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

2 SYNOPSIS

SPONSOR:	Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.	
COMPOUND NAME:	MK-3102	
INDICATION:	Diabetes	
PROTOCOL TITLE:	A 66-Week Extension to: A Phase IIb, Randomized, Placebo-Controlled, Dose-Range Finding Clinical Trial to Study the Safety and Efficacy of MK-3102 in Patients with Type 2 Diabetes Mellitus and Inadequate Glycemic Control	
TRIAL IDENTIFIERS:	Protocol Number:	006-13
	Clinical Phase:	IIb
	EudraCT Number:	2010-022193-13 for all countries except Finland and Lithuania 2011-000656-42 for Finland and Lithuania
ETHICS:	This trial was conducted in conformance with applicable country or local requirements regarding ethical committee review, informed consent, and other statutes or regulations regarding the protection of the rights and welfare of human subjects participating in biomedical research. [redacted]	
TRIAL CENTERS:	This trial was conducted in 112 trial centers which received study drug worldwide including, 27 sites in US, 41 in Asia, 22 in Europe, 7 in South America and 15 in other countries around the world.	

DESIGN:	This was a 66-week extension to MK-3102 P006, a multicenter, double-blind, randomized, placebo-controlled, dose-range finding study. This trial was designed to assess the long-term safety and tolerability of MK-3102, dosed once-weekly (q.w.), in patients with T2DM who have inadequate glycemic control on diet and exercise. [redacted]	
	Planned duration of main phase: Planned duration of run-in phase: Planned duration of extension phase:	not applicable not applicable 66 Weeks
Objectives	After 78 weeks, in patients with T2DM who have inadequate glycemic control on diet and exercise: Primary: To assess the safety and tolerability of MK-3102 treatment. Secondary: (1) To assess the changes from baseline in A1C with MK-3102 treatment. (2) To assess the changes from baseline in 2-hour Post-Meal Glucose (PMG) with MK-3102 treatment. (3) To assess the changes from baseline in fasting plasma glucose (FPG) with MK-3102 treatment. Exploratory: To assess the changes from baseline in body weight with MK-3102 treatment.	
Hypotheses	There is no hypothesis testing in the extension study.	
Treatments groups	MK-3102 25 mg capsules or matching placebo administered once-weekly (q.w.)	405 Patients Randomized
	Pioglitazone 30 mg or matching placebo administered as two 15 mg oral tablets or capsules, once-daily (q.d.).	80 Patients Randomized
	Metformin or matching placebo administered in a blinded manner, as 500 mg tablets at a starting dose of 500 mg once daily up-titrated to 1000 mg b.i.d.	Note: Due to removal of pioglitazone in the extension study, subjects discontinued pioglitazone 30 mg and switched to blinded metformin after blinded metformin supplies became available at the sites.

Clinical Supplies Dispensed to Subjects

Drug	Potency	Formulation Number	Dosage Form	Control Number
MK-3102	25mg	[redacted]	Capsule	[redacted]
MK-3102	25mg		Capsule	
MK-3102	25mg Placebo		Capsule	
Pioglitazone (US)	15mg		Tablet	
Pioglitazone (US)	15mg		Tablet	
Pioglitazone (US)	15mg		Tablet	
Pioglitazone (UK)	15mg		Tablet	
Pioglitazone (UK)	15mg		Tablet	
Pioglitazone O/E (UK)	15mg		Capsule	
Pioglitazone O/E (UK)	15mg		Capsule	
Pioglitazone	15mg Placebo		Tablet	
Pioglitazone (O/E)	15 mg Placebo		Capsule	
Pioglitazone (O/E)	15 mg Placebo		Capsule	
Metformin	500mg		Tablet	
Metformin	500 mg Placebo		Tablet	
Metformin	500 mg Placebo		Tablet	
Metformin	500 mg Placebo		Tablet	
Glimepiride (rescue)	1mg		Tablet	
Glimepiride (rescue)	2mg		Tablet	

