Name of Sponsor/Company: Bristol-Myers Squibb	Individual Study Table Referring to the Dossier	*(For National Authority Use Only)*
Name of Finished Product:		
Name of Active Ingredient:		

SYNOPSIS

Final Clinical study Report MB102003

TITLE OF STUDY: A Double-Blind, Placebo-Controlled, Randomized, Multiple-Dose Study to Evaluate the Safety, Pharmacokinetics, and Pharmacodynamics of BMS-512148 in Diabetic Subjects

INVESTIGATORS/STUDY CENTERS:

[redacted]

CLINICAL PHASE: 2a

PUBLICATIONS: None

STUDY PERIOD: Study Initiation Date: 06-Apr-2005

Study Completion Date: 25-Aug-2005

OBJECTIVES:

Primary Objective: To assess the safety and tolerability of multiple oral doses of BMS-512148 administered alone or concomitantly with metformin in diabetic subjects for 14 days.

Secondary Objectives:

- To assess the PK of BMS-512148 and its pharmacologically active metabolite, BMS-511926, when BMS-512148 is administered alone or concomitantly with metformin on Days 1 and 14.
- To assess the pharmacodynamic effect of BMS-512148, administered alone or concomitantly with metformin, on fasting and post-prandial serum glucose, serum fructosamine, serum insulin, serum C-peptide, urinary glucose and urinary calcium.
- To assess the effect of BMS-512148, administered alone or concomitantly with metformin, on the following safety markers in urine: calcium, magnesium, sodium, potassium, phosphate, chloride, uric acid, oxalate, citrate, total protein, albumin, osmolality, deoxypyridinoline (D-pyr) cross-links, C-telopetide (CTX), N-acetyl-β-D-glucosaminidase (NAG), and β2-microglubulin (β2-MG).

- To assess the effect of BMS-512148, administered alone or concomitantly with metformin, on the following safety markers in serum: osteocalcin, parathyroid hormone (PTH), 25-hydroxyvitamin D, and 1,25-dihydroxyitamin D.
- To assess the effect of BMS-512148 administered alone or concomitantly with metformin on the percent inhibition of renal glucose reabsorption
- To assess the effects of BMS-512148 on the PK of metformin in diabetic subjects.
- To identify potential biomarkers in both urine and blood.

METHODOLOGY: This was a double-blind, placebo-controlled, randomized, parallel group, multiple-dose study. Forty-seven (47) subjects were randomly assigned to 1 of 4 treatment groups: placebo, 5 mg, 25 mg, or 100 mg BMS-512148.

Subjects underwent screening evaluations to determine eligibility within 21 days prior to randomization. To assess for idiopathic hypercalciuria, a spot urine sample for calcium and creatinine was to be collected at the screening visit.

Subjects taking a stable dose of metformin for at least 4 weeks were maintained on their maintenance dose throughout the study.

Subjects began a fixed calorie, carbohydrate, phosphate, calcium, and sodium chloride diet on Day -6 (enrollment). This diet was to last for the duration of the study. Several baseline measurements were performed prior to receiving BMS-512148 or placebo on Day 1. Subjects were fasted on the evening of Day 3 (from approximately 10 h prior to the anticipated time of dosing on Day 1). Measurements on Day 2 included collection of blood samples for clinical lab assessments and an Oral Glucose Tolerance Test (OGTT). The OGTT began at 0 h (relative to the anticipated time of dosing on Day 1) when subjects were given a 75 gram glucola oral solution. Serum glucose and insulin were measured for 4 hours.

The baseline assessments on Day -1 included collection of a urine sample over a 24 h period (from the second void on Day -1 to the first void on Day 1) for measurement of glucose (measured at 4 h intervals), calcium, creatinine, magnesium, sodium, potassium, phosphate, chloride, uric acid, oxalate, citrate, total protein, albumin, osmolality, D-pyr cross-links, CTX, NAG, and β2-MG. Serial blood samples were collected for serum concentrations of insulin, C-peptide, and glucose. A blood sample for the assessment of serum fructosamine and serum creatinine was also collected at 0 h and 12 h respectively. In addition, a blood sample was collected for the evaluation of the safety markers PTH, osteocalcin, 25-hydroxyvitamin D, and 1,25-dihydroxyvitamin D. Subjects began fasting on the evening of Day 2 (from approximately 8h prior to the anticipated time of dosing on Day 1) and continued fasting on Day -1 until the collection of the 8 h blood sample. On Day 1, subjects received a single oral dose BMS-512148 or matched placebo and continued to receive the same dose once-daily for 14 days.

