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-0634
MK-0634, Tablets
Overactive Bladder/Urinary Incontinence

CLINICAL STUDY REPORT SYNOPSIS

PROTOCOL TITLE/NO.: A Multicenter, Double-Blind, Randomized, Placebo-Controlled, Parallel-Group, Dose-Ranging Study of MK-0634 (L-000796568) in Postmenopausal Women With Overactive Bladder #007

INVESTIGATOR(S)/STUDY CENTER(S): Multicenter (57) in Australia (5), Ireland (3), New Zealand (4) South Africa (3), United Kingdom (3), and United States (39)

PUBLICATION(S):

PRIMARY THERAPY PERIOD: 04- Oct-2005 to 12-Sept-2006

CLINICAL PHASE: IIb

DURATION OF TREATMENT: Placebo Run-In (Period I): 1 Week; Treatment (Period II): 8 Weeks

OBJECTIVE(S): In postmenopausal women with overactive bladder:

Primary: (1) To investigate a dose-related reduction, in average number of daily micturitions after 8 weeks of treatment with L-000796568 (from here on will be referenced as MK-0634) (375, 125, or 50 mg once daily), compared with placebo. (2) To evaluate the safety and tolerability of daily treatment with MK-0634 (375, 125, or 50 mg/d). Secondary: (1) To determine whether daily treatment with MK-0634 (375, 125, or 50 mg/d) decreases the average number of total incontinence episodes and urge incontinence episodes per day compared with placebo. (2) To determine whether daily treatment with MK-0634 (375, 125, or 50 mg/d) decreases the average number of urgency (strong urge to urinate immediately) episodes per day compared with placebo. Exploratory: To explore the effect of daily treatment with MK-0634 (375, 125, or 50 mg/d) on patient-perceived efficacy assessed by questionnaires (patient global questions, ability to defer urination without leaking, bother of urinary symptoms and disease-specific quality of life).

STUDY DESIGN: This was a multicenter, double-blind, randomized, placebo controlled, parallel-group dose-ranging study comparing clinical effect of 3 doses (375, 125, and 50 mg once daily) of MK-0634 with placebo in postmenopausal women with overactive bladder over an 8-week treatment period. A 1-week screening period was followed by a 1-week placebo run-in (Period I). After the placebo run-in, eligible patients were randomized to the 8-week double-blind treatment period (Period II). Patients who completed the base study were given the option of entering into an off study drug 4-week extension to obtain additional plasma samples for pharmacokinetic analyses.

SUBJECT/PATIENT DISPOSITION:

	Placebo	MK-0634 50 mg	MK-0634 125 mg	MK-0634 375 mg	Total
SCREENING FAILURES					499
RANDOMIZED:	112	108	111	110	441
Male (age range)	0	0	0	0	0
Female: (age range---years)	112 (40 to 75)	108 (40 to 74)	111 (40 to 74)	110 (40 to 74)	441 (40 to 75)
COMPLETED:	103	102	95	99	399
DISCONTINUED:	9	6	16	11	42
Clinical adverse experience:	3	1	5	6	15
Laboratory adverse experience:	0	0	0	0	0
Other:	1	0	0	0	1

DOSAGE/FORMULATION NOS: MK-0634 (and matching placebo) were provided as 125-mg or 50-mg film-coated tablets. Patients were randomized to receive 1 of 4 treatments. Each patient took 4 tablets once daily in the morning immediately following a light meal or snack, such as toast, crackers, etc. The drug could have been taken with a larger meal, if desired.

Treatment Group	Bottle A	Bottle B	Bottle C	Bottle D	Formulation Numbers
MK-0634 375 mg	MK-0634 125 mg	MK-0634 125 mg	MK-0634 125 mg	Placebo for MK-0634 50 mg	[redacted]
MK-0634 125 mg	MK-0634 125 mg	Placebo for MK-0634 125 mg	Placebo for MK-0634 125 mg	Placebo for MK-0634 50 mg	
MK-0634 50 mg	Placebo for MK-0634 125 mg	Placebo for MK-0634 125 mg	Placebo for MK-0634 125 mg	MK-0634 50 mg	
Placebo	Placebo for MK-0634 125 mg	Placebo for MK-0634 125 mg	Placebo for MK-0634 125 mg	Placebo for MK-0634 50 mg	

DIAGNOSIS/INCLUSION CRITERIA: Postmenopausal women ≥ 40 years of age with a history of increased frequency of micturitions (on average, ≥8 micturitions per diary day) and of urge incontinence (on average, ≥1 urge incontinence episodes per diary day) and the total number of urge incontinence episodes had to exceed the total number of stress incontinence episodes as assessed by the patient diary during screening and placebo run-in.

