased * 1		
# participants affected / at risk	**6/222 (2.70%)**	**11/219 (5.02%)**
Metabolism and nutrition disorders		
Hypoglycaemia * 1		
# participants affected / at risk	**30/222 (13.51%)**	**13/219 (5.94%)**
Nervous system disorders		
Headache * 1		
# participants affected / at risk	**14/222 (6.31%)**	**5/219 (2.28%)**

* Events were collected by non-systematic assessment

1 Term from vocabulary, MedDRA (9.0)

Limitations and Caveats

Hide Limitations and Caveats

Limitations of the study, such as early termination leading to small numbers of participants analyzed and technical problems with measurement leading to unreliable or uninterpretable data
No text entered.

More Information

Hide More Information

Certain Agreements:

Principal Investigators are **NOT** employed by the organization sponsoring the study.
There **IS** an agreement between Principal Investigators and the Sponsor (or its agents) that restricts the PI's rights to discuss or publish trial results after the trial is completed.
The agreement is: ☐ The only disclosure restriction on the PI is that the sponsor can review results communications prior to public release and can embargo communications regarding trial results for a period that is **less than or equal to 60 days**. The sponsor cannot require changes to the communication and cannot extend the embargo. ☐ The only disclosure restriction on the PI is that the sponsor can review results communications prior to public release and can embargo communications regarding trial results for a period that is **more than 60 days but less than or equal to 180 days**. The sponsor cannot require changes to the communication and cannot extend the embargo. Other disclosure agreement that restricts the right of the PI to discuss or publish trial results after the trial is completed. ☑ **Restriction Description:** Merck agreements may vary with individual investigators, but will not prohibit any investigator from publishing. Merck supports the publication of results from all centers of a multi-center trial but requests that reports based on single-site data not precede the primary publication of the entire clinical trial.

Results Point of Contact:

Name/Title: Senior Vice President, Global Clinical Development
Organization: Merck Sharp & Dohme Corp.
phone: 1-800-672-6372
e-mail: ClinicalTrialsDisclosure@merck.com

Publications:

Hermansen K, Kipnes M, Luo E, Fanurik D, Khatami H, Stein P; Sitagliptin Study 035 Group. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor, sitagliptin, in patients with type 2 diabetes mellitus inadequately controlled on glimepiride alone or on glimepiride and metformin. Diabetes Obes Metab. 2007 Sep;9(5):733-45. Epub 2007 Jun 26.

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