Blood and urine samples for PK and PD (serum fructosamine, insulin, C-peptide, and glucose) assessments were collected from all subjects on Days 1 and 14. Subjects began fasting on the evening (from 8 h prior to the anticipated clock time corresponding to study drug administration) of Days 1 and 13. Additional blood samples were collected on Days 2, 4, 6, and 15 for plasma concentrations of BMS-512148 and BMS-511926. Subjects continuing treatment with metformin had blood samples taken for PK assessment of this agent on Days -1 and Day 14. Subjects began fasting on the evening (from 8 h prior to the anticipated clock time corresponding to anticipated time of dosing on Day 1) of Days -2 and 13.

On Days 1, 2 and 3 urine samples were collected over a 24 h period to measure magnesium, sodium, potassium, phosphate, chloride, uric acid, oxalate, citrate, total protein, albumin, osmolality, and calcium. Glucose (measured at 4 h intervals) and creatinine were included on Day 1. The urine collection on these days began from the second void and continued through the first void of the next day (Days 2, 3, and 4 respectively). In addition, urine collection was performed over a 24 h period on Day 8 for measurement of calcium, glucose (measured at 4 h intervals), and creatinine, Day 13 for measurement of calcium, chloride,

magnesium, oxalate, potassium, phosphate, sodium, uric acid, citrate, total protein, albumin, osmolality, D-pyr cross-links, CTX, NAG, and β2-MG and Day 14 for glucose (measured at 4 h intervals) and creatinine. The urine collection on Days 8, 13, and 14 began from the second void and continued through the first void of the next day (i.e., Day 9, 14 and 15 respectively). Urine volume was measured at all 24 intervals.

A blood sample was collected at 12 h for the assessment of serum creatinine on Days 8 and 14. A blood sample was also collected for serum concentrations of PTH, osteocalcin, 25-hydroxyvitamin D, and 1,25-dihydroxyvitamin D on Day 13. On Days 2 and 13 after a 10 h fast, subjects were given a standardized OGTT (75 g of glucose) at 0 h relative to time of dosing and serum glucose and insulin were measured for 4 hours.

The meal schedule and meal content were identical on the days samples were collected for PK and/or PD assessments (Days -2, -1, 1, 2, 8, 13, and 14).

Subjects were released from the clinical facility on Day 15. Subjects were requested to return to the clinical facility on Day 21 for study discharge procedures.

Physical examinations, vital sign measurements, and clinical laboratory evaluations were performed at selected times throughout the study.

Subjects were closely monitored for adverse events (AEs) throughout the study.

NUMBER OF SUBJECTS (Planned and Analyzed): A total of 47 subjects were enrolled into this study. One (1) subject discontinued prior to completing the study. Thirty-nine (39) subjects received BMS-512148 and 8 subjects received placebo.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION: Subjects with Type 2 Diabetes mellitus (T2DM), male or female, between the ages of 18 to 70 years, inclusive. Female subjects must not have been nursing, pregnant, or of childbearing potential. Subjects must have been treated with metformin or diet alone (drug naive). Subjects must have had a fasting glucose (FG) ≤ 240 mg/dl, and a hemoglobin A1c between 6.0 and 10.0% inclusive while on their current permitted antidiabetic agent or diet. All subjects must have been otherwise considered healthy as determined by medical history, physical examination, 12-lead electrocardiogram, and clinical laboratory evaluations to be eligible to participate in the study. Subjects must also have been able to demonstrate acceptable renal (defined by a serum creatinine ≤ 1.4 mg/dL for women and 1.5 mg/dL for men) and liver function (defined by an alanine aminotransferase ≤ 1.5 x upper limit of normal (ULN) and total serum bilirubin of ≤ 2x ULN. Women must have had a negative pregnancy test within 24 hours prior to start of study medication.

TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, DURATION OF TREATMENT, BATCH NUMBERS: On Day 1, subjects meeting criteria for inclusion were randomized to 1 of 4 dose groups. Subjects received a daily oral dose of 5 (Treatment B), 25 (Treatment C), or 100mg (Treatment D) BMS 512148 for 14 days.

