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-0812, Tablet Relapsing-Remitting Multiple Sclerosis	**CLINICAL STUDY REPORT SYNOPSIS**

PROTOCOL TITLE/NO.: A Randomized, Double-Blind, Placebo-Controlled, Parallel Groups Study to Assess the Effects of MK-0812 on Disease Activity in Patients With Relapsing-Remitting Multiple Sclerosis as Measured by MRI #003

PROTECTION OF HUMAN SUBJECTS: This study 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.

INVESTIGATOR(S)/STUDY CENTER(S): International Multicenter 32 sites participated, 23/32 sites screened patients (9 US; 14 ExUS); 18/23 sites randomized patients (8 US, 10 ExUS)

PUBLICATION(S):

PRIMARY THERAPY PERIOD:	**CLINICAL PHASE:** IIa
Base study: 09-Oct-2004 to 22-Dec-2005 Open Label Extension (OLE): 19-Aug-2005 to 08-Jan-2006	

DURATION OF TREATMENT: Base study 3 months; OLE 3 months

OBJECTIVE(S):

Primary Objectives: (1) To assess the effect of MK-0812 in reducing the baseline-adjusted accrual rate of new gadolinium (Gd)-enhancing brain lesions in patients with Relapsing-Remitting Multiple Sclerosis (RRMS) as assessed by Magnetic Resonance Imaging (MRI). (2) To assess the safety and tolerability of MK-0812 in patients with Multiple Sclerosis.

Secondary Objectives: (1) To assess the effect of MK-0812 in reducing the baseline-adjusted volume of Gd-enhancing lesions; (2) To assess the effect of MK-0812 in reducing the cumulative number of new Gd-enhancing brain lesions; and (3) To assess the effect of MK-0812 on the cumulative number of persistent Gd-enhancing lesions.

Exploratory Objectives: (1) To assess the effect of MK-0812 on the per patient proportion of MRI scans with new Gd-enhancing brain lesions: (2) To assess the effect of MK-0812 on the proportion of patients with new Gd-enhancing brain lesions: (3) To assess the effect of MK-0812 on the baseline-adjusted accrual rate of new Gd-enhancing brain lesions for Months 2 and 3; and (4) To assess the effect of MK-0812 on the following clinical endpoints: (a) reducing the proportion of patients with relapses requiring corticosteroid treatment (b) reducing the proportion of patients with objective relapse; (c) reducing the proportion of patients with relapse; (d) reducing the change from baseline on the Expanded disability status scale (EDSS).

STUDY DESIGN: Randomized, double-blind (with in-house blinding), placebo-controlled, parallel group

SUBJECT/PATIENT DISPOSITION:

Overall Disposition of Patients

	MK-0812 10 mg		Placebo		Total	
	N	(%)	N	(%)	N	(%)
BASE STUDY	**25**		**16**		**41**	
Male (age range in years)	8 (19-50)		6 (20-42)		14 (19-50)	
Female (age range in years)	17 (20-52)		10 (21-52)		27 (20-52)	
COMPLETED STUDY	**19**	**(76.0)**	**13**	**(81.3)**	**32**	**(78.0)**
Completed Base Study Only	10	(52.6)	7	(53.8)	17	(53.1)
Completed Base Study, Entered OLE	9	(47.4)	6	(46.2)	15	(46.9)
DISCONTINUED DRUG/ COMPLETED STUDY	**1**	**(4.0)**	**0**	**(0.0)**	**1**	**(2.4)**
Clinical adverse experience	1	(100)[†]	0	(0.0)	1	(100)[†]
DISCONTINUED STUDY	**5**	**(20.0)**	**3**	**(18.8)**	**8**	**(19.5)**
Clinical adverse experience	1	(20.0)[†]	0	(0.0)	1	(12.5)[†]
Terminated by sponsor	4	(80.0)[†]	3	(100)[†]	7	(87.5)[†]
ENTERED OPEN LABEL EXTENSION[‡]	**9**		**6**		**15**	
Discontinued OLE early/terminated by sponsor	9	(100)	6	(100)	15	(100)

[†] Percent for subcategories is based on the main category N.
[‡]Patients all elected to be on MK-0812 10 mg in the Open Label Extension (OLE). Patients were counted according to the randomized treatment group from the base study.
N = Number of patients.

DOSAGE/FORMULATION NOS.: Patients received either MK-0812 10 mg (in the form of two 5-mg tablets) or matching placebo and were instructed to take both tablets orally at the same time each day. At the completion of treatment Month 3, patients were allowed to enroll in an Open Label Extension (OLE). Patients consented to either OLE and dosed daily with open label MK-0812 10 mg (in the form of two 5-mg tablets) or to the comparator group comprised of those patients who did not take open label drug and returned to "usual care" while continuing OLE clinic visits.

