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-0822 [redacted], Tablet Osteoarthritis	**CLINICAL STUDY REPORT SYNOPSIS**

PROTOCOL TITLE/NO.: A Phase IIa Randomized, Placebo-Controlled Clinical Trial to Study the Safety and Efficacy of MK-0822 in Patients with Osteoarthritis #011

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. [redacted]

INVESTIGATOR(S)/STUDY CENTER(S): At the time of study termination, 10 investigators in the United States, and 10 investigators in Chile, Colombia, Mexico, Poland, and United Kingdom had screened patients for this study. Two investigators in the United States had dosed patients [redacted]

PRIMARY THERAPY PERIOD: 15-Feb-2007 (first patient in/first dose taken) to 01-Apr-2007 (last dose taken). Last patient completed follow-up (last patient out): 05-Apr-2007. All data corrections applied (frozen file): 07-Jun-2007.	**CLINICAL PHASE:** IIa

DURATION OF TREATMENT: Following a multi-visit screening period of approximately 4 weeks, eligible patients were to be randomized into a 52-week treatment period. Two patients were randomized into the study; one patient received MK-0822 for 46 days and one patient received placebo for 1 day [redacted]

OBJECTIVE(S): Primary: (1) To evaluate the efficacy of MK-0822 5 mg once daily relative to placebo in the prevention of knee cartilage loss over 12 months of treatment based on Magnetic Resonance Imaging (MRI) assessments of the medial tibial cartilage normalized volume; (2) To investigate the overall safety and tolerability of MK-0822 in osteoarthritis (OA) patients over a 12 month treatment period.

STUDY DESIGN: This was a randomized, parallel-group, double blind, placebo-controlled study designed to evaluate the safety and efficacy of MK-0822 as a disease modifying OA drug in the prevention of knee cartilage loss. This study was to be conducted at 36 clinical centers and 12 MRI centers worldwide. Clinical centers were grouped by geographic vicinity to allow centralization of MRI center for multiple sites in a specific region.

Clinical, radiographic, and MRI criteria were used to identify patient knees that are predicted to show medial compartment cartilage loss within a reasonable period (e.g. 52 weeks). Patients who met clinical and radiographic criteria at Visit 1 were subsequently screened with MRI at Visit 2. The screening MRI at Visit 2 was to be used as the baseline for determining change in cartilage structural endpoints. Eligible patients were randomized at Visit 3 in a 1:1 ratio to receive either placebo or MK-0822 5 mg once daily for 52 weeks.

Three hundred twenty patients were planned to be randomized in this study. Patients were allowed to continue taking any prescription or over-the-counter oral pain medication for their knee OA during the trial, except during scheduled washout periods prior to Baseline (Visit 3), Months 1, 3, 6, and 12. Acetaminophen/paracetamol were to be provided to all patients to be taken as needed for breakthrough OA pain during the washout periods, with the exception of the 24 hours prior to the visits at Baseline (Visit 3), Months 1, 3, 6, and 12, when the clinical severity of knee OA was to be assessed.

Radiographic and MRI efficacy data were to be collected at Baseline and Month 12. Clinical evaluations and laboratory measurements were to be performed at Baseline and Months 1, 3, 6, 9, and 12. Urinary CTX-II biomarker and pharmacokinetic data were to be collected at Baseline, and Months 3, 6, and 12. Reports of all adverse experiences (nonserious and serious) were to be collected throughout the trial and up to 21 days after the last dose of study medication. Patients were to be contacted by telephone each month when a clinic visit was not required to ensure compliance and follow-up.

Patients who discontinue treatment early were to have end-of-study assessments identical to those to be performed at Month 12, except the knee MRI was to be obtained only for patients on study therapy for 6 months or longer due to the slow rate of cartilage change in OA. All patients who discontinued treatment early were to have a standardized knee radiograph for assessment.

Routine safety monitoring for this study was planned to be supplemented with a Data Safety Monitoring Committee with attention to skin, skeletal, dental and immune system adverse experiences. However, study was terminated by the Sponsor prior to the implementation of this committee.

[redacted]

SUBJECT/PATIENT DISPOSITION: Summary of patient accounting is presented below. Of the 164 non-randomized patients, the eligibility of 60 patients (36.6%) could not be determined because these patients did not complete all screening procedures prior to study termination by sponsor. The screen failure rate was high due to the need to enrich for patients with OA progression factors. The majority of the non-randomized patients (53.7%, 88 of 164) were excluded due to failure to satisfy the radiographic criteria for population enrichment, which included the following: Kellgren-Lawrence score of 2 or 3, varus mal-alignment, and minimum joint-space width in the medial compartment [redacted]. The screen failure rate based on this radiographic criteria alone was 91.7% (88 of the 96 patients screened with radiographs) [redacted]

Of the 8 patients that were eligible based on Visit 1 clinical and radiographic assessments (including the protocol violator noted below), 7 patients were examined by MRI at Visit 2, and 4 of these patients were deemed eligible to receive study drug treatment [redacted] at Visit 3. Two of the 4 patients received study drug prior to study termination by sponsor [redacted]