Test product was supplied by Bristol-Myers Squibb as listed in the following table:

MB102003: Drug Information

Unit	Formulation	Product ID Number	Route	Label Batch Number	Product Batch Number
2.5 mg BMS-512148	[redacted]		Oral	[redacted]	
10 mg BMS-512148			Oral		
100 mg BMS-512148			Oral		
Placebo to match 2.5 mg			Oral		
Placebo to match 10 mg			Oral		
Placebo to match 100 mg			Oral		

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, DURATION OF TREATMENT, BATCH NUMBERS: Subjects randomized to dose group 1 (Treatment A) received a daily oral dose of placebo to match BMS-512148 for 14 days.

Reference therapy was supplied by Bristol-Myers Squibb as listed in the following table:

MB102003: Drug Information

Unit	Formulation	Product ID Number	Route	Label Batch Number	Product Batch Number
Placebo to match 2.5 mg	[redacted]		Oral	[redacted]	
Placebo to match 10 mg			Oral		
Placebo to match 100 mg			Oral		

CRITERIA FOR EVALUATION:

Safety: Safety assessments were based on medical review of adverse event reports and the results of vital sign measurements, electrocardiograms, physical examinations, and clinical laboratory tests. The incidence of AEs was tabulated and reviewed for potential significance and clinical importance. The following urine safety markers were assessed: calcium, magnesium, sodium, potassium, phosphate, chloride, uric acid, oxalate, citrate, total protein, albumin, osmolality, D-pyr cross-links, CTX, NAG, and β2-MG. The following serum safety markers will be assessed: osteocalin, PTH, 25-hydroxyvitamin D, and 1,25-dihydroxyvitamin D.

Pharmacokinetics: Pharmacokinetic parameters (Cmax, Cmin, Tmax, AUC(TAU), T-HALF, percent urinary recovery [%UR], CLR, accumulation index [AI], and molar ratio [MR] of metabolite to parent) were derived from BMS plasma concentration versus time and urinary excretion data.

Pharmacodynamics: Fasting and post-prandial serum glucose, serum fructosamine, serum insulin, serum c-peptide, the total amount of glucose excreted in the urine over a dosing interval, the total amount of calcium excreted in the urine over a dosing interval, and the percent inhibition of renal glucose reabsorption over a dosing interval.

STATISTICAL METHODS:

Sample Size: Although the number of subjects was not based on statistical power considerations, administration of BMS-512148 to 8 or 16 subjects in each group provided 80% probability of observing at least one occurrence of any adverse event in a group which would have occurred with 18% or 10% incidence respectively, in the population from which the sample was drawn.

Statistical Methods: PK Analyses: Summary statistics were tabulated for the PK parameters by BMS-512148 dose and study day, for each analyte.

PD Analyses: Summary statistics were tabulated for the total amount of glucose excreted in urine over 24 hours, and for the changes from baseline, by treatment and study day. The mean for the total amount of glucose excreted in urine 24 hours were plotted versus study day, for all treatments. Summary statistics were also tabulated for the rate of glucose excretion over each collection interval, by treatment and study day. The mean for the rate of glucose excretion over each collection interval was plotted versus midpoint of each collection interval, for each study day and for all treatments.

Serum glucose AUC values over 4 hours following OGTT were summarized by BMS-512148 dose and study day.

Summary statistics were tabulated for the total amount of calcium excreted in urine over 24 hours (absolute and corrected for creatinine), and for the changes from baseline, by treatment and study day. The mean for the changes from baseline in the total amount of calcium excreted in urine over 24 hours (absolute and corrected for creatinine excretion) was plotted versus study day for all treatments.

Summary statistics were tabulated for the percent inhibition of renal glucose resorption over each collection interval, by treatment and study day. The mean for the percent inhibition of renal glucose resorption over each collection interval was plotted versus midpoint of each collection interval, for each study day and for all treatments.

Serum fructosamine concentrations and the corresponding changes from baseline were tabulated by treatment and study day. Serum glucose concentrations and the corresponding changes from baseline were tabulated by treatment, study day and time point. Similar analyses were performed on serum insulin and serum c-peptide.

Summary statistics were tabulated for the insulinogenic index and insulin sensitivity by treatment and study day.

Safety Analyses: For each safety marker in urine, summary statistics were tabulated for the total amount excreted in urine over 24 hours (absolute and corrected for creatinine), and for the corresponding changes from baseline, by treatment and study day.

