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-0724
L-001220241, IV
Middle Cerebral Artery Stroke

CLINICAL STUDY REPORT SYNOPSIS

PROTOCOL TITLE/NO.: A Phase IIa Randomized, Double-Blind, Parallel-Groups, Placebo-Controlled Clinical Trial to Study the Efficacy and Safety of MK-0724 Intravenous Infusion on the Amelioration of Neurological Damage and Recovery from Middle Cerebral Artery Ischemic Stroke #018

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): Multicenter (31) in the United States, Canada, Columbia, Italy and Taiwan [redacted]

PRIMARY THERAPY PERIOD: 04-Jul-2007 to 07-Oct-2008 **CLINICAL PHASE:** IIa

DURATION OF TREATMENT: The duration of the in-patient treatment period will be a maximum of 7 days, with a post-treatment follow-up visit 13 days (+/- 1 day) after the onset of stroke; long-term follow-up will be performed at Months 1, 2, and 3 post-stroke onset.

OBJECTIVE(S): This study enrolled male and female patients 18-80 years of age diagnosed with middle cerebral artery ischemic stroke (MCA).

Primary: To compare the efficacy MK-0724 8 mg/kg/hr x 1 hr daily for 7 days to placebo in patients with middle cerebral artery ischemic stroke using the Day 90 ARAT scores.

Secondary: To compare the efficacy MK-0724 8 mg/kg/hr x 1 hr daily for 7 days to placebo in patients with middle cerebral artery ischemic stroke using (1) the Day 90 Stroke Arm Strength score, (2) the Day 90 modified Rankin Scale (mRS), and (3) the Day 90 Barthel Index (BI) score.

STUDY DESIGN: Randomized, double-blind (with in-house blinding), placebo-controlled, parallel-group study. Patients were randomized and received 8 mg/kg/hr x 1 hr daily intravenous MK-0724 or placebo initiated 8 to 36 hours post-stroke. Patients were hospitalized for in-patient treatment administration for 7 days. Patients were assessed at Week 2 (Day 13 +/-1 day) post-stroke onset and long-term follow-up was performed at Months 1, 2, and 3 post-stroke. [redacted]

SUBJECT/PATIENT DISPOSITION: [redacted]

	Treatment Sequence		
	MK-0724	Placebo	Total
SCREENING FAILURES:			4
RANDOMIZED:	12	12	24
Male (age range)	8 (30-78)	4 (49-77)	12 (30-78)
Female (age range)	6 (63-79)	6 (43-80)	12 (43-80)
COMPLETED:	13	9	22
DISCONTINUED:	1	1	2
Clinical adverse experience	1	1	2
Laboratory adverse experience	0	0	0
Other	0	0	0

DOSAGE/FORMULATION NOS.: Patients received either 8 mg/kg/hr x 1 hr daily intravenous MK-0724 or placebo for 7 days and treatment was initiated 8 to 36 hours post-stroke during in-patient hospitalization. The intervals between the start of the initial and the second infusion and between the start of the second and the third infusion were ≥ 12 but ≤ 27 hours. The intervals between the start of infusions #3 through #7 were 24 ± 3 hours.

DIAGNOSIS/INCLUSION CRITERIA: Men and women between ≥18 and ≤80 years of age with a diagnosis of middle cerebral artery (MCA) ischemic stroke were randomized and patients received their first infusion of blinded study medication between 8 hours to 36 hours after the initial onset of stroke symptoms. Additionally, patients had a baseline National Institutes of Health Stroke Scale (NIHHS) score of 6-18 inclusive; baseline age-adjusted NIHSS (NIHSS + age/5) score of 19-32 inclusive; collateral arm weakness as evidenced by a score ≥1 on NIHSS question #5; a measurable focal neurological deficit for a minimum duration of 60 minutes which persisted from stroke onset and up to the time of first infusion of blinded study medication without clinically meaningful fluctuations.; and no evidence of significant neglect (score <2 on NIHSS question # 11).

EVALUATION CRITERIA:

EFFICACY MEASUREMENTS: The following efficacy measurements were obtained during the Prestudy and Treatment phases of the study: NIHSS, mRS, ARAT, Stroke Arm and Leg Strength questions, Grip Strength Test, Trail Making Test, and the Boston Naming Test. S100β and proteomic samples were drawn at prestudy and at each treatment visit. The Barthel Index was performed in addition to the other efficacy tests during the post-treatment Follow-up visits.

SAFETY MEASUREMENTS: Blood chemistry, urinalysis, hematology, serum βhCG test, urine pregnancy test, CT Scan or MRI (was performed within 6 hours prior to the first infusion of blinded study drug), vital measurements, physical exam, resting 12-lead ECG was performed throughout the study. Follow-up MRI or CT information was collected at Infusion Day #5. The ECG was performed at screening and pre- and post-infusions #1 and #5 of the Treatment phase.