EVALUATION CRITERIA:

EFFICACY: Primary Endpoint: Average daily micturitions from the patient voiding diary. Secondary Endpoints: Average daily urinary urge incontinence episodes, total incontinence episodes, and urge episodes (strong urge to urinate) as assessed by the patient voiding diary. Exploratory Endpoints: Individual scores of the Urinary Incontinence Global Questionnaire (UIGQ), and individual and domain scores of the Urge Urogenital Distress Inventory (UUDI), King's Health Questionnaire (KHQ) (8 domains) and on a single item of the Urgency Perception Scale (UPS).

SAFETY: Overall frequency of clinical and laboratory adverse experiences (AEs), frequency of laboratory values outside predefined limits for selected laboratory safety tests, ECGs and vital signs.

STATISTICAL PLANNING AND ANALYSIS:

EFFICACY: The change from baseline in the number of micturitions per day averaged over a diary week at Week 8 was the primary efficacy endpoint. A longitudinal linear model was used to assess effects of treatment. The primary efficacy endpoint was analyzed using a stepwise linear trend test based on the longitudinal model. This approach adjusts for multiplicity and, thus, preserves the Type I error rate. Pairwise comparisons between MK-0634 doses and placebo were performed to corroborate the results from the trend test. Estimates of the within- and between-group treatment effects at Week 8

STATISTICAL PLANNING AND ANALYSIS (CONT.):

as well as at other time points can be ascertained from the longitudinal model by constructing appropriate estimate statements, but hypothesis testing will only be performed at the primary time point of Week 8 and not at other time points. An all-Patients-as-treated (APaT) approach was used in the efficacy analyses. Other diary endpoints (total incontinence episodes, urge incontinence episodes, and urgency episodes) and questionnaires were analyzed in the same manner as the primary endpoint.

A sample size of 94 patients per group provided 80% power (α=0.05) to detect a difference of 0.7 between an active dose of MK-0634 and placebo on average daily number of micturitions. The study had 90% power to detect a difference of 0.8. To ensure sufficient number of patients at later time points in order to assess the responses at each dose level over time, the target number of randomized patients was increased to account for an expected loss of approximately 12% of the patients by the end of the study. Therefore, 106 patients per group, or a total of 424 patients, were planned.

SAFETY: Safety and tolerability of MK-0634 were assessed by a clinical evaluation of all relevant safety parameters. The analysis of adverse experiences will follow a multitiered approach in the analysis of the study data. For tier 1 clinical adverse experiences, inferential testing via the Cochran-Armitage linear trend test were performed. If a statistically significant result was observed, then pairwise comparisons between an active dose of MK-0634 with placebo was conducted to further assess the difference using the Fisher's exact test. The estimated difference in proportions along with the 95% confidence intervals of the difference between an active dose of MK-0634 and placebo were provided. For other adverse experiences and predefined limits of change in laboratory variables, the estimated difference in proportions along with the 95% confidence interval of the difference between an active dose of MK-0634 and placebo were provided.

RESULTS:

EFFICACY: The results of the primary endpoint, change from baseline in average daily number of micturitions at Week 8, via a longitudinal linear model using the Full-Analysis-Set approach (FAS) are displayed in the table below. Statistically significant decreases from baseline, and as compared to placebo were seen in all three MK-0634 doses.

Analysis of Average Daily Number of Micturitions
Change from Baseline at Week 8 Using Mixed Model Approach
(Full Analysis Set Population)

Treatment	N	Daily Number of Micturitions		Change from Baseline in Daily Number of Micturitions[†]		
		Baseline Mean (SD)	Treatment[†] Mean (SD)	Median	Mean (SD)	LS Mean[‡] (95% CI)
Placebo	95	10.8 (2.4)	9.9 (2.7)	-1.0	-0.9 (1.7)	-0.9 (-1.3, -0.6)
MK-0634 50 mg	100	11.2 (2.4)	9.5 (2.6)	-1.6	-1.7 (1.9)	-1.8 (-2.1, -1.4)
MK-0634 125 mg	93	11.3 (2.6)	9.2 (2.7)	-1.9	-2.0 (2.0)	-2.1 (-2.4, -1.7)
MK-0634 375 mg	101	11.3 (2.7)	9.2 (2.5)	-2.1	-2.1 (1.7)	-2.1 (-2.4, -1.8)

Step-Down Trend Test Results	
Doses Included in the Current Test	p-Value
Placebo to MK-0634 375 mg	<0.001
Placebo to MK-0634 125 mg	<0.001
Placebo to MK-0634 50 mg	<0.001

Pairwise Comparisons from Mixed Model[‡]			
Estimated Difference with Placebo	Difference in LS Means	95% CI for Difference in LS Means	p-Value
MK-0634 375 mg vs Placebo	-1.20	(-1.67, -0.72)	<0.001
MK-0634 125 mg vs Placebo	-1.14	(-1.62, -0.67)	<0.001
MK-0634 50 mg vs Placebo	-0.85	(-1.32, -0.37)	<0.001