Endpoints and definitions	Key efficacy endpoints	A1C (%) 2-hour PMG (mg/dL) FPG (mg/dL) Body weight (kg)	1. Change from baseline in A1C at Week 78 2. Change from baseline in 2-hour PMG at Week 78 3. Change from baseline in FPG at Week 78 4. Change from baseline in body weight at Week 78
	Safety endpoints	Overall safety Tier 1 hypoglycemia Patients meeting (PDLC) in laboratory parameters Laboratory parameters, ECG, lipids and vital signs.	Tier 1 safety endpoints are adverse events of symptomatic hypoglycemia Other safety endpoints include adverse experiences, additional hypoglycemia endpoints, percentages of patients meeting predefined limits of change in laboratory parameters, change (or percent change) from baseline at Week 78 in laboratory parameters, ECG, lipids and vital signs.
Database lock	1-May-2013	Trial status	14-Feb-2011 *first subject first visit* to 1-Apr-2013 *last subject last visit trial completed*
RESULTS AND ANALYSIS:	All analyses for efficacy and safety were performed according to the protocol.		

Patient Characteristics
Demographic and Anthropometric Characteristics
(All Patients who Entered in Extension)

	Placebo/Metformin		Pooled MK-3102		Total	
	n	(%)	n	(%)	n	(%)
Patients in population	80		405		485	
Gender						
Male	49	(61.3)	230	(56.8)	279	(57.5)
Female	31	(38.8)	175	(43.2)	206	(42.5)
Age (Years)						
<65	67	(83.8)	345	(85.2)	412	(84.9)
>=65	13	(16.3)	60	(14.8)	73	(15.1)
Mean	56.0		55.1		55.3	
SD	8.1		8.9		8.8	
Median	57.5		56.0		56.0	
Range	32 to 69		24 to 70		24 to 70	
Race						
American Indian Or Alaska Native	2	(2.5)	17	(4.2)	19	(3.9)
Asian	28	(35.0)	124	(30.6)	152	(31.3)
Black Or African American	2	(2.5)	17	(4.2)	19	(3.9)
Multi-Racial	7	(8.8)	25	(6.2)	32	(6.6)
Native Hawaiian Or Other Pacific Islander	1	(1.3)	4	(1.0)	5	(1.0)
White	40	(50.0)	218	(53.8)	258	(53.2)
Ethnicity						
Hispanic Or Latino	23	(28.8)	99	(24.4)	122	(25.2)
Not Hispanic Or Latino	57	(71.3)	306	(75.6)	363	(74.8)
Body Weight (kg)						
Patients with data	80		405		485	
Mean	80.9		82.3		82.1	
SD	20.4		17.5		18.0	
Median	81.0		80.9		80.9	
Range	40.5 to 153.3		40.0 to 139.0		40.0 to 153.3	
Body Mass Index (kg/m2)						

Patient Characteristics
Demographic and Anthropometric Characteristics
(All Patients who Entered in Extension)

	Placebo/Metformin		Pooled MK-3102		Total	
	n	(%)	n	(%)	n	(%)
Body Mass Index (kg/m2)						
Patients with data	80		404		484	
Mean	29.1		29.8		29.7	
SD	5.5		5.2		5.3	
Median	29.1		29.4		29.4	
Range	18.0 to 42.9		18.2 to 42.1		18.0 to 42.9	
Region						
North America (USA, Canada)	12	(15.0)	78	(19.3)	90	(18.6)
Latin America (including Mexico)	14	(17.5)	59	(14.6)	73	(15.1)
Europe (including Russia)	19	(23.8)	111	(27.4)	130	(26.8)
Asia (excluding Japan)	7	(8.8)	24	(5.9)	31	(6.4)
Other (Australia, New Zealand, South Africa)	9	(11.3)	41	(10.1)	50	(10.3)
Japan	19	(23.8)	92	(22.7)	111	(22.9)

Disposition of Patients
(All Patients who Entered in Extension)

