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

MERCK SHARP & DOHME CORP., A SUBSIDIARY OF MERCK & CO., INC. MK-3102 [redacted], Capsules T2DM	**CLINICAL STUDY REPORT SYNOPSIS**

PROTOCOL TITLE/NO.: 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 #006

INVESTIGATOR(S)/STUDY CENTER(S): One hundred thirty-three (133) sites received study drug worldwide including, 27 sites in US, 42 in Asia, 35 in Europe, 11 in South America and 18 other countries around the world.

PUBLICATION(S): n/a

PRIMARY THERAPY PERIOD: 3-Nov-10 to 3-Jan-12 | **CLINICAL PHASE:** IIb

DURATION OF TREATMENT: 12-week study

OBJECTIVE(S): In patients with T2DM who have inadequate glycemic control on diet and exercise: Primary: (1) After 12 weeks, to assess the effect of treatment with MK-3102 compared with placebo on A1C. (2) To assess the safety and tolerability of MK-3102. Secondary: (1) After 12 weeks, to assess the effect of treatment with MK-3102 compared with placebo on 2-hour Post Meal Glucose (PMG). (2) After 12 weeks, to assess the effect of treatment with MK-3102 compared with placebo on FPG. Exploratory: After 12 weeks, to assess the effect of treatment with MK-3102 on body weight.

HYPOTHESES:

Primary: (1) After 12 weeks, treatment with MK-3102 compared with placebo provides greater reduction in A1C in a dose-related manner. Secondary: (1) After 12 weeks, treatment with MK-3102 compared with placebo provides greater reduction in 2-hour PMG in a dose-related manner. (2) After 12 weeks, treatment with MK-3102 compared with placebo provides greater reduction in FPG in a dose-related manner.

STUDY DESIGN: This was a multicenter, double-blind, randomized, placebo-controlled, dose-range finding study. The duration of the study was up to 23 weeks (with 8 clinic visits) for each patient. This included a 1-week screening period [**Visits 1 to 2**]; a diet/exercise and oral antihyperglycemic agent (AHA) "wash-off" (for patients on oral AHAs) period of *up to* 8 weeks [**Visit 2 to Visit 3/Week -2, including a phone contact at Week -6**]**;** a 2-week single-blind placebo run-in period [**Visit 3/Week -2 to Visit 4/Day 1**], and a 12-week double-blind treatment period. Patients with T2DM who were not on AHA medication (off for ≥14 weeks) at **Visit 1** and who met all other enrollment criteria directly entered into the 2-week single-blind placebo run-in period at a combined **Visit 2/3**. For details on the run-in duration and visit schedule, see Section 2.4.3.3.

At **Visit 4/Day 1**, patients who met the study enrollment criteria entered the double-blind treatment period. They were randomized to receive administration of one of five doses of MK-3102 or placebo in a 1:1:1:1:1:1 ratio. At randomization, patients were stratified according to their use of AHA at **Visit 1** (on AHA or not on AHA), and site location (Japan or ex-Japan).

After **Visit 4/Day 1**, patients not meeting progressively stricter protocol-specified glycemic goals had rescue therapy initiated with metformin. The investigator was responsible for the management of metformin therapy including the dose and titration regimen for each individual patient.

A 66-week extension study is currently ongoing after the completion of the 12-week base study. Eligible patients who completed the base study continued into the extension.

SUBJECT/PATIENT DISPOSITION:

	Placebo	MK-3102 0.25 mg	MK-3102 1 mg	MK-3102 3 mg	MK-3102 10 mg	MK-3102 25 mg	Total
NOT RANDOMIZED							880
RANDOMIZED	114	113	115	114	115	114	685
Male	65	65	67	65	56	69	387
(age range)	(32-69)	(32-70)	(28-70)	(28-70)	(27-70)	(39-70)	(27-70)
Female	49	48	48	49	59	45	298
(age range)	(39-68)	(35-70)	(35-70)	(34-68)	(34-70)	(24-68)	(24-70)
COMPLETED	105	106	110	107	113	99	640
DISCONTINUED	9	7	5	7	2	15	45
Adverse event	1	1	0	1	0	4	7
ALT/AST	0	1	0	0	0	0	1
Excluded medication	0	0	0	0	0	1	1
Lack of Efficacy	1	0	0	0	0	0	1
Lost to follow-up	0	0	0	1	1	3	5
Physician decision	0	0	0	0	0	1	1
Protocol violation	2	1	0	0	0	1	4
Withdrawal by subject	5	4	5	5	1	5	25