STATISTICAL PLANNING AND ANALYSIS: The primary efficacy measurement will be the Day 90 ARAT score (range 0-57) for patients treated with MK-0724 8 mg/kg/hr x 1 hr daily for seven days as compared to those treated with placebo based on the Full Analysis Set (FAS). A longitudinal (mixed) model will be used for the comparison, under the assumption that missing data are missing at random (i.e., ignorable missingness). The model will include baseline ARAT score (i.e., the first ARAT administered, up to the point of Study Drug Infusion #2), baseline NIHSS Q5 stratum (baseline NIHSS Question #5 score of 1 or 2 versus score of 3), region stratum (United States, Canada, Austria/Hungary/Italy, Taiwan/Columbia, treatment, and time of visit. Interactions of time by treatment, time by region stratum, and time by NIHSS Q5 stratum will be investigated separately in a supportive analysis. The comparison between treatment groups will be a contrast of the Day 90 mean scores in the context of this longitudinal model. Patients who die will be censored for the purposes of the primary efficacy analysis. In the event that the Day 90 results deviate substantially from a normal distribution, a nonparametric approach to the primary analysis will be conducted. A fixed sample size of 75 patients per arm will provide ~80% power at two-sided α=0.05 for a two-sample t-test, if the true treatment effect (relative to placebo) is 7.0 (σ=15) points. Because the study was terminated early, efficacy was not considered for this report. No interim analysis was performed.

RESULTS:

EFFICACY: Because the study was terminated early, efficacy was not considered for this report.

SAFETY: MK-0724 was generally well tolerated in this study. Clinical adverse experiences were reported in 20 (87%) of the 23 treated patients; 10 (76.9%) of 13 in the MK-0724 group and 10 (100%) of 10 in the placebo group. One (1) patient in the MK-0724 treatment group reported a drug-related adverse experience. One (1) of the 24 randomized patients did not receive study drug due to ECG changes and was excluded from the safety analyses. Serious adverse experiences were reported by 5 patients during the treatment period: One (1) patient (7.7%) in the MK-0724 group and 4 patients (40%) in the placebo group. One of the serious adverse experiences in the placebo group resulted in death. None of the serious adverse events were considered drug-related by the investigators. Laboratory adverse experiences were reported in 9 (39.1%) of the 23 treated patients: 4 patients (30.8%) in the MK-0724 treatment group and 5 patients (50%) in the placebo group. Drug-related lab adverse experiences were reported in 1 patient (7.7%) in the MK-0724 group and 1 patient (10%) in the placebo group.

In summary, safety information generated in the limited patient population enrolled in this study suggests that MK-0724 is generally well tolerated. [redacted]

Clinical Adverse Experience Summary

	MK-0724 8mg/kg/hr x 1 hr IV (N = 13)		Placebo (N = 10)	
	n	(%)	n	(%)
Number (%) of patients:				
With one or more adverse experiences	10	(76.9)	10	(100)
With no adverse experience	3	(23.1)	0	(0.0)
With drug-related adverse experiences†	1	(7.7)	0	(0.0)
With serious adverse experiences	1	(7.7)	4	(40.0)
With serious drug-related adverse experiences	0	(0.0)	0	(0.0)
Who died	0	(0.0)	1	(10.0)
Discontinued due to adverse experiences	1	(7.7)	1	(10.0)
Discontinued due to drug-related adverse experiences	0	(0.0)	0	(0.0)
Discontinued due to serious adverse experiences	1	(7.7)	1	(10.0)
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.

Laboratory Adverse Experience Summary

	MK-0724 8mg/kg/hr x 1 hr IV (N = 13)		Placebo (N = 10)	
	n	(%)	n	(%)
Number (%) of patients:				
With at least one lab test postbaseline	13		10	
With one or more adverse experiences	4	(30.8)	5	(50.0)
With no adverse experience	9	(69.2)	5	(50.0)
With drug-related adverse experiences†	1	(7.7)	1	(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	0	(0.0)	0	(0.0)
Discontinued due to drug-related adverse experiences	0	(0.0)	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.
‡ The percent = number of patients within the laboratory adverse experience category / number of patients with one or more laboratory tests postbaseline.

CONCLUSIONS: In this randomized, double-blind (with in-house blinding), placebo-controlled, parallel-groups study in adults with a diagnosis of Middle Cerebral Artery (MCA) ischemic stroke, MK-0724 was generally well tolerated.

AUTHORS

[redacted]