	Placebo/Metformin		Pooled MK-3102		Total	
	n	(%)	n	(%)	n	(%)
Patients in population	80		405		485	
Study Disposition						
Completed	60	(75.0)	314	(77.5)	374	(77.1)
Discontinued	20	(25.0)	91	(22.5)	111	(22.9)
Adverse Event	5	(6.3)	19	(4.7)	24	(4.9)
Alt/Ast	0	(0.0)	2	(0.5)	2	(0.4)
Contraindication To Study Medication	0	(0.0)	1	(0.2)	1	(0.2)
Creatinine/Egfr	1	(1.3)	11	(2.7)	12	(2.5)
Death	0	(0.0)	1	(0.2)	1	(0.2)
Excluded Medication	0	(0.0)	2	(0.5)	2	(0.4)
Lack Of Efficacy	0	(0.0)	3	(0.7)	3	(0.6)
Lost To Follow-Up	1	(1.3)	9	(2.2)	10	(2.1)
Non-Compliance With Study Drug	1	(1.3)	0	(0.0)	1	(0.2)
Physician Decision	1	(1.3)	4	(1.0)	5	(1.0)
Protocol Violation	1	(1.3)	2	(0.5)	3	(0.6)
Site Discontinued Study Participation	2	(2.5)	7	(1.7)	9	(1.9)
Withdrawal By Subject	8	(10.0)	30	(7.4)	38	(7.8)
Each patient is counted once for Study Disposition based on the latest corresponding disposition record.						

Analysis description	Key Efficacy Analysis: Change from baseline in A1C, 2-hour PMG and FPG at Week 78 Statistical methodology: longitudinal data analysis (LDA) model controlling for treatment, prior AHA therapy status (yes/no), geographic region (Japan/ex-Japan), and the interaction of time by treatment, time by prior AHA therapy status.
Analysis population and time point description	Extension FAS population: consists of all randomized patients who receive at least one dose of extension study treatment, have baseline and at least one post-randomization observation for the analysis endpoint subsequent to at least one dose of extension study treatment.
Summary	The results show that, compared to baseline, all treatment groups had reductions in A1C, 2-hour PMG and FPG at Week 78, as generally reflected by the point estimates and 95% CIs.
Analysis description	Other efficacy analysis: Change from baseline in body weight at Week 78 Statistical methodology: longitudinal data analysis (LDA) model controlling for treatment, prior AHA therapy status (yes/no), geographic region (Japan/ex-Japan), and the interaction of time by treatment, time by prior AHA therapy status.
Analysis population and time point description	Extension FAS population
Summary	No meaningful change from baseline in body weight was observed in the MK-3102 treatment groups.
Analysis description	Safety analysis: For other adverse experiences (not in Tier 1) and predefined limits of change in laboratory variables, summary tabulations and 95% confidence intervals (CIs) for between-group differences were provided (similar to Tier 1) when at least 4 patients experienced the same event in at least one treatment group; otherwise, only summary tabulations were provided. Membership in Tier 2 required that at least 4 patients in any treatment group exhibited the event or met the predefined limits of change (PDLC) criteria. All other adverse events and PDLCs belonged to Tier 3. Changes from baseline in laboratory measurements, lipids, ECG and vital signs were considered Tier 3 safety parameters.