DOSAGE/FORMULATION NOS.: MK-3102 and matching placebo were administered in a blinded manner as two capsules once-weekly (q.w.) to result in MK-3102 doses of 0.25 mg, 1 mg, 3 mg, 10 mg and 25 mg. The formulation numbers used for MK-3102 placebo to match all strengths was [redacted] The formulation numbers used for MK-3102, .25mg were [redacted] for MK-3102, 10mg were [redacted] for MK-3102, 25 mg were [redacted] for MK-3102, 1 mg were [redacted] and MK-3102 1.5 mg were [redacted]

Open-label metformin were supplied for rescue therapy locally by the subsidiary, investigational site, or by prescription.

Section 9.4.2 contains detailed information about formulation numbers.

DIAGNOSIS/INCLUSION CRITERIA: Patients with T2DM and ≥18 and ≤70 years of age on the day of signing the informed consent form. For Japan: Patients with T2DM and ≥20 and ≤70 years of age. Patients either (1) not on oral antihyperglycemic medication (off for ε14 weeks) and had a Visit 1/Screening Visit A1C ≥7.0 and ≤10.0% or (2) Patient was currently on oral AHA medication monotherapy or low-dose (i.e., ≤50% maximum labeled dose of each agent) dual oral combination therapy [except thiazolidinediones (TZDs)] and had a **Visit 1/ Screening Visit A1C ≥6.5 and ≤9.0%** AND based upon review of the patient's current diet, medical regimen, and Visit 1 A1C, patient was considered by the investigator to be likely to meet **Visit 3/Week -2** inclusion criterion of **A1C ≥7.0 and ≤10.0% AFTER the 8-week wash-off period prior to Visit 3/Week-2 (Visit 2/Week -10 to Visit 3/ Week -2)**.

EVALUATION CRITERIA:

EFFICACY MEASURMENTS: Primary Endpoint: A1C. Other Endpoints: FPG, 2-hour PMG, MK-3102 pharmacokinetics, DPP-4 inhibition, HOMA-beta and body weight.

SAFETY MEASUREMENTS: Safety endpoints include the collection of adverse experiences, laboratory safety parameters, vital signs, physical examination, and electrocardiograms (ECGs). Laboratory safety studies included blood chemistry (including alanine aminotransferase [ALT], aspartate aminotransferase [AST], creatine phosphokinase [CK], total bilirubin, alkaline phosphatase), hematology (including complete blood count [CBC], differential, and absolute neutrophil count, platelet count), lipid panel, eGFR, serum creatinine, urinalysis, and urine pregnancy testing (performed in women of childbearing potential). Laboratory safety studies included vital signs. Electrocardiograms were collected and read centrally (except at Visit 2 with a local reading only).

STATISTICAL PLANNING AND ANALYSIS:

Efficacy: To address the efficacy hypotheses, the change from baseline in the respective endpoint at Week 12 was analyzed using a constrained longitudinal data analysis (cLDA) model. This model assumes a common mean across treatment groups at baseline and a different mean for each treatment at each of the post-baseline time points. In this model, the response vector consists of baseline values and the values observed at each post-baseline time point. Time was treated as a categorical variable so that no restriction was imposed on the trajectory of the means over time. The analysis model adjusted 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. The treatment difference in terms of mean change from baseline to a given time point was estimated and tested from this model. An unstructured covariance matrix was used to model the correlation among repeated measurements.

