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 RESEARCH LABORATORIES MK-6913 L-001246956, 75 mg Treatment of moderate to very severe vasomotor symptoms in postmenopausal women	**CLINICAL STUDY REPORT SYNOPSIS**

PROTOCOL TITLE/NO.: A Phase IIa, Randomized, Double-Blind, Placebo- and Active-Controlled Study to Evaluate the Efficacy, Safety, and Tolerability of MK-6913 for the Treatment of Vasomotor Symptoms in Postmenopausal Women #004

INVESTIGATOR(S)/STUDY CENTER(S): Multicenter (26) in the United States (14) and Europe (12)

PUBLICATION(S): N/A

PRIMARY THERAPY PERIOD: 29-Dec-2009 to 13-Jul-2010 **CLINICAL PHASE:** IIa

DURATION OF TREATMENT: Stage I- 4 weeks; Stage II- 4 weeks

OBJECTIVE(S): Primary: (1) To assess the effect of 4 weeks of treatment with MK-6913 on percent change from baseline in weekly frequency of hot flashes of moderate or greater severity. (2) To assess the safety and tolerability of 4 weeks of treatment with MK-6913. Secondary (1) To assess the effect of 4 weeks of treatment with MK-6913 on percent change from baseline in weekly hot flash severity score. (2) To assess the effect of 4 weeks of treatment with MK-6913 on reduction in FSH. (3) To assess the effect of 4 weeks of treatment with 17β-estradiol 1 mg versus placebo on weekly hot flash frequency and severity score. (4) To compare the effect of 4 weeks of treatment with MK-6913 versus 1 mg 17β-estradiol on weekly hot flash frequency and severity score. (5) To assess the effect of 4 weeks of treatment with MK-6913 on serum lipid parameters.

STUDY DESIGN: Two-Stage, Double-blind, placebo- and active-controlled

SUBJECT/PATIENT DISPOSITION:

	MK-6913 75mg	Estradiol 1mg	Placebo	Total
SCREENING FAILURES:				255
RANDOMIZED:	34	32	33	99
Female (age range)	34 (40-60)	32(35-59)	33 (40-60)	99
COMPLETED:	33 (97.1)	28 (87.5)	33 (100.0)	94
DISCONTINUED:	1 (2.9)	4 (12.5)	0 (0.0)	5 (5.1)
Adverse experience	0 (0.0)	1 (3.1)	0 (0.0)	1 (1.0)
Other	1 (2.9)	3 (9.4)	0 (0.0)	4 (4.0)

DOSAGE/FORMULATION NOS.: Stage I: MK-6913 25 mg capsules [redacted] and matching placebo ([redacted] Three (3) capsules for a total of 75 mg were taken once daily in the morning. US sourced 17β-estradiol 1 mg tablet ([redacted] US: supplied by Mylan Pharmaceuticals; Ex-US: supplied by Meda Pharmaceuticals Ltd.) and matching placebo ([redacted]

A physical defect was observed in one lot of 120cc HDPE bottles (LOT [redacted] used for packaging some clinical supplies that were used in this study. An inspection/replacement plan was implemented to identify potentially affected bottles and removed them from the clinical supply chain. Of the 1080 bottles potentially affected 1059 were inspected and 0 were found to have holes as defects. Not all bottles potentially affected were inspected due to the following reasons: A) Bottles were returned prior to the defect being identified, and B) study was completed. Stability assessments did not identify any potential impact, due to the bottle defect, on drug potency, dissolution, disintegration or degradate levels which could cause patients to have experienced differences in the effects of the study drug or impact the measured outcomes of the study. The study blinding was not broken during implementation of the plan and no patients were excluded from analysis due to the bottle defect.