Analysis population and time point description	The analyses for all safety outcomes were performed in the extension All Patients as Treated (APaT) population, defined as all randomized patients who received at least one dose of extension study treatment. Patients were included in the treatment group corresponding to the study treatment they actually received for the analysis of safety data using the APaT population. At least one laboratory or vital sign measurement obtained subsequent to at least one dose of extension study treatment is required for inclusion in the analysis of each specific parameter. To assess change from baseline, a baseline measurement was also required.
Summary	Adverse events presented in Section 12 of this CSR include those that began in the extension. Hypoglycemia tables in Section 12 represent hypoglycemia events that occurred during the extension study (from Week 12 to Week 78). Changes from baseline in laboratory safety parameters (blood chemistry, hematology, ECG, lipids) and vital signs represent changes from Week 0 to last measurement during the extension. Predefined limits of change (PDLC) represent percentages of patients meeting criteria for PDLC from Week 12 through Week 78. The incidences of adverse events by summary measure were generally similar between the Pooled MK-3102 and Placebo/Metformin groups (the 95% CIs for the between-treatment group differences for all SOC included "0"). The incidences of overall adverse events grouped by system organ class (SOC) were generally comparable between the Pooled MK-3102 group and the Placebo/Metformin (the 95% CIs for the between-treatment group differences for all SOC included "0"). However, numerically higher incidences of overall adverse events were observed in the Pooled MK-3102 group compared with the Placebo/Metformin group in the Infections and Infestations SOC (primarily due to the increased incidence of the adverse event of nasopharyngitis), Metabolism and Nutrition Disorders SOC (primarily due to the increased incidence of the adverse events of hyperglycemia and hypoglycemia), and the Respiratory, Thoracic and Mediastinal Disorders SOC during the extension study (due to a variety of disparate adverse events).

	In the Gastrointestinal Disorders SOC there was one report of acute pancreatitis attributed to gallstones and one report of worsening of chronic pancreatitis in the Pooled MK-3102 group; both patients completed the study on study drug. There were no reports of serious hypersensitivity reactions in the Pooled MK-3102 group. The incidences of cardiovascular events were low. These CV events will contribute to the meta-analysis of CV events in the MK-3102 Phase II/III program. Fifteen patients (3.8%) in the Pooled MK-3102 group compared with no patients in the Placebo/Metformin group were reported to have at least one adverse event of hypoglycemia (symptomatic or asymptomatic). Three patients in the Pooled MK-3102 group experienced a severe episode of hypoglycemia requiring medical assistance. There were no significant changes from baseline (Week 0) in laboratory safety measures including liver function, creatinine/eGFR, or creatine phosphokinase (CK) in the Pooled MK-3102 group that would indicate a hepatic, renal or muscle safety signal. Small increases from baseline in uric acid, WBC and neutrophils were observed in both treatment groups, but are not considered to be clinically meaningful. Serum lipids including total cholesterol, LDL-C, HDL-C and TG were generally unchanged. No clinically meaningful changes from baseline at Week 78 were observed in heart rate or blood pressure. No clinically meaningful changes from baseline at Week 78 were observed in ECG intervals, including QTc interval.

Analysis Results for the Key Efficacy Endpoints
Least Square Means for Change from Baseline at Week 78 with 95 % CI
(Extension FAS)

Treatment	A1C (%)	2-Hour Post-Meal Glucose (mg/dL)	Fasting Plasma Glucose (mg/dL)
LS Means Estimates (95% CI)			
Placebo/Metformin	-0.88 (-1.19, -0.57)	-40.3 (-58.1, -22.6)	-19.6 (-34.1, -5.1)
MK-3102 0.25 mg/25 mg	-0.57 (-0.89, -0.25)	-37.0 (-54.1, -20.0)	-7.4 (-22.4, 7.6)
MK-3102 1 mg/25 mg	-0.55 (-0.85, -0.26)	-21.3 (-38.2, -4.4)	-11.3 (-25.0, 2.5)
MK-3102 3 mg/25 mg	-0.30 (-0.62, 0.02)	-18.0 (-35.9, -0.1)	-2.0 (-17.1, 13.1)
MK-3102 10 mg/25 mg	-0.60 (-0.93, -0.28)	-27.6 (-46.3, -8.9)	-10.0 (-25.0, 5.0)
MK-3102 25 mg/25 mg	-0.46 (-0.80, -0.11)	-43.2 (-62.0, -24.4)	-0.7 (-16.7, 15.3)

Analysis of Adverse Event Summary
Excluding Data After Glycemic Rescue
(Extension APaT)