The primary hypothesis was assessed by a step-down trend test using linear contrasts, comparing doses of MK-3102 to placebo at Week 12, from the above cLDA model. This step-down procedure first included all doses of MK-3102 and placebo for the test of trend. If a statistically significant result was observed, the highest dose group was deemed significantly different from placebo. Then the highest dose is removed from the linear contrast and the trend test is repeated among remaining doses. This statistical process proceeds in a stepwise fashion until lack of significance is observed to determine the minimal effective dose that is statistically significantly different from placebo. This step-down trend test is a closed testing procedure and preserves the overall Type I error rate for testing the primary hypothesis.

The primary analysis population was the Full Analysis Set, which included all randomized patients who received at least one dose of study medication and had a baseline or a post-baseline outcome measurement. It was expected that 95 patients per group would be available for the analysis for the primary hypothesis at Week 12. Using a conditional standard deviation (SD) of 1.0% from an analysis model with baseline as a covariate, this sample size would provide 90% (80%) power to detect a true difference of 0.47% (0.41%) in the mean change from baseline in A1C at Week 12 between two treatment groups (2-sided test, α=0.05). The half-width of the 95% CI would be 0.29%. Note that the step-down trend test has at least the same or greater power as the analysis using comparisons of 2 individual treatments on which these power calculations are based.

Safety: The analyses for all safety outcomes were performed in the All Patients as Treated (APaT) population, defined as all randomized patients who received at least one dose of study treatment. The analysis of safety results followed a tiered approach. For Tier 1 clinical adverse experience (symptomatic hypoglycemia), between-group differences for the incidence rates were estimated, along with p-values and 95% confidence intervals using the Miettinen and Nurminen method. 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.

RESULTS:

Efficacy:

Once-weekly treatment with MK-3102 for 12 weeks resulted in a dose-dependent reduction in A1C (the primary endpoint), 2-hour PMG and FPG (secondary endpoints). Therefore, the criteria for success for the primary and secondary hypotheses were met, i.e. that after 12-weeks, treatment with MK-3102 compared with placebo provides a greater reduction in A1C, 2-hour PMG and FPG. The maximum A1C reduction for MK-3102 was achieved at 25 mg, the top dose studied. The step-down trend test showed a significant trend on A1C reduction from placebo through 25 mg and this significant treatment effect was maintained through the lowest dose of MK-3102 tested ($p \leq 0.012$). Similarly, a significant trend in reduction of 2-hour PMG was observed across all doses from placebo through the 25-mg dose of MK-3102. A significant trend in FPG was observed through all doses of MK-3102 with the exception of 0.25 mg (i.e., no statistical significant difference between placebo and 0.25 mg was observed). No clinically meaningful treatment effect was observed for body weight in any of the MK-3102 treatment groups. The following table provides results at Week 12 for the dose-response relationship and placebo-subtracted treatment effect from the analyses of the primary and secondary endpoints.

Analysis Results for the Primary and Secondary Efficacy Hypotheses
Dose-Response Relationship and Least Square Means for Change from Baseline
at Week 12 with 95 % CI (FAS)

Treatment	A1C (%)	2-Hour Post-Meal Glucose (mg/dL)	Fasting Plasma Glucose (mg/dL)
Pairwise LS Means Difference (95% CI)			
MK-3102 25 mg versus Placebo	-0.71 (-0.93, -0.50)	-44.9 (-59.0, -30.7)	-21.4 (-29.4, -13.4)
MK-3102 10 mg versus Placebo	-0.67 (-0.88, -0.45)	-41.6 (-55.3, -27.8)	-13.5 (-21.3, -5.7)
MK-3102 3 mg versus Placebo	-0.49 (-0.70, -0.27)	-35.1 (-48.9, -21.3)	-14.3 (-22.2, -6.3)
MK-3102 1 mg versus Placebo	-0.50 (-0.71, -0.28)	-33.5 (-47.3, -19.7)	-19.0 (-26.9, -11.2)
MK-3102 0.25 mg versus Placebo	-0.28 (-0.50, -0.06)	-18.8 (-32.9, -4.8)	-2.5 (-10.4, 5.5)
p-Value for Step-down Trend Test			
Placebo to MK-3102 25 mg	<0.001	<0.001	<0.001
Placebo to MK-3102 10 mg	<0.001	<0.001	<0.001
Placebo to MK-3102 3 mg	<0.001	<0.001	<0.001
Placebo to MK-3102 1 mg	<0.001	<0.001	<0.001
Placebo to MK-3102 0.25 mg	0.012	0.009	0.539