For each safety marker in serum, summary statistics were tabulated for the serum concentration values and for the corresponding changes from baseline, by treatment and study day.

Analysis: Statistical analyses were performed by the Global Biometric Sciences Department of the Bristol-Myers Squibb Pharmaceutical Research Institute. All available data from all subjects who received study medication were included in the summaries of physical examination findings, clinical laboratory data, vital signs, and AEs.

SUMMARY OF RESULTS:

Demographics and Other Pertinent Baseline Characteristics:

Demographic Characteristics

Characteristic	BMS-512148 DOSE PANELS			Treatment A (Placebo) n=8
	Treatment B (5 mg) n=11	Treatment C (25 mg) n=12	Treatment D (100 mg) n=16	
Age, years				
Mean	58	55	60	57
SD	7	6	5	10
Range	44-67	47-67	53-68	36-66
Gender, n (%)				
Male	3 (27)	6 (50)	6 (38)	4 (50)
Female	8 (73)	6 (50)	10 (63)	4 (50)
Race, n (%)				
White	8(73)	12(100)	14(88)	6(75)
Black or African American	3(27)	0	1(6)	1(13)
Asian	0	0	0	1(13)
American Indian/Alaskan	0	0	0	0
Other Race	0	0	0	0
	0	0	1(6)	0
Weight (kg)				
Mean	86.5	91.1	83.7	85.1
SD	16.6	20.9	18.6	17.4
Range	69.0-123.0	63.0-128.3	58.4-110.0	60.0-115.2

Demographic Characteristics

Characteristic	BMS-512148 DOSE PANELS			Treatment A (Placebo) n=8
	Treatment B (5 mg) n=11	Treatment C (25 mg) n=12	Treatment D (100 mg) n=16	
Height (cm)				
Mean	159.7	168.1	161.8	163.3
SD	10.0	8.6	11.1	7.3
Range	148.0-180.0	158.0-181.5	146.5-185.5	153.9-173.0
Body Mass Index, (kg/m^2)				
Mean	33.9	32.2	31.8	31.9
SD	5.2	6.8	5.2	5.7
Range	27.5-41.8	23.2-41.4	23.4-41.6	23.7-41.6

MB102003

Source: Appendix 8.3, Supplemental Tables S.8.3A and S.8.3B

Abbreviations: SD, standard deviation

Efficacy Results: Not applicable.

Safety Results:

There were no deaths or discontinuations due to AEs. Four (4) serious adverse events (SAEs) occurred in 2 non-randomized subjects (ie, after the subjects had signed the informed consent and undergone screening procedures, but prior to entering the study).

A total of 56 AEs that counted occurred in 27 subjects. Of these events, 37 occurred in 20 of the 39 subjects (51.3%) who received BMS-512148. Nineteen (19) AEs occurred in 7 of the 8 subjects (87.5%) who received placebo. The incidence of AEs was slightly lower in subjects who received BMS-512148 versus placebo and did not appear to be dose-related. This was also the case for subjects who were continued on metformin.

The most frequently reported treatment-emergent AEs in this study were gastrointestinal in nature and included constipation, reported by 7 subjects (3 subjects received BMS-512148 alone (1 at 5 mg, 1 at 25 mg, and 1 at 100 mg), 1 subject received BMS-512148 100 mg plus metformin; 1 subject received placebo alone; 2 subjects received placebo plus metformin), nausea reported by 5 subjects all on metformin (2 subjects received 5 mg BMS-512148 plus metformin, 2 subjects received 100 mg BMS-512148 plus metformin, 1 subject received placebo plus metformin), and diarrhea reported by 4 subjects all on metformin, (3 subjects received BMS-512148 plus metformin [1 at 5 mg, and 2 at 100 mg BMS-512148], 1 subject received placebo plus metformin). All of these events were mild in intensity with the exception of 1 AE of constipation, which was reported as severe in a subject who received placebo plus metformin.

One (1) AE (flank pain) was reported to be severe in intensity in a subject who received 5 mg BMS-512148 plus metformin. This AE was judged by the Investigator to be possibly related to study drug. This subject was treated with a heating pad and resolved the following day.

