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-6096L-002061532, 2.5-mg, 5-mg, 10-mg and 20-mg tablets of MK-6096 or matching placebo Insomnia	CLINICAL STUDY REPORT SYNOPSIS

PROTOCOL TITLE/NO.: A Phase IIb, Multicenter, Randomized, Double-Blind, Placebo-Controlled, 2-Period Adaptive Crossover Polysomnography Study to Evaluate the Safety and Efficacy of MK-6096 in Patients with Primary Insomnia	011

INVESTIGATOR(S)/STUDY CENTER(S): Multicenter (51) in the United States (23), Germany, (2), United Kingdom (1), Spain (5), Finland (3) and Japan (17).	
PRIMARY THERAPY PERIOD: 20-DEC-2009 to 1-FEB-2011.	**CLINICAL PHASE:** IIb
DURATION OF TREATMENT: 4 weeks of treatment.	
OBJECTIVE(S): (1) To evaluate the efficacy of MK-6096 compared with placebo in improving sleep efficiency (SE) as measured by polysomnography (PSG) on Night 1 and at the end of 4 weeks of treatment, where SE is defined as 100 times total sleep time (minutes) divided by time in bed (minutes). (2) To evaluate the safety and tolerability of MK-6096.	
STUDY DESIGN: This was a multinational, randomized, double-blind (with in-house blinding), placebo-controlled, 2-period cross-over PSG study to assess the safety, tolerability, and efficacy of four doses of MK 6096 (2.5, 5, 10, or 20 mg) in the treatment of patients with primary insomnia. The duration of the study was approximately 13 weeks and comprised a 3-week screening period, and two 4-week double-blind treatment periods, with an intervening 2-week washout period (consisting of 3 days of single-blind placebo followed by 11days off study drug). Each treatment period consisted of 29 ± 3 days of treatment and included an overnight PSG visit on the first and last nights of the treatment period, with a clinic office visit on Day 15.	

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SUBJECT/PATIENT DISPOSITION:

Patient Disposition	Placebo	MK6096 2.5mg	MK6096 5mg	MK6096 10mg	MK6096 20mg	MK-6096 Total	Study Overall*
Randomized	315	79	78	80	81	318	326**
Female (age range)	198 (18 to 65)	49 (18 to 64)	49 (22 to 64)	50 (20 to 63)	50 (29 to 65)	198 (18 to 65)	203 (18 to 65)
Male (age range)	117 (21 to 64)	30 (21 to 63)	29 (21 to 63)	30 (23 to 63)	31 (28 to 64)	120 (21 to 64)	123 (21 to 64)
Completed	305 (96.8%)	75 (94.9%)	76 (97.4%)	76 (95%)	79 (97.5%)	306 (96.2%)	299 (91.7%)
Discontinued	10 (3.2%)	4 (5.1%)	2 (2.6%)	4 (5%)	2 (2.5%)	12 (3.8%)	27 (8.3%)
Adverse Event	5 (1.6%)	4 (5.1%)	1 (1.3%)	2 (2.5%)		7 (2.2%)	13 (4.0%)
Lack Of Efficacy				1 (1.3%)		1 (0.3%)	1 (0.3%)
Lost To Follow-Up							1 (0.3%)
Physician Decision	1 (0.3%)						1 (0.3%)
Pregnancy			1 (1.3%)			1 (0.3%)	1 (0.3%)
Protocol Violation	2 (0.6%)						4 (1.2%)
Withdrawal By Subject	2 (0.6%)			1 (1.3%)	2 (2.5%)	3 (0.9%)	6 (1.8%)

* Represents the final overall disposition status of patients.
** Three hundred and twenty –six (326) patients were randomized into the study and of those, 324 treated with study medication.

DOSAGE/FORMULATION NOS.: MK-6096 2.5-mg and 5-mg oral compressed tablets and respective matching placebos were used in the study to achieve doses of 2.5, 5, 10, and 20 mg per administration. To maintain blinding, a double dummy design was used. Study medication was packaged in bottles to achieve the various MK-6096 dose levels. Placebo for MK-6096 was packaged similarly to provide a range of supplies matching the active dose levels. Each patient was instructed to take 1 tablet from each of 4 different bottles (labeled A, B, C, and D, respectively) throughout the entire course of the study, including the single-blind placebo run-in period and the washout period.