Safety:

At a summary level, the percentage of patients with one or more adverse event and one or more adverse event classified as drug-related were similar among all treatment groups, including placebo. The numerical imbalance in discontinuations due to adverse events in the 25-mg dose group was due to adverse events of a diverse nature and was not considered to represent a dose-related trend in adverse events.

The incidences of specific adverse events in the MK-3102 treatment groups in all system organ classes (SOC) were low and generally similar to the incidences observed in the placebo group. This included SOCs that encompassed adverse events that have been associated with daily DPP-4 inhibitors either from clinical study data or postmarketing reports, including the Gastrointestinal Disorders SOC and Nervous Systems Disorder SOC. In the Infections and Infestations SOC, the incidence of the adverse event of bronchitis was higher, compared with placebo, in patients in the MK-3102 0.25-mg group (4 reports in the 0.25 mg group versus none in the placebo group); however the incidences (0-2 patients) in other MK-3102 groups did not indicate dose-dependence. The incidence of symptomatic hypoglycemia was low in all treatment groups and there was no severe hypoglycemia. There were no reports of serious hypersensitivity reactions and there were no deaths in the study.

No significant changes in laboratory safety measures including liver function, creatinine/eGFR, or creatine phosphokinase (CK) were observed that would indicate a hepatic, renal or muscle safety signal. No clinically meaningful changes in ECG intervals, including QTc interval, were observed based on the assessment of ECG changes from baseline at Week 12 across all MK-3102 doses compared to placebo. No clinically meaningful changes were observed in heart rate or blood pressure. Serum lipids including total cholesterol, LDL-C, HDL-C and TG were generally unchanged.

A summary table of clinical adverse experiences is presented below.

Adverse Event Summary
Excluding Data after Glycemic Rescue
(APaT)

	Placebo		MK-3102 0.25 mg		MK-3102 1 mg		MK-3102 3 mg		MK-3102 10 mg		MK-3102 25 mg		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Patients in population	113		113		115		114		115		114		684	
with one or more adverse events	35	(31.0)	42	(37.2)	50	(43.5)	42	(36.8)	42	(36.5)	38	(33.3)	249	(36.4)
with no adverse event	78	(69.0)	71	(62.8)	65	(56.5)	72	(63.2)	73	(63.5)	76	(66.7)	435	(63.6)
with drug-related[†] adverse events	9	(8.0)	7	(6.2)	6	(5.2)	9	(7.9)	9	(7.8)	8	(7.0)	48	(7.0)
with serious adverse events	0	(0.0)	0	(0.0)	1	(0.9)	0	(0.0)	2	(1.7)	3	(2.6)	6	(0.9)
with serious drug-related adverse events	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.9)	1	(0.1)
who died	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued[‡] due to an adverse event	1	(0.9)	1	(0.9)	0	(0.0)	1	(0.9)	0	(0.0)	4	(3.5)	7	(1.0)
discontinued due to a drug-related adverse event	1	(0.9)	0	(0.0)	0	(0.0)	1	(0.9)	0	(0.0)	1	(0.9)	3	(0.4)
discontinued due to a serious adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.9)	1	(0.1)
discontinued due to a serious drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.9)	1	(0.1)

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

CONCLUSIONS:

(1) In patients with T2DM with inadequate glycemic control on diet and exercise, once-weekly treatment for 12 weeks with MK-3102, compared with placebo, provides dose-related reductions in A1C, 2-hour PMG and FPG and was associated with a neutral effect on body weight.

(2) In patients with T2DM with inadequate glycemic control on diet and exercise, once-weekly treatment for 12 weeks with MK-3102 (all doses) is generally well tolerated with a low incidence of hypoglycemia.

AUTHORS:

[redacted]