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.

MK-0812 Prot. No. 008-02
Efficacy, Tolerability, and Safety Study in Rheumatoid Arthritis

2. Synopsis

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Rheumatoid Arthritis

CLINICAL STUDY REPORT SYNOPSIS

PROTOCOL TITLE/NO.: A Placebo-Controlled, Parallel-Group, Double-Blind, 12-Week Study to Assess the Clinical Efficacy, Safety, and Tolerability of MK-0812 in Rheumatoid Arthritis Patients #008-02

INVESTIGATOR(S)/STUDY CENTER(S): Multicenter Ex-US (35)

PUBLICATION(S):

PRIMARY THERAPY PERIOD: 25-Jun-2004 to 09-May-2005 **CLINICAL PHASE:** IIa

DURATION OF TREATMENT: 12 Weeks

OBJECTIVE(S): (1) To demonstrate the clinical efficacy of MK-0812 in the treatment of rheumatoid arthritis (RA); (2) To demonstrate the safety and tolerability of MK-0812 0.4 and 10.0 mg once daily for 12 weeks in RA patients.

STUDY DESIGN: Double-Blind, Parallel-Group, Placebo-Controlled

SUBJECT/PATIENT DISPOSITION:

	Placebo	MK-0812 0.4 mg	MK-0812 10.0 mg
SCREENING FAILURES:			
RANDOMIZED:	46	50	53
Male (age range)	11 (27 to 61)	15 (38 to 68)	8 (50 to 65)
Female (age range)	35 (24 to 65)	35 (24 to 65)	45 (19 to 63)
COMPLETED:	27	30	28
DISCONTINUED:	19	20	25
Clinical adverse experience	2	3	5
Laboratory adverse experience	0	0	0
Other	17	17	20

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Rheumatoid Arthritis

CLINICAL STUDY REPORT SYNOPSIS
-2-

DOSAGE/FORMULATION NOS.: MK-0812 0.4mg or 10 mg or matching placebo once daily for 12 weeks.

DIAGNOSIS/INCLUSION CRITERIA: Patients' diagnosis of rheumatoid arthritis (RA) must meet or have met 1987 ARA (American Rheumatism Association) revised diagnostic criteria. Patients must have active RA with a minimum level of disease activity including at least 10 swollen joints and 10 tender or painful joints, a Patient Global Assessment of Disease Activity of > 40 mm (on a 100 mm Visual Analog Scale [VAS]), an Investigator Global Assessment of Disease Activity of fair, poor, or very poor (on a 5-point Likert scale), and 1 of the following: an erythrocyte sedimentation rate (ESR) greater than or equal to 26, a C-reactive protein (CRP) of at least 2.0 mg/dL, or morning stiffness that lasts at least 45 minutes at Visits 1.0 and Visit 2.0

EVALUATION CRITERIA:

EFFICACY MEASUREMENTS:

Primary: Swollen Joint Count. Secondary: American College of Rheumatology 20% (ACR20) responder criteria (the proportion of patients in each treatment group meeting the [ACR20] for their average response at Weeks 8, 10, 12, and not discontinuing in the 12-week treatment period), tender joint count, Patient Global Assessment of Disease Activity, Patient Global Assessment of Response to Therapy, and Investigator's Global Assessment of Disease Activity, Health Assessment Questionnaire (HAQ disability scales), patient's global assessment of pain, and serum C-reactive protein levels.

SAFETY MEASUREMENTS: Clinical monitoring of vital signs, physical examination, electrocardiograms (ECGs), and clinical and laboratory adverse experiences.

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MK-0812
L-000124467, Tablets
Rheumatoid Arthritis

CLINICAL STUDY REPORT SYNOPSIS
-3-

STATISTICAL PLANNING AND ANALYSIS:

Efficacy: The primary response for each continuous efficacy variable was the average change from baseline at post-baseline efficacy period, i.e. average response from Study Weeks 8, 10, and 12. None of these values were imputed; only those values observed at these study weeks were included in the computation of each individual patient's average response. If all of the Week 8, 10, and 12 observations were missing, then the last observed value was used as that patient's average response. The analysis of ACR20 was based on similar approach. The primary analysis was based on all-patients-treated (APT) approach; i.e., all patients with a baseline and at least one postbaseline observation were included in the analysis. Additionally, analysis based on per-protocol approach was carried out for the primary endpoint, Swollen Joint Count. Plots over time of Least Squares (LS) mean changes from baseline (±SE) by treatment group were provided for all continuous efficacy variables and selected safety variables. For purposes of these efficacy variable plots only, missing observations were imputed by the last observed value.

All efficacy variables except for the proportion of patients meeting the ACR20 criteria were assessed by an analysis of covariance (ANCOVA) model. The model included terms for stratum (DMARD use), baseline value of the efficacy variable being analyzed as a 1-degree-of-freedom covariate, and treatment group. Patient Global Assessment of Disease Activity at baseline was used as the covariate for patient global response to therapy since response to therapy was not measured at baseline. Study centers were not included in the ANCOVA model for the analysis, but the treatment effects for the primary efficacy endpoint were summarized by study center. The proportion of patients satisfying the ACR20 criteria and completing the study was assessed using the Cochran-Mantel-Haenszel (CMH) test with DMARD use as a stratification factor.

