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-0952 L-001037116, Tablet Alzheimer's Disease	**CLINICAL STUDY REPORT SYNOPSIS**

PROTOCOL TITLE/NO.: A Phase IIa, Randomized, Double-Blind, Placebo-Controlled, 2-Period Crossover Study to Assess the Efficacy and Safety of MK-0952 in Patients With Alzheimer's Disease [redacted] #004

INVESTIGATOR(S)/STUDY CENTER(S): Multi-center (9) in the United Kingdom and South Africa [redacted]

PRIMARY THERAPY PERIOD: 08-Dec-2006 to 02-Nov-2007 | **CLINICAL PHASE:** IIa

DURATION OF TREATMENT: The duration of the study was ~114 days, beginning with a Screening Visit approximately 14 days prior to Baseline Visit, followed by two, 28-day treatment periods, separated by a 28-day placebo-washout period, and ending with a 14-day, poststudy visit

OBJECTIVE(S): This study enrolled male and female patients ≥55 years of age diagnosed with mild-to-moderate Alzheimer's disease (AD).

Primary: (1) To evaluate the efficacy of MK-0952 37.5 mg daily over a 4-week treatment period in improving cognitive function in patients with mild-to-moderate AD as assessed by the 0- to 24-hour difference in Word List Learning-Selective Reminding (WLL-SR) Summary Score and the 2- to 24-hour correct response percentage difference in the Word List Learning-Delayed Recognition (WLL-DR) test of the Computerized Neuropsychological Test Battery (CNTB). (2) To evaluate the safety and tolerability of MK-0952 37.5 mg daily in patients with mild-to-moderate AD. **Secondary**: (1) To evaluate the efficacy of MK-0952 37.5 mg daily over a 4-week treatment period in improving cognitive function in patients with mild-to-moderate AD as measured by the total score from the 11 tasks of the Alzheimer's Disease Assessment Scale- Cognitive Subscale (ADAS-Cog). (2) To evaluate the efficacy of MK-0952 37.5 mg daily over a 4-week treatment period in improving cognitive function in patients with mild-to-moderate AD as measured by a Memory Summary Score (MSS) derived from the Route test result and the following CNTB memory test scores: Summary Score from WLL-SR (0-hour), Recall Retention Index from WLL-DRCall (2-hour), Recognition Retention Index from WLL-DR (2-hour), correct percentage from the VMEM test, 0- to 24-hour Summary Score difference from WLL-SR, and 2- to 24-hour correct response percentage difference from WLL-DR. **Exploratory**: (1) To evaluate the efficacy of MK-0952 37.5 mg daily over a 4-week treatment period in improving cognitive function in patients with mild-to-moderate AD as assessed by the Total Summary Score (TSS) derived from the correct response percentage from the Route test and the following CNTB memory test scores: Summary Score from WLL-SR (0-hour), Recall Retention Index from WLL-DRCall (2-hour), Recognition Retention Index from WLL-DR (2-hour), correct percentage from the VMEM test, 0- to 24-hour Summary Score difference from WLL-SR, 2- to 24-hour correct response percentage difference from WLL-DR, correct response percentage from the Object Naming Test (ONT), and percentage of response in the Choice Reaction Time (CRT). (2) To evaluate the efficacy of MK-0952 37.5 mg daily over a 4-week treatment period in improving cognitive function in patients with mild-to-moderate AD as assessed by the individual scores of the Route test, Everyday Memory Questionnaire (EMQ), Mazes from ADAS-Cog and each of the following individual CNTB modules: ONT, VMEM, Simple Reaction Time (SRT), CRT, WLL-SR, WLL-DRCall, and WLL-DR.

STUDY DESIGN: Double-blind (with in-house blinding), placebo-controlled, two-period crossover study. Patients were allocated in a 1:1 ratio to one of two treatment sequences: either MK-0952 37.5 mg followed by placebo for MK-0952 37.5 mg or placebo for MK-0952 37.5 mg followed by MK-0952 37.5 mg. Each treatment in the sequence was administered for 28 days (Periods I and II), with a 28-day placebo washout between treatments.

SUBJECT/PATIENT DISPOSITION: [redacted]

	Treatment Sequence		
	MK0952-PBO	PBO-MK0952	Total
SCREENING FAILURES:			20
RANDOMIZED:	12	12	24
Male (age range in years)	8 (57 to 78)	7 (62 to 81)	15 (57 to 81)
Female (age range in years)	4 (69 to 80)	5 (72 to 83)	9 (69 to 83)
COMPLETED:	8	9	17
DISCONTINUED:	4	3	7
Clinical adverse experience	1	0	1
Laboratory adverse experience	0	0	0
Pat. Discon for Other	1	0	1
Pat. Withdrew consent	2	3	5

DOSAGE/FORMULATION NOS.: MK-0952 12.5-mg oral tablets or matching placebo tablets were used in a randomized crossover design to yield a total daily dose of 37.5 mg (3 x 12.5 mg) for each patient. During Treatment Period I, patients received either three MK-0952 12.5-mg tablets once daily or matching placebo. In the subsequent washout period, patients received matching placebo tablets. During Treatment Period II, patients received either three MK-0952 12.5-mg tablets once daily or matching placebo (crossing over from treatment received during Treatment Period I). Patients were instructed to take 3 tablets daily each morning with a meal.