DIAGNOSIS/INCLUSION CRITERIA: Postmenopausal woman with ≥ 50 moderate-to-very severe hot flash episodes per week during the second week of the placebo run-in period as confirmed by electronic diary; age either ≥ 45 and ≤ 60 years, if naturally menopausal, or ≥ 35 and ≤ 60 years of age if surgically menopausal (having undergone a bilateral oophorectomy, with or without hysterectomy). Women must have had at least 6 months of spontaneous amenorrhea and a serum FSH level >40 mIU/mL at the time of Visit 1, OR undergone a bilateral oophorectomy, with or without hysterectomy, at least 6 weeks prior to Visit 1, and a serum FSH level of 40 mIU/mL; not receiving hormone therapy (estrogen alone or estrogen/progestin); body mass index (BMI) of ≥ 18 and ≤ 40 kg/m^2; normal mammogram within 6 months of the Screening Visit, normal Papanicoloau smear test within 6 months of the Screening Visit; and able to complete the hot flash e-diary.

EVALUATION CRITERIA:

EFFICACY MEASUREMENTS: Primary: Percentage reduction in the number of hot flashes on Week 4 compared to Baseline (second week of the placebo run-in period), as recorded by the ediary. Secondary and Exploratory: Hot flash severity score, Pittsburgh Sleep Quality Index (PSQI), Hot Flash Related Daily Interference Scale (HFRDIS), Menopause Quality of Life Questionnaire (MENQOL), Women's Health Questionnaire (WHQ; Stage II only), FSH measurements, hormonal markers (LH, prolactin, testosterone, and SHBG)

SAFETY MEASUREMENTS: Adverse experience assessments, physical examinations (including breast and pelvic), vital signs, 12-Lead ECG, and laboratory safety evaluations (hematology, serum chemistry, serum lipid parameters, and urinalysis).

STATISTICAL PLANNING AND ANALYSIS: All hypotheses and objectives were planned to be addressed at the end of Stage 2 combining patients from Stage 1 and Stage 2. However, the study was terminated at the end of Stage 1 based on the results of an interim futility analysis. Therefore the hypotheses and objectives could not be assessed. A limited analysis, similar to the analysis planned for the end of Stage 2, was performed based on the patients who were randomized into Stage 1.

The percent change from baseline in weekly moderate or worse hot flash frequency at Week 4 was the primary efficacy endpoint. Analyses excluding outliers of weekly moderate or worse hot flash frequency were considered the primary approach for the primary efficacy endpoints. The percent change from baseline in weekly hot flash severity score (combining severe and very severe in same category) at Week 4 was one of the key secondary endpoints. The change from baseline in Follicle Stimulating Hormone (FSH) levels at Week 4 was also a key secondary endpoint. The Full Analysis Set (FAS) population served as the primary population for the analysis of efficacy data except the pharmacodynamic endpoint (FSH). Sensitivity analysis for primary and key secondary hot flash related endpoints was planned to be performed based on the Per-Protocol (PP) population. The following assessments were made at the interim analysis based on the primary endpoint: futility of MK-6913, robustness of estradiol.

The percent changes from baseline in weekly moderate or worse hot flash frequency and in weekly hot flash severity score were analyzed based on the longitudinal data analysis (LDA) model with terms for treatment, time, region, and interaction of time by treatment. Time was treated as a categorical variable. The treatment difference in terms of percent change from baseline at Week 4 was estimated from this model. An unstructured covariance matrix was used to model the correlation among repeated measurements. The change from baseline in FSH at Week 4 was analyzed using an analysis of covariance model (ANCOVA) with terms for treatment, region, stage of the trial, and baseline value as a covariate in the PP population only.

Safety and tolerability were assessed by a review of all safety parameters including all adverse events, laboratory safety measurements and vital signs. Tabulations were performed for adverse experiences and summary statistics over time were provided for vital signs and laboratory safety parameters.

RESULTS:

Efficacy: In the analysis of percent change from baseline in weekly moderate or worse hot flash frequency at Week 4 and in the analysis of percent change from baseline in weekly hot flash severity score at Week 4, there were numerically greater reductions in both the estradiol and MK-6913 groups compared to placebo, although the differences were not statistically significant. Based on the minimal reduction in hot flash frequency in the MK-6913 group, the futility criterion for MK-6913 was met and the study was stopped at Stage I. A similar effect was observed for the endpoint of hot flash severity score. Least Square (LS) Mean reductions from baseline to Week 4 in FSH were nominally similar in both MK-6913 group and placebo group, and significantly larger in the estradiol group. Analyses including outliers of weekly moderate or worse hot flash frequency were similar to the primary approach (excluding outliers) for the primary efficacy endpoints.