Drug	Potency	Dosage Form	Clinical Batch No.
MK-6096 Placebo	2.5 mg 5 mg	Tablet	[redacted]

DIAGNOSIS/INCLUSION CRITERIA: Patients were men and women between 18 and <65 years of age, in good physical and mental health who met the following criteria: diagnosis of primary insomnia based on Diagnostic and Statistical Manual of Mental Disorder-Category IV-Text Revision (DSM-IV-TR) criteria; report ≤6.5 hours of total sleep time on at least 3 out of 7 nights in a week, ≥30 minutes in sleep latency on at least 3 out of 7 nights in a week, and ≥1 hour of wakefulness after sleep onset; spend 6.5 to 9 hours nightly in bed; and on PSG assessments, demonstrate latency to persistent sleep (LPS) ≥20 minutes and wake after sleep onset (WASO) ≥45 minutes.

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EVALUATION CRITERIA: The primary and secondary efficacy endpoints in this study were derived from PSG measures. PSG values for statistical analysis were based on standardized readings from a central lab. The primary endpoint was SE as derived from total sleep time (TST). Secondary endpoints included wakefulness after persistent sleep onset (WASO) and latency to onset of persistent sleep (LPS). Exploratory endpoints included subjective assessments of sleep based on responses provided daily via the morning and evening diaries and additional PSG measures. Other assessments included pharmacokinetic sampling of MK-6096 concentrations, self-reported daytime functioning as measured by the evening diary, Insomnia Severity Index (ISI), Sheehan Disability Scale (SDS), Quick Inventory of Depressive Symptomatology (QIDS), and the Stress Vulnerability Scale (SVS).

STATISTICAL PLANNING AND ANALYSIS:

The primary efficacy endpoint (SE) and secondary efficacy endpoints (WASO and LPS), at Night 1 and at the end of 4 weeks of treatment, were compared between each dose of MK-6096 and placebo using a mixed effects model including terms for baseline value (pre-randomization), geographic region (Japan vs. ex-Japan), gender, treatment, sequence, period, time (as a categorical variable), and treatment-by-time and period-by-time interactions for each dose. An unstructured covariance matrix was used for within-subject correlation assuming independence for between-subject correlation. The model was used to provide an estimate of the treatment effect for the comparison of each MK-6096 dose with placebo. A confidence interval and p-value (based upon a normal approximation) was also computed. The shape of the dose-response was explored, graphically, based upon these estimates. The population for the efficacy analyses was the Full Analysis Set (FAS) which included all randomized patients who took at least one dose of study medication, and had a post-dose assessment of the primary efficacy measure in either treatment period. Patients were analyzed according to the treatment sequence to which they were randomized for the efficacy analyses.

Safety and tolerability were assessed by review of the data which included: adverse events (AEs), laboratory values, ECGs, vital signs, next day residual effects, rebound insomnia and withdrawal effects. The population for the safety analyses was the All Patients Treated (APaT) approach which included all randomized patients who received at least one dose of study medication. A patient's treatment group was determined by the actual treatment received for the safety analyses.

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RESULTS:

Efficacy: All doses of MK-6096 (2.5, 5, 10, and 20 mg) were superior to placebo in improving insomnia as measured by the primary efficacy endpoint, SE, on Night 1 and at the end of Week 4, and as measured by the secondary efficacy endpoint WASO on Night 1 and at the end of Week 4. The two higher doses of MK-6096 (i.e., 10 mg and 20 mg) were more effective than placebo in improving sleep onset as measured by the secondary efficacy endpoint, latency to onset of persistent sleep (LPS), at Night 1 and at the end of Week 4, according to the multiplicity testing strategy. In addition, nominal p-values for LPS with the two lower doses of MK-6096 also suggested evidence of effect compared to placebo on Night 1 (p-values of <0.001 and 0.022 for MK-6096 5 mg and 2.5 mg, respectively.)

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Analysis of Sleep Efficiency (SE) (%), Wakefulness after Persistent Sleep Onset (WASO) (minutes) and Latency to Onset of Persistent Sleep (LPS) (minutes)
(Full Analysis Set / Data-as-Observed)