DIAGNOSIS/INCLUSION CRITERIA: Male and female patients (aged 18 to 55 years) with RRMS onset within 10 years and at least one Gd-enhancing lesion on the screening MRI, EDSS ≤4.5, and at least one exacerbation within the last 1 year. Patients with a recent clinically isolated syndrome (CIS) suggestive of MS occurring between 3 and 12 months (inclusive) before screening and a previously identified MRI lesion consistent with demyelination, were also included in the study if the screening MRI revealed a new Gd-enhancing lesion.

EVALUATION CRITERIA:

EFFICACY MEASUREMENTS: Monthly brain MRI measurements, change from baseline in EDSS scores, and monitoring of MS relapses

SAFETY MEASUREMENTS: Frequency of adverse experiences, physical examination, vital signs, body weight, laboratory safety studies—serum chemistry, complete blood count (CBC), urinalysis, electrocardiograms (ECGs), and retinal eye examinations with photograph. A Data Monitoring Committee (DMC) was unblinded to all safety and tolerability data prior to unblinding for the scheduled formal analyses.

STATISTICAL PLANNING AND ANALYSIS:

The primary efficacy measurement was the baseline-adjusted accrual rate of new Gd-enhancing brain lesions for patients treated with MK-0812 as compared to those treated with placebo. The comparison between treatment groups (randomized in a 2:1 ratio of MK-0812:Placebo) was based on a 2-sided Wilcoxon-Mann-Whitney test using a significance level (2-sided) of 0.05. The critical significance level for the primary efficacy analysis at the completion of the study was planned to be adjusted for a single interim efficacy analysis. This interim efficacy analysis was planned for the time point at which approximately 67% of patients had completed the study, however, this analysis was not performed due to study termination. Interim safety analyses were produced for and reviewed by the Data Monitoring Committee.

RESULTS:

EFFICACY:

The primary endpoint, the median baseline-adjusted accrual rate of new Gd-enhancing lesions, was expected to be close to 0 for the placebo group (assuming patients' activity levels at baseline were maintained during the trial), and was expected to be a negative number for an active compound that was effective in the prevention of the accrual of new Gd-enhancing lesions. The results for the two treatment groups were similar (p>0.999) for the primary endpoint, with observed median (mean) adjusted accrual rates of 0.0 (-0.2) for the MK-0812 10 mg group and 0.2 (0.0) for the Placebo group.

Both the baseline and on-treatment mean values for the number of new enhancing lesions were somewhat higher for the MK-0812 10 mg group versus the placebo group, though the medians were similar. Results overall were quite similar between the two treatment groups.

Summary of New Gd-Enhancing Lesions Shown on Brain MRI
Modified Intention-to-Treat (MITT) Population

Parameter	Treatment Group		p-value
	MK-0812 10 mg	Placebo	
Baseline no. of new Gd lesions/patient	N=25	N=16	
Mean (SE)	2.4 (0.7)	1.4 (0.4)	
Median (Q1, Q3)	1.0 (0.0, 2.0)	1.0 (0.0, 2.0)	nps
Cumulative no. of new Gd lesions/patient†	N=25	N=16	
Mean (SE)	6.5 (2.1)	3.4 (0.8)	
Median (Q1, Q3)	3.0 (1.0, 6.0)	3.5 (0.5, 6.0)	0.746
Baseline-Adjusted Accrual Rate of new Gd lesions/patient	N=25	N=16	
Mean (SE)	-0.2 (0.5)	0.0 (0.4)	
Median (Q1, Q3)	0.0 (-1.0, 1.0)	0.2 (-0.8, 0.5)	>0.999
Cumulative no. of new Gd lesions† - no. of patients n (%)			
No lesions	6 (24.0)	4 (25.0)	
1-3 lesions	8 (32.0)	4 (25.0)	
4-6 lesions	5 (20.0)	4 (25.0)	
7-9 lesions	3 (12.0)	4 (25.0)	
10-12 lesions	0 (0.0)	0 (0.0)	
>12 lesions	3 (12.0)	0 (0.0)	
Proportion of Patients with a New Gd-Enhancing Lesion n (%)	19 (76.0)	12 (75.0)	>0.999

† Indicates that endpoint is based on on-treatment MRI scans
Note: p-values for continuous data based on the Mann-Whitney Wilcoxon test; p-values for proportions based on the Chi-Square test of proportions.
Note: SE = Standard error; Q1 = 1st quartile; Q3 = 3rd quartile.
nps = Not pre-specified for statistical analysis.