The effect of DMARD stratum and other subgroup factors were also be assessed. Because of the small sample size in this study, the subgroup analyses were viewed as exploratory. The primary analysis of clinical efficacy was based on the combined strata.

Safety: Incidence of adverse experiences was summarized by treatment group. Predefined limits of change from baseline have been established for clinically important increases and decreases in selected laboratory tests. Counts by treatment group were generated for the number of patients exceeding the predefined limits of change.

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L-000124467, Tablets
Rheumatoid Arthritis

CLINICAL STUDY REPORT SYNOPSIS
-4-

RESULTS:

EFFICACY: For the primary efficacy endpoint, Swollen Joint Count, the LS mean changes from baseline over Weeks 8, 10, and 12 were -6.35, -7.10, and -4.60 for placebo, MK-0812 0.4 mg, and MK-0812 10 mg, respectively. There was no statistically significant treatment difference between MK-0812 10 mg and placebo. For the per-protocol analysis for swollen joint count, the LS mean changes from baseline over Weeks 8, 10, and 12 were -7.69, -6.93, and -4.05 for placebo, MK-0812 0.4 mg, and MK-0812 10 mg, respectively. MK-0812 10 mg showed a significantly smaller improvement than placebo. For tender joint count, patient global assessment of disease activity, investigator global assessment of disease activity, patient global assessment of pain, and patient global assessment of response to therapy, MK-0812 10 mg demonstrated significant smaller improvement in LS mean changes from baseline than placebo. For all other efficacy endpoints (health assessment questionnaire and serum C-reactive protein), no significant differences between MK-0812 10 mg and placebo were observed. For ACR 20 response rate, MK-0812 10 mg had a similar response rate to placebo. The effect of DMARD stratum and other subgroup factors (methotrexate use and corticosteroid use) indicated that there was no treatment by subgroup interaction.

SAFETY: MK-0812 was generally safe and well tolerated. One or more adverse experiences were reported by 21 (45.7%) patients in the placebo group, 23 (46.0%) patients in the 0.4 mg group, and 37 (69.8%) in the 10.0 mg group. The incidence of drug-related clinical adverse experiences was higher for the 10 mg dose compared with the 0.4 mg dose and placebo. Discontinuations due to serious adverse experiences were higher in the placebo and 0.4 mg groups compared to the 10.0 mg group Discontinuations due to adverse experiences were higher in the 10.0 mg group than the 0. 4 mg and placebo groups.. Laboratory adverse experiences were reported by 1 patient in the 0.4 mg group and 1 patient in the 10.0 mg group. The incidence of serious drug-related adverse experiences was low in all treatments groups.

Clinical and laboratory adverse experience summary tables follow.

Clinical Adverse Experience Summary

	Placebo (N = 46)		MK-0812 0.4 mg (N = 50)		MK-0812 10 mg (N = 53)	
	n	(%)	n	(%)	n	(%)
Number (%) of patients:						
With one or more adverse experiences	21	(45.7)	23	(46.0)	37	(69.8)
With no adverse experience	25	(54.3)	27	(54.0)	16	(30.2)
With drug-related adverse experiences†	11	(23.9)	8	(16.0)	18	(34.0)
With serious adverse experiences	1	(2.2)	3	(6.0)	2	(3.8)
With serious drug-related adverse experiences	0	(0.0)	0	(0.0)	1	(1.9)
Who died	0	(0.0)	0	(0.0)	0	(0.0)
Discontinued due to adverse experiences	1	(2.2)	3	(6.0)	5	(9.4)
Discontinued due to drug-related adverse experiences	0	(0.0)	1	(2.0)	5	(9.4)
Discontinued due to serious adverse experiences	1	(2.2)	2	(4.0)	0	(0.0)
Discontinued due to serious drug-related adverse experiences	0	(0.0)	0	(0.0)	0	(0.0)

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

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MK-0812
L-000124467, Tablets
Rheumatoid Arthritis

CLINICAL STUDY REPORT SYNOPSIS
-5-

Laboratory Adverse Experience Summary

	Placebo (N = 46)		MK-0812 0.4 mg (N = 50)		MK-0812 10 mg (N = 53)	
	n	(%)‡	n	(%)‡	n	(%)‡
Number (%) of patients:						
With at least one lab test postbaseline	46		50		53	
With one or more adverse experiences	0	(0.0)	1	(2.0)	1	(1.9)
With no adverse experience	46	(100.0)	49	(98.0)	52	(98.1)
With drug-related adverse experiences†	0	(0.0)	1	(2.0)	0	(0.0)
With serious adverse experiences	0	(0.0)	0	(0.0)	0	(0.0)
With serious drug-related adverse experiences	0	(0.0)	0	(0.0)	0	(0.0)
Who died	0	(0.0)	0	(0.0)	0	(0.0)
Discontinued due to adverse experiences	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)
Discontinued due to serious adverse experiences	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)

† 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. There is no evidence of clinically meaningful efficacy of either 0.4 or 10 mg MK-0812 once daily in the treatment of rheumatoid arthritis over 12 weeks.
2. MK-0812 0.4 and 10 mg once daily are generally safe and well-tolerated over 12 weeks in rheumatoid arthritis patients

AUTHORS:

[redacted]