AEs of clinical interest included hypoglycemia and vulvovaginal mycotic infection, each reported in 2 subjects. One (1) subject received 5 mg BMS-512148 plus metformin and experienced a mild AE of hypoglycemia and 1 subject received 25 mg BMS-512148 plus metformin and experienced a moderate AE of hypoglycemia. Both AEs resolved soon after receiving treatment with 10 oz of orange juice. Vulvovaginal mycotic infection was reported by 2 subjects, 1 who received 100 mg BMS-512148 plus metformin and 1 subject who received 25 mg BMS-512148 alone. Both occurrences of vulvovaginal mycotic infection were considered to be mild in intensity and resolved after miconazole treatment.

The frequencies of AEs mapping to a specific system organ class or described by a specific preferred term were not appreciably higher in subjects who received BMS-512148 compared with subjects who received placebo except possibly asthenia, dizziness, hypoglycemia and vulvovaginal mycotic infection. Three (3) subjects each receiving BMS-512148 reported dizziness or asthenia, while no subject receiving placebo reported these AEs. However, all 3 subjects reporting dizziness also received metformin, and 2 of 3 subjects reporting asthenia also received metformin. No dose-related trends were observed. AEs which occurred only in subjects receiving metformin plus BMS-512148 or placebo included: nausea, diarrhea, dizziness, and hypoglycemia.

Few hematology or serum chemistry MAs occurred in either the BMS-512148 or placebo groups. There was no apparent relationship between the frequency of chemistry or hematology MAs and dose. Marked elevations in urine glucose was noted in most subjects who received BMS-512148. This elevated urine glucose was expected and directly related to the pharmacodynamic action of BMS-512148. No MA was considered by the Investigator to be an adverse event.

There was no apparent affect of BMS-512148, administered alone or concurrently with metformin on, any of the biomarkers for bone resorption, general renal tubular function, or renal tubule toxicity. In addition, there were no clinically relevant vital sign abnormalities, ECG abnormalities or physical examination

findings. ECGs were collected only at screening and at the end of dosing. No subject had an ECG with a QT interval that was greater than 500 msec or an increase in QTc > 60 msec.

In summary, multiple oral doses of 5, 25, and 100 mg BMS-512148 administered alone or plus metformin in diabetic subjects for 14 days was determined to be safe and generally well tolerated. Analysis of all secondary urine and serum safety markers appear to indicate no appreciable difference in any of these parameters between subjects who received placebo and subjects randomized to any of the active groups.

Pharmacokinetic: The pharmacokinetic results were determined using a validated noncompartmental analysis.

BMS-512148 and BMS 511926 Pharmacokinetics

Cmax and AUC(TAU) values of BMS-512148 increased approximately equal to the increment in dose in subjects administered 5 and 25 mg, and increased slightly more than the increment in dose in subjects administered 100 mg BMS-512148. An AI of approximately 1.3 (range: 1.2 - 1.3) was observed for BMS-512148 and BMS-511926 upon repeated daily dosing of BMS 512148 on Day 14 within each dose panel.

BMS-512148 was rapidly absorbed after oral administration with a median Tmax values of 1 hour (range: 0.5 to 4.0 h). Concentrations of BMS-511926, an active metabolite of BMS-512148, were observed only at doses of 25 and 100 mg BMS-512148 and median Tmax values ranged from 1.0 to 1.5 h (range: 1.0 to 4.0 h). BMS-512148 T-HALF values observed in this study ranged from 5.4 to 12.6 h [shorter than the T-HALF value of approximately 17 h observed reported in the single ascending dose study in healthy subjects (MB102001)]. The shorter T-HALF observed in this study is likely a result of only sampling out to 24 h post-dose, versus 120 h post-dose in the single ascending dose study.

Renal elimination did not play a significant role in the elimination of BMS 512148. After 14 days of dosing, approximately 2.5% and 0.1 % of the dose of BMS-512148 was excreted in the urine as BMS-512148 and BMS-511926, respectively. The mean renal clearance values for BMS 512148 and BMS-511926 ranged from 3 to 6 mL/min and 49 to 128 mL/min (25 and 100 mg doses only), respectively. Additional studies are needed to further clarify the mechanisms by which BMS-512148 is removed from the body.