Clinical relapses were assessed during the course of the study. A similar proportion of patients between the two treatment groups (12.0% of patients on MK-0812 10 mg versus 6.25% of patients on Placebo) experienced an objective relapse during the base study (p>0.999). A higher proportion of patients (24.0% of patients on MK-0812 10 mg versus 6.25% of patients on Placebo, p=0.0215) experienced a relapse of any classification (objective or non-objective; patient-reported relapses were excluded).
During the OLE, 15 patients opted to receive MK-0812 10 mg. Two additional relapses were recorded among these patients, both of which were objective relapses. One of the relapses occurred on Day 35 of the OLE in a patient initially assigned to Placebo. The other relapse occurred on Day 16 of the OLE in a patient initially assigned to MK-0812 10 mg (total number of days on MK-0812 10 mg was 100).

SAFETY:
Overall, MK-0812 10 mg was generally well tolerated relative to placebo. A numerically higher proportion of patients in the MK-0812 10 mg group had 1-any adverse experiences 2-drug-related adverse experiences, and 3-adverse experiences that were in the general category of infections and infestations versus placebo, though none of these differences were statistically significant. One patient on MK-0812 10 mg had a serious drug-related adverse experience that was considered an other important medical event; this was the only adverse experience that resulted in treatment discontinuation during the study.

A relatively low proportion of patients had laboratory adverse experiences: 5 (20.0%) patients on MK-0812 10 mg and 1 (6.3%) patient on placebo. The majority of these adverse experiences were considered to be drug-related.

Clinical Adverse Experience Summary
Base Study
All Patients as Treated (APaT) Population

Term	MK-0812 10 mg N=25 (A) n (%)	Placebo N=16 (B) n (%)	Difference of Proportions A%-B%	95% CI	p-Value
With one or more adverse experiences	19 (76.0)	10 (62.5)	13.5	(-14.7, 42.0)	0.485
With no adverse experiences	6 (24.0)	6 (37.5)			
With drug-related† adverse experiences	10 (40.0)	5 (31.3)	8.8	(-21.9, 36.2)	0.742
With serious adverse experiences	1 (4.0)	0 (0.0)	4.0	(-16.1, 19.8)	> 0.999
With serious drug-related adverse experiences	1 (4.0)	0 (0.0)	4.0	(-16.1, 19.8)	> 0.999
Who died	0 (0.0)	0 (0.0)	0.0	(-19.8, 13.6)	nps
Discontinued therapy due to adverse experiences	2 (8.0)	0 (0.0)	8.0	(-12.4, 25.2)	0.512
Discontinued therapy due to drug-related adverse experiences	2 (8.0)	0 (0.0)	8.0	(-12.4, 25.2)	nps
Discontinued therapy due to serious adverse experiences	1 (4.0)	0 (0.0)	4.0	(-16.1, 19.8)	nps
Discontinued therapy due to serious drug-related adverse experiences	1 (4.0)	0 (0.0)	4.0	(-16.1, 19.8)	nps
With Infections and Infestations	9 (36.0)	4 (25.0)	11.0	(-19.2, 37.2)	0.513

† Determined by the investigator to possibly, probably, or definitely study drug related.
CI = Confidence Interval.
p-Value from Fisher's exact test.
nps = Not pre-specified for statistical analysis.

Laboratory Adverse Experience Summary
Base Study
APaT Population

Term	MK-0812 10 mg N=25 (A) n (%)	Placebo N=16 (B) n (%)	Difference of Proportions A%-B%	95% CI	p-Value
With one or more adverse experiences	5 (20.0)	1 (6.3)	13.8	(-11.4, 34.7)	0.376
With no adverse experiences	20 (80.0)	15 (93.8)			
With drug-related† adverse experiences	5 (20.0)	0 (0.0)	20.0	(-1.3, 39.4)	0.137
With serious adverse experiences	0 (0.0)	0 (0.0)	0.0	(-19.8, 13.6)	nps
With serious drug-related adverse experiences	0 (0.0)	0 (0.0)	0.0	(-19.8, 13.6)	nps
Who died	0 (0.0)	0 (0.0)	0.0	(-19.8, 13.6)	nps
Discontinued therapy due to adverse experiences	0 (0.0)	0 (0.0)	0.0	(-19.8, 13.6)	nps
Discontinued therapy due to drug-related adverse experiences	0 (0.0)	0 (0.0)	0.0	(-19.8, 13.6)	nps
Discontinued therapy due to serious adverse experiences	0 (0.0)	0 (0.0)	0.0	(-19.8, 13.6)	nps
Discontinued therapy due to serious drug-related adverse experiences	0 (0.0)	0 (0.0)	0.0	(-19.8, 13.6)	nps

† Determined by the investigator to possibly, probably, or definitely study drug related.
CI = Confidence Interval.
p-Value from Fisher's exact test.
nps = Not pre-specified for statistical analysis.

CONCLUSIONS:

1. MK-0812 10 mg daily for 3 months was not superior to placebo in reducing the baseline-adjusted accrual rate of new Gd-enhancing brain lesions in patients with RRMS.
2. MK-0812 10 mg daily was generally well tolerated in patients with RRMS.

AUTHORS: [redacted]