Pairwise Comparison among MK doses	Difference in LS Means	95% CI for Difference in LS Means
MK-0634 375 mg vs 125 mg	-0.05	(-0.52, 0.42)
MK-0634 375 mg vs 50 mg	-0.35	(-0.82, 0.12)
MK-0634 125 mg vs 50 mg	-0.30	(-0.78, 0.18)

Effect	p-Value	Pooled SD
Treatment	<0.001	1.71
Study Center	0.037	
Baseline	<0.001	

[†]At Week 8;
[‡]Based on mixed model with terms for treatment, study center, baseline, baseline*time, and treatment*time;
SD = Standard Deviation; CI = Confidence Interval; LS Mean = Least Squares Mean.

SAFETY: MK-0634 was generally well tolerated. One or more adverse experiences were reported by 58 (51.8%) patients in the placebo group, 59 (54.6%) patients in the MK-0634 50 mg group, 61 (55.0%) in the MK-0634 125 mg group and 72 (65.5%) in the MK-0634 375 mg group. GI-related adverse experiences occurred in 19 (17.0%) patients in the placebo group, 20 (18.5%) patients in the MK-0634 50 mg group, 17 (15.3%) patients in the MK-0634 125 mg group, and 43 (39.1%) patients in the MK-0634

375 mg treatment group. Discontinuations due to adverse experiences and drug-related adverse experiences were higher in the MK-0634 375 mg group than in the placebo group. Laboratory adverse experiences were reported by 2 (1.8%) patients in the placebo group, 1 (0.9%) patient in the MK-0634 50 mg group, 1 (0.9%) patient in the MK-0634 125 mg group, and 4 (3.6%) patients in the MK-0634 375 mg group. No patients discontinued study therapy due to drug-related laboratory adverse experience in any of the treatment groups.

Clinical and laboratory adverse experience summary tables follow**.**

Clinical Adverse Experience Summary

	Placebo (N = 112)		MK-0634 50 mg (N = 108)		MK-0634 125 mg (N = 111)		MK-0634 375 mg (N = 110)	
	n	(%)	n	(%)	n	(%)	n	(%)
Number (%) of patients:								
With one or more adverse experiences	58	(51.8)	59	(54.6)	61	(55.0)	72	(65.5)
With no adverse experience	54	(48.2)	49	(45.4)	50	(45.0)	38	(34.5)
With drug-related adverse experiences†	13	(11.6)	12	(11.1)	20	(18.0)	27	(24.5)
With serious adverse experiences	2	(1.8)	2	(1.9)	2	(1.8)	4	(3.6)
With serious drug-related adverse experiences	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.9)
Who died	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Discontinued due to adverse experiences	3	(2.7)	1	(0.9)	5	(4.5)	6	(5.5)
Discontinued due to drug-related adverse experiences	1	(0.9)	0	(0.0)	2	(1.8)	5	(4.5)
Discontinued due to serious adverse experiences	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.9)
Discontinued due to serious drug-related adverse experiences	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.9)

† Determined by the investigator to be possibly, probably or definitely drug related.

Laboratory Adverse Experience Summary

	Placebo (N = 112)		MK-0634 50 mg (N = 108)		MK-0634 125 mg (N = 111)		MK-0634 375 mg (N = 110)	
	n	(%)	n	(%)	n	(%)	n	(%)
Number (%) of patients:								
With at least one lab test postbaseline	112		108		111		110	
With one or more adverse experiences	2	(1.8)	1	(0.9)	1	(0.9)	4	(3.6)
With no adverse experience	110	(98.2)	107	(99.1)	110	(99.1)	106	(96.4)
With drug-related adverse experiences†	0	(0.0)	0	(0.0)	0	(0.0)	3	(2.7)
With serious adverse experiences	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
With serious drug-related adverse experiences	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 adverse experiences	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Discontinued due to drug-related adverse experiences	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Discontinued due to serious adverse experiences	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Discontinued due to serious drug-related adverse experiences	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

† Determined by the investigator to be possibly, probably or definitely drug related.

‡ The percent = number of patients within the laboratory adverse experience category / number of patients with one or more laboratory tests postbaseline.

CONCLUSIONS: 1) Compared to placebo, MK-0634 demonstrated dose-related efficacy which was statistically significant for the primary endpoint of average daily micturition. 2) MK-0634 was generally well tolerated. A dose-related increase in adverse experiences, primarily GI was noted for MK-0634 versus placebo. 3) Efficacy results for the secondary endpoints of urgency episodes, total incontinence episodes, and urge incontinence episodes were consistent with the primary endpoint. 4) Results of exploratory endpoints were also consistent with results of the primary endpoint.

AUTHORS:

[redacted]