Endpoint	Timepoint	Treatment	Diff in LS Means vs. Placebo (SE)†	95% CI	p-Value
SE	Night 1	MK6096 2.5 mg	8.4 (1.59)	(5.3, 11.5)	<.001
		MK6096 5 mg	9.9 (1.59)	(6.8, 13.1)	<.001
		MK6096 10 mg	10.7 (1.57)	(7.7, 13.8)	<.001
		MK6096 20 mg	13.4 (1.57)	(10.3, 16.5)	<.001
	Week 4	MK6096 2.5 mg	4.6 (1.43)	(1.8, 7.4)	<.001
		MK6096 5 mg	4.1 (1.42)	(1.3, 6.9)	0.004
		MK6096 10 mg	9.7 (1.43)	(6.9, 12.5)	<.001
		MK6096 20 mg	8.7 (1.43)	(5.9, 11.5)	<.001
WASO	Night 1	MK6096 2.5 mg	-30.8 (6.29)	(-43.2, -18.4)	<.001
		MK6096 5 mg	-32.5 (6.31)	(-44.9, -20.1)	<.001
		MK6096 10 mg	-30.9 (6.21)	(-43.2, -18.7)	<.001
		MK6096 20 mg	-45.8 (6.22)	(-58.0, -33.5)	<.001
	Week 4	MK6096 2.5 mg	-15.5 (5.65)	(-26.7, -4.4)	0.006
		MK6096 5 mg	-13.2 (5.66)	(-24.1, -2.1)	0.020
		MK6096 10 mg	-25.7 (5.67)	(-36.8, -14.5)	<.001
		MK6096 20 mg	-30.0 (5.69)	(-41.2, -18.8)	<.001
LPS	Night 1	MK6096 2.5 mg	-10.2 (4.43)	(-18.9, -1.5)	0.022
		MK6096 5 mg	-15.7 (4.44)	(-24.5, -7.0)	<.001
		MK6096 10 mg	-23.5 (4.38)	(-32.1, -14.9)	<.001
		MK6096 20 mg	-20.3 (4.38)	(-29.0, -11.7)	<.001
	Week 4	MK6096 2.5 mg	-8.9 (4.61)	(-18.0, 0.2)	0.055
		MK6096 5 mg	-8.7 (4.61)	(-17.8, 0.4)	0.060
		MK6096 10 mg	-19.5 (4.62)	(-28.6, -10.4)	<.001
		MK6096 20 mg	-11.3 (4.63)	(-20.5, -2.2)	0.015

† Results based on a mixed effects model with terms for baseline value, region, gender, treatment, sequence, period, time, treatment-by-time and period-by-time interactions; all terms are specific to each 2x2 crossover study (i.e., multiplied by indicator variables for each 2x2 crossover study) with the exception of the treatment effect so as to pool placebo information across the 2x2 crossover studies.

Safety: Treatment with MK-6096 was generally well-tolerated. A dose-related increase in overall AE rate was observed with MK-6096. The most common AEs in patients receiving MK-6096 were somnolence and headache. These were also the most commonly reported drug-related AEs. Three patients discontinued treatment due to drug-related AEs while receiving MK-6096, including two patients due to headache (MK-6096 2.5 mg) and one patient due to fatigue (MK-6096 2.5 mg). All patients recovered following discontinuation of study medication. Five patients reported serious AEs, 3 of which (periorbital cellulitis, atrial fibrillation, and cholecystitis) occurred during treatment with MK-6096; none of these were considered by the Investigator to be related to MK-6096**.** One death (completed suicide) occurred during the washout period, 8 days following the last dose of placebo during Treatment Period 1**.**

Overall, from a safety perspective, no new or unexpected findings were observed in this study that

would significantly alter the risk profile established for MK-6096.

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CONCLUSIONS:
Based on evaluation of the primary and key secondary endpoints for Periods 1 and 2 combined:

1. All doses of MK-6096 (i.e., 20 mg, 10 mg, 5 mg and 2.5 mg) were more effective than placebo in improving insomnia as measured by the primary endpoint of sleep efficiency (SE), both on Night 1 and at the end of Week 4.

2. All doses of MK-6096 (i.e., 20 mg, 10 mg, 5 mg and 2.5 mg) were more effective than placebo in improving sleep maintenance as measured by the secondary endpoint of wakefulness after persistent sleep onset (WASO), both on Night 1 and at the end of Week 4.

3. The two highest doses of MK-6096 (i.e., 10 mg and 20 mg) were more effective than placebo in improving sleep onset as measured by the secondary efficacy endpoint latency to persistent sleep (LPS), both on Night 1 and at the end of Week 4, according to the protocol predefined multiplicity strategy. In addition, nominal p-values for LPS with the two lower doses of MK-6096 also suggested evidence of effect compared to placebo on Night 1 (p-values of <0.001 and 0.022 for MK-6096 5 mg and 2.5 mg, respectively.)

Doses of MK-6096 ranging from 2.5 mg to 20 mg were generally well-tolerated in patients with insomnia treated for up to 4 weeks.

AUTHORS:	Clinical Scientist	Statistician	Clinical Monitor
	[redacted]		