The pharmacokinetics of BMS-512148 are summarized in the following table:

Summary Statistics for BMS-512148 Pharmacokinetic Parameters

Pharmacokinetic Parameter	BMS-512148 Dose	Study Day	
		Day 1	Day 14
Cmax (ng/mL)	5 mg (n=11)	66 (37)	68[c] (32)
Geometric Mean	25 mg (n=12)	279 (19)	288 (41)
(C.V. %)	100 mg (n=16)	1490 (40)	1617[b] (46)
AUC(TAU) (ng·h/mL)	5 mg (n=11)	220 (32)	281[c] (28)
Geometric Mean	25 mg (n=12)	1037 (25)	1373 (31)
(C.V. %)	100 mg (n=16)	5427 (30)	7070[b] (36)
A.I.	5 mg (n=11)	-- --	1.23[c] (16)
Geometric Mean	25 mg (n=12)	-- --	1.32 (17)
(C.V. %)	100 mg (n=16)	-- --	1.33[b] (11)

Summary Statistics for BMS-512148 Pharmacokinetic Parameters

Pharmacokinetic Parameter	BMS-512148 Dose	Study Day	
		Day 1	Day 14
Tmax (h)	5 mg (n=11)	1.00 (0.50, 2.00)	1.00[c] (0.50, 2.00)
Median	25 mg (n=12)	1.00 (1.00, 2.00)	1.00 (1.00, 2.00)
(Min, Max)	100 mg (n=16)	1.00 (1.00, 4.00)	1.00[b] (0.50, 4.00)
%UR	5 mg (n=11)	1.44 (0.75)	2.02[c] (1.21)
Mean	25 mg (n=12)	0.83 (0.34)	1.28 (0.66)
(S.D.)	100 mg (n=16)	1.49 (0.80)	2.41[b] (0.90)
CLR (mL/min)	5 mg (n=11)	5.88 (4.07)	6.37[c] (3.91)
Mean	25 mg (n=12)	3.44 (1.83)	3.95 (2.47)
(S.D.)	100 mg (n=16)	4.41 (1.89)	5.50[b] (1.89)

Note: Day 14 data from Subjects [redacted] were excluded from the summary statistics.

a: n=11

b: n=14

c: n=10

The pharmacokinetics of BMS-511926 are summarized in the following table:

Summary Statistics for BMS-511926 Pharmacokinetic Parameters

Pharmacokinetic Parameter	BMS-512148 Dose	Study Day	
		Day 1	Day 14
Cmax (ng/mL)	5 mg	-- --	-- --
Geometric Mean	25 mg (n=8)	1.89 (53)	1.88 (36)
(C.V. %)	100 mg (n=16)	7.56 (47)	8.96[b] (49)
AUC(TAU) (ng·h/mL)	5 mg	-- --	-- --
Geometric Mean	25 mg	-- --	-- --
(C.V. %)	100 mg (n=16)	37[b] (32)	48[b] (43)
A.I.	5 mg	-- --	-- --
Geometric Mean	25 mg	-- --	-- --
(C.V. %)	100 mg (n=16)	-- --	1.39[c] (17)
Tmax (h)	5 mg	-- --	-- --
Median	25 mg (n=8)	1.50 (1.00, 2.00)	1.50 (1.00, 2.00)
(Min, Max)	100 mg (n=16)	1.50 (1.00, 4.00)	1.00[b] (1.00, 4.00)
T-HALF (h)	5 mg	-- --	-- --
Mean	25 mg	-- --	-- --
(S.D.)	100 mg (n=16)	2.94[b] (1.45)	4.75[b] (2.63)

Summary Statistics for BMS-511926 Pharmacokinetic Parameters

Pharmacokinetic Parameter	BMS-512148 Dose	Study Day	
		Day 1	Day 14
%UR	5 mg (n=11)	0.13 (0.04)	0.14[d] (0.06)
Mean	25 mg (n=12)	0.05 (0.02)	0.07 (0.03)
(S.D.)	100 mg (n=16)	0.07 (0.04)	0.12[b] (0.08)
CLR (mL/min)	5 mg	-- --	-- --
Mean	25 mg	-- --	-- --
(S.D.)	100 mg (n=16)	49 (17)	50[b] (20)
MR	5 mg	-- --	-- --
Geometric Mean	25 mg	-- --	-- --
(C.V. %)	100 mg (n=16)	0.01[b] (29)	0.01[b] (29)

Note: Day 14 data from Subjects [redacted] were excluded from the summary statistics. Molar ratio was calculated as (BMS-511926 AUC(TAU)/BMS-512148 AUC(TAU))*(408/380).

a: n=13

b: n=14

c: n=12

d: n=10

Metformin Pharmacokinetics

Although this study was not powered to conclude an absence of effect of BMS-512148 on the pharmacokinetics of metformin, the present results indicate that there is no apparent effect of multiple doses of BMS-512148 on the pharmacokinetics of metformin when administered for 14 days. When BMS-512148 was co-administered, the geometric means for Cmax and AUC(TAU) of metformin increased by 6% and 11%, respectively, relative to those observed following administration of metformin alone.