[redacted]

	Total	Placebo	MK-0822 5 mg
NON-RANDOMIZED†:	164		
Ineligible	98		
Patient withdrew consent	4		
Site terminated‡	62		
RANDOMIZED:	2	1	1
Male (age range)	2 (51-56)	1 (51)	1 (56)
Female (age range)	0	0	0
COMPLETED:	0	0	0
DISCONTINUED:	2	1	1
Clinical adverse experience	1	1	0
Laboratory adverse experience	0	0	0
Site terminated	1	0	1

† Patients excluded during the multi-visit screening period, including patients whose eligibility could not be determined due to study being terminated.
‡ Includes 2 patients who were eligible for study but not randomized due to study being terminated.
[redacted]

DOSAGE/FORMULATION NOS.: Two patients were randomized into the study and received either a daily dose of MK-0822 5 mg (N=1) or matching placebo (N=1) by mouth in a double blind fashion. Acetaminophen/paracetamol was to be provided to randomized patients for breakthrough OA pain during the treatment period.

Identity of Clinical Supplies

Drug Product and Potency	Dosage Form	Formulation Number	Study/Control Number
For Allocation Range 2000-2191			
MK-0822 5 mg	OCT	[redacted]	
MK-0822 5 mg placebo	OCT		
Acetaminophen 500 mg	OCT		
For Allocation Range 2192-2479			
MK-0822 5 mg	OCT		
MK-0822 5 mg placebo	OCT		
Standard image placebo†	OCT		
Paracetamol 500 mg	OCT		

† Identical in image and composition to MK-0822 5 mg placebo.
OCT= Oral Compressed Tablet.
[redacted] Acetaminophen [redacted]
Paracetamol [redacted]
Placebo [redacted]

Data Source: Not Applicable

DIAGNOSIS/INCLUSION CRITERIA: Male or female patients ≥40 years of age, with symptomatic knee OA, who fulfill the American College of Rheumatology (ACR) classification criteria for OA, and were enriched for disease progression (based on body mass index, and specific radiographic and MRI criteria) were eligible to enter the study after providing written informed consent [redacted]

EVALUATION CRITERIA:

Efficacy: For the evaluation of treatment efficacy, an MRI scan of the index knee was to be obtained at Visit 2 (Baseline/Screening) and Visit 8 (End-of-Study) or Discontinuation (if on-therapy for 6 months or longer). The MR images were to be submitted to a Central Imaging Vendor for quantitative analyses of cartilage and bone changes at the 2 timepoints. For the primary endpoint analysis, the Imaging Vendor was to quantify the changes in the cartilage volume (normalized to subchondral bone surface area) in the medial tibial region of the index knee.

Safety: The safety and tolerability of MK-0822 (or matching placebo) was evaluated by clinical assessment of data collected from physical examination, vital sign measurements, electrocardiogram, and laboratory safety analyses, as well as spontaneous adverse experience reporting. Skin-related disorders, fractures, dental adverse experiences, and incidences of low absolute lymphocyte counts (<1000/microL) were also monitored and reported.

STATISTICAL PLANNING AND ANALYSIS: No formal statistical analysis was performed for efficacy or safety due to limited data as a result of study discontinuation.
Summary statistics were performed on the screening radiographic data to examine the baseline characteristics of clinically eligible patients prior to undergoing further screening for population enrichment[redacted]

RESULTS:

Efficacy: No efficacy data were available. The study was prematurely terminated for administrative reasons, as new external data suggested that the study's primary endpoints change more slowly than the trial is designed to demonstrate[redacted]

Safety: Summary of clinical adverse experiences is presented below. [redacted]

There were no serious adverse experiences reported in any treatment group.

There were no laboratory adverse experiences reported in any treatment group. [redacted]

Clinical Adverse Experience Summary

	Placebo (N = 1)		MK-0822 5 mg (N = 1)	
	n	(%)	n	(%)
Number (%) of patients:				
With one or more adverse experiences	1	(100)	0	(0.0)
With no adverse experience	0	(0.0)	1	(100)
With drug-related adverse experiences[†]	1	(100)	0	(0.0)
With serious adverse experiences	0	(0.0)	0	(0.0)
With serious drug-related adverse experiences	0	(0.0)	0	(0.0)
Who died	0	(0.0)	0	(0.0)
Discontinued due to adverse experiences	1	(100)	0	(0.0)
Discontinued due to drug-related adverse experiences	1	(100)	0	(0.0)
Discontinued due to serious adverse experiences	0	(0.0)	0	(0.0)
Discontinued due to serious drug-related adverse experiences	0	(0.0)	0	(0.0)

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

[redacted]

CONCLUSIONS: No conclusions regarding the efficacy or safety of MK-0822 in the treatment of knee OA can be drawn based on limited data availability from this study. As expected, this study had a high screen failure rate due to the inclusion criteria to enrich for patients at risk of cartilage loss over time. The feasibility to conduct studies of OA in enriched patient populations will likely depend on the choice of inclusion criteria.

AUTHORS: [redacted]