Least Square Means and Associated 95% Confidence Intervals of Primary and Key Secondary Endpoints at Week 4

Treatment	LS Mean (95% CI)		Differences in LS Means (95% CI)	
% Change from Baseline in Weekly Moderate or Worse HF Frequency (Excluding Outliers)				
MK-6913 75 mg	-40.69	(-54.82, -26.56)	-6.28	(-24.20, 11.64)
Estradiol 1 mg	-51.86	(-66.38, -37.34)	-17.45	(-36.28, 1.38)
Placebo	-34.41	(-48.99, -19.83)		
% Change from Baseline in Weekly HF Severity Score (combining Severe and very Severe)				
MK-6913 75 mg	-39.92	(-54.57, -25.26)	-6.05	(-25.06, 12.96)
Estradiol 1 mg	-45.09	(-60.15, -30.02)	-11.22	(-31.03, 8.59)
Placebo	-33.87	(-48.92, -18.81)		
Change from Baseline in FSH at Week 4				
MK-6913 75 mg	-2.02	(-7.91, 3.87)	0.94	(-6.19, 8.07)
Estradiol 1 mg	-17.48	(-23.08, -11.89)	-14.52	(-21.73, -7.32)
Placebo	-2.96	(-8.54, 2.62)		
LS=Least Square; CI=Confidence Interval; HF=Hot Flash				

Safety: MK-6913 75-mg was well tolerated. There were no serious adverse experiences or deaths. One or more adverse experiences were reported by 16 (48.5%) patients in the placebo group, 17 (50.0%) patients in the MK-6913 75-mg group, and 15 (46.9%) in the estradiol 1-mg group. The percentage of patents with drug-related AEs was similar in all 3 treatment groups. One (3.1%) patient in the estradiol group discontinued due to a drug-related adverse experience (liver function test abnormal). The tier 1 event of breast pain was reported by a total of 3 (9.1%) patients, all in the placebo group. Two (5.9%) patients in the MK-6913 75-mg group and 4 (12.5%) patients in the estradiol 1-mg group reported the tier 1 AE of vaginal bleeding. The two most common AEs were headache (MK-6913 75-mg, 0 (0%); estradiol 1-mg, 1 (3.1%); placebo 4 (12.1%)) and vaginal hemorrhage (MK-6913 75-mg, 2 (5.9%); estradiol 1-mg, 3 (9.4%)). No other AEs were observed in more than two patients in any one treatment group.

Adverse Event Summary

	MK-6913 75 mg		Estradiol 1 mg		Placebo		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Patients in population	34		32		33		99	
with one or more adverse events	17	(50.0)	15	(46.9)	16	(48.5)	48	(48.5)
with no adverse event	17	(50.0)	17	(53.1)	17	(51.5)	51	(51.5)
with drug-related[†] adverse events	7	(20.6)	9	(28.1)	8	(24.2)	24	(24.2)
with serious adverse events	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
with serious drug-related adverse events	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
who died	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued[‡] due to an adverse event	0	(0.0)	1	(3.1)	0	(0.0)	1	(1.0)
discontinued due to a drug-related adverse event	0	(0.0)	1	(3.1)	0	(0.0)	1	(1.0)
discontinued due to a serious adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued due to a serious drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

[†] Determined by the investigator to be related to the drug.

[‡] Study medication withdrawn.

CONCLUSIONS: In postmenopausal women with moderate to severe vasomotor symptoms: 1) MK-6913 75-mg was not significantly different from placebo for reduction of hot flash frequency after 4 weeks of treatment. 2) MK-6913 75-mg is not significantly different from placebo for reduction of hot flash severity score after 4 weeks of treatment. 3) 1 mg estradiol showed a significant reduction relative to placebo for both hot flash frequency and hot flash severity score. 4) For reduction from baseline in FSH at Week 4, MK-6913 75-mg was similar to placebo while there was a significant reduction in FSH relative to placebo in the 1 mg estradiol group. 5) MK-6913 was generally well tolerated.

AUTHORS: [redacted]