DIAGNOSIS/INCLUSION CRITERIA: Men and women age ≥55 years with NINCDS-ADRDA diagnosis of probable Alzheimer's disease were randomized into this study. Additionally, patients had a Mini-Mental State Examination (MMSE) score between 18 and 26, inclusive; Modified Hachinski Ischemic Scale (MHIS) score of ≤4; and Global CDR score of 1 or 2, or, if the Global CDR was 0.5, then the CDR Sum of Boxes was at least 3.5.

EVALUATION CRITERIA:

EFFICACY MEASUREMENTS: Computerized Neuropsychological Test Battery (CNTB), Alzheimer's Disease Assessment Scale—Cognitive Subscale (ADAS-Cog) With Mazes, Everyday Memory Questionnaire (EMQ), and the Route Test.

SAFETY MEASUREMENTS: Frequency of adverse experiences, physical and neurological evaluation, vital signs, orthostatic vital signs, body weight, electrocardiograms (ECGs), MRI/CT scans, laboratory safety tests-serum chemistry, hematology, urinalysis and fecal occult blood tests. Serum β-hCG and FSH levels for women whose cessation of menses was <12 months prior to Visit 1.

STATISTICAL PLANNING AND ANALYSIS: (see results section)

RESULTS:

EFFICACY: The study was terminated early. There was no interim analysis planned or performed. Efficacy analysis was not provided in this report, but will be provided in a separate document.

SAFETY: MK-0952 was generally well tolerated in this study. There were no serious adverse experiences reported. Clinical adverse experiences were reported in 10 (42.0%) of the 24 randomized patients; 7 (29.2%) patients experienced an AE during the treatment period for MK-0952 and 3 (15.0%) patients experienced an AE during the placebo treatment period. Drug-related adverse experiences were reported by: 4 (16.7%) patients during the MK-0952 treatment period and 2 (10.0%) patients during the placebo treatment period. Two Events of Clinical Interest (ECI) were reported during the MK-0952 treatment period: (1) nausea (mild intensity) and (2) diarrhoea (moderate intensity). Causality for both of these ECIs was reported as probably related to study drug. The patient who experienced the diarrhoea was the only patient who discontinued from the study due to an adverse experience.

No laboratory adverse experiences were reported during the MK-0952-Placebo or Placebo-MK-0952 treatment sequences. One patient assigned to the Placebo-MK-0952 treatment sequence experienced 1 laboratory (white blood cell count increased) and 1 clinical (loose stools) adverse experience during the placebo-washout period.

Of the 24 randomized patients, 4 patients in the MK-0952-Placebo sequence completed only the first period of the crossover design; therefore, the following table shows 24 patients treated with MK-0952 and 20 patients treated with placebo. In summary, safety information generated in this study suggests that MK-0952 is generally well tolerated. [redacted]

Clinical Adverse Experience Summary Treatment Phase

	MK-0952 37.5 mg (N = 24)		Placebo (N = 20)	
	n	(%)	n	(%)
Number (%) of patients:				
With one or more adverse experiences	7	(29.2)	3	(15.0)
With no adverse experience	17	(70.8)	17	(85.0)
With drug-related adverse experiences[†]	4	(16.7)	2	(10.0)
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	(4.2)	0	(0.0)
Discontinued due to drug-related adverse experiences	1	(4.2)	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.

Number (%) of Patients With Specific Clinical Adverse Experiences (Incidence >0% in One or More Treatment Groups) by System Organ Class - Treatment Phase - AEs of Special Interest

	MK-0952 37.5 mg (N = 24)		Placebo (N = 20)	
	n	(%)	n	(%)
Patients With One Or More Adverse Experiences	2	(8.3)	0	(0.0)
Patients With No Adverse Experience	22	(91.7)	20	(100)
Gastrointestinal Disorders	2	(8.3)	0	(0.0)
Diarrhoea	1	(4.2)	0	(0.0)
Nausea	1	(4.2)	0	(0.0)
Although a patient may have had two or more clinical adverse experiences, the patient is counted only once within a category. The same patient may appear in different categories.				

CONCLUSIONS:

- In this 2-period crossover study in adults with a diagnosis of Alzheimer's disease, MK-0952 was generally well tolerated.

AUTHORS: (CRS) (Statistician) (Clin. Monitor)

[redacted]