Pharmacodynamic Results: The cumulative amount of glucose eliminated in the urine over 24 h at doses of 25 and 100 mg was similar after the first dose and after 14 days of BMS-512148 administration. The cumulative 24 h urine glucose values following 5 mg BMS-512148 were approximately 50% of the amounts observed at doses of 25 and 100 mg BMS 512148.

On Day 8, subjects administered 5 and 25 mg BMS-512148 had 24 h urine glucose values that were increased by approximately 110 and 81%, respectively, when compared to Day 1 values, whereas the Day 14 values were similar to the Day 1 values. A definitive explanation for this apparent increase on Day 8 only in subjects administered 5 and 25 mg BMS 512148 was not determined. However, 7 of the 10 subjects enrolled at one clinical site had an increase in their average Day 8 cumulative 24 h urine glucose value by approximately 177% compared to the Day 1 value. Per randomization assignment (and consistent with PK data), all 7 subjects were administered either 5 or 25 mg BMS-512148. In contrast, all subjects from the remaining 4 clinical sites had Day 8 24 h urine glucose values less than 20% above their Day 1 values. Additionally, the same 7 subjects that had increased Day 8 cumulative 24 h urine glucose values also had an increase in their Day 8 urine volume of 379% compared to Day 1. In contrast, all subjects from the remaining 4 clinical sites had Day 8 urine volumes that were increased by less than 15%.

In subjects administered placebo, mean cumulative amounts of glucose in the urine on Days 1 and 14 were low and remained virtually unchanged from baseline levels at all time points. On Day 8, Subject

[redacted]assigned to placebo) had a cumulative 24 h urine glucose value of 98.7 g versus values of 0.6 and 3.0 on Days 1 and 14, respectively. While glucosuria of this magnitude is suggestive that this subject was mistakenly administered BMS-512148, pharmacokinetic sampling was not performed on this day and therefore a medication error could not be documented.

The administration of a multiple oral doses of 5, 25 or 100 mg of BMS 512148 did not change the cumulative amount of calcium in the urine or the rate of calcium elimination versus placebo over the 24 h post dose interval after 1, 8 or 14 days of dosing.

Subjects administered 25 and 100 mg BMS-512148 appeared to have a greater reduction in fasting serum glucose compared to subjects administered placebo or 5 mg BMS 512148. There was no apparent difference in the fasting serum glucose profiles between subjects administered placebo and 5 mg BMS-512148.

Following an OGTT, the mean serum glucose 4 h AUC on BMS 512148 was lower than the corresponding placebo values. There was no clear dose-dependency in the extent of reduction of glucose 4 h AUC values over the BMS 512148 dose range studied, perhaps due to the small number of subjects in each group. Lower glucose 4 h AUC values were observed on Day 13 compared to Day 2 in BMS-512148-treated subjects.

Doses of 25 and 100 mg BMS-512148 appeared to provide the maximal percent inhibition of renal glucose resorption. Pre BMS 512148 administration in all subjects. Therefore, in all subjects, despite fasting serum glucose levels of up to 240 mg/dL, approximately 100% of filtered glucose was reabsorbed by the kidney (Day -1). Therefore, in all dose panels, predose renal glucose clearance was approximately 0. However, after administration of a single dose of 5, 25 and 100 mg BMS-512148, glucose clearance increased to approximately 19.4, 35.2 and 35.1 mL/min, respectively, corresponding to inhibition of glucose resorption by approximately 19.5, 33.6 and 36.2%, respectively. There were no apparent further increases in the degree of inhibition of glucose resorption from Day 1 to Day 14 within any dose group.

Serum insulin levels did not appear to change in subjects administered BMS-512148. While HOMA-IR and percent beta cell function analysis results suggested a possible increase in insulin sensitivity and beta cell function in subjects administered BMS-512148, the large variability in data makes a definitive assessment difficult.

CONCLUSIONS:

- [redacted]

- [redacted]

DATE OF REPORT: 21-Dec-2006