Treatment	n	(%)	Difference in % vs Placebo/Metformin Estimate (95% CI)[†]
Patients in population			
Placebo/Metformin	76		
Pooled MK-3102	392		
with one or more adverse events			
Placebo/Metformin	50	(65.8)	
Pooled MK-3102	262	(66.8)	1.0 (-9.8, 13.1)
with no adverse events			
Placebo/Metformin	26	(34.2)	
Pooled MK-3102	130	(33.2)	-1.0 (-13.1, 9.8)
with drug-related[‡] adverse events			
Placebo/Metformin	14	(18.4)	
Pooled MK-3102	65	(16.6)	-1.8 (-12.6, 6.4)
with serious adverse events			
Placebo/Metformin	3	(3.9)	
Pooled MK-3102	22	(5.6)	1.7 (-5.6, 5.6)
with serious drug-related adverse events			
Placebo/Metformin	1	(1.3)	
Pooled MK-3102	0	(0.0)	
who died			
Placebo/Metformin	1	(1.3)	
Pooled MK-3102	3	(0.8)	
discontinued[§] due to an adverse event			
Placebo/Metformin	4	(5.3)	
Pooled MK-3102	15	(3.8)	-1.4 (-9.1, 2.6)
discontinued due to a drug-related adverse event			
Placebo/Metformin	3	(3.9)	

Analysis of Adverse Event Summary
Excluding Data After Glycemic Rescue
(Extension APaT)

Treatment	n	(%)	Difference in % vs Placebo/Metformin Estimate (95% CI)[†]
discontinued due to a drug-related adverse event			
Pooled MK-3102	6	(1.5)	-2.4 (-9.5, 0.7)
discontinued due to a serious adverse event			
Placebo/Metformin	2	(2.6)	
Pooled MK-3102	7	(1.8)	-0.8 (-7.4, 1.8)
discontinued due to a serious drug-related adverse event			
Placebo/Metformin	1	(1.3)	
Pooled MK-3102	0	(0.0)	

[†] Based on Miettinen & Nurminen method.
[‡] Determined by the investigator to be related to the drug.
[§] Study medication withdrawn.
Estimated differences and confidence intervals are provided in accordance with the statistical analysis plan.

Analysis of Hypoglycemia Adverse Events
Excluding Data After Glycemic Rescue
(Extension APaT)

	Placebo/ Metformin n (%)	Pooled MK-3102 n (%)	Difference in % vs. Placebo/Metformin Estimate (95% CI)[†]
Patients in population	76	392	
With one or more:			
Adverse events of hypoglycemia (symptomatic or asymptomatic)	0 (0.0)	15 (3.8)	3.8 (-1.0, 6.2)
Symptomatic	0 (0.0)	11 (2.8)	2.8 (-2.0, 5.0)
Severe	0 (0.0)	3 (0.8)	0.8
Requiring non-medical assistance	0 (0.0)	0 (0.0)	0.0
Requiring medical assistance	0 (0.0)	3 (0.8)	0.8
Asymptomatic	0 (0.0)	5 (1.3)	1.3 (-3.6, 3.0)

[†] Based on Miettinen & Nurminen method. The 95% CI was computed only for those endpoints with at least 4 patients having events in one or more treatment groups.
n = Number of patients with one or more events.
Patients are counted a single time for each applicable category.
Symptomatic episode: Episode with clinical symptoms attributed to hypoglycemia, without regard to glucose level.
Asymptomatic episode: Episode without symptoms attributed to hypoglycemia, but with a glucose level ≤ 70 mg/dL.
Severe episode: Episode that required assistance, either medical or non-medical. Episodes with a markedly depressed level of consciousness, a loss of consciousness, or seizure were classified as having required medical assistance, whether or not medical assistance was obtained.

CONCLUSIONS:	In patients with T2DM with inadequate glycemic control on diet and exercise, once-weekly treatment with MK-3102 over a 78-week treatment period: 1. provides reductions in A1C, 2-hour PMG, and FPG compared to baseline as generally reflected by the observed point estimates and 95% CIs; 2. is well tolerated with a low incidence of hypoglycemia and a neutral effect on body weight.
REPORT DATE	21-OCT-2014