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-0677 ibutamoren mesylate, Film-Coated Tablet Hip-Fracture Recovery	**CLINICAL STUDY REPORT SYNOPSIS**

PROTOCOL TITLE/NO.: A 24-Week, Double-Blind, Randomized, Placebo-Controlled, Multicenter Study to Assess the Safety and Efficacy of MK-0677 for the Treatment of Sarcopenia in Patients Recovering From Hip Fracture #032

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): Multicenter (31). US (11) ex-US (20)

PRIMARY THERAPY PERIOD: 26-Oct-2005 to 10-Jul-2007 **CLINICAL PHASE:** IIb

DURATION OF TREATMENT: 4 weeks study

OBJECTIVES: Primary: In patients who have recently experienced a hip fracture, to demonstrate an improvement in overall physical functional performance (as measured by the Continuous Scale Physical Functional Performance 10-item Test [henceforth abbreviated as PFP-10]) following administration of MK-0677 (ibutamoren mesylate) 25-mg once daily for 24 weeks relative to placebo.

Secondary: In patients who have recently experienced a hip fracture, following administration of MK-0677 (25-mg once daily) for 24 weeks, to evaluate, relative to placebo: (1) the safety and tolerability of MK-0677, (2) the change in disability (as measured by the Physical & Movement domain of the Activity Measure for Post-acute Care using Computer Adaptive Testing [henceforth abbreviated as AM-PAC]), (3) return to independence in home ambulation and community ambulation (as measured by achievement of a threshold in the Physical & Movement domain of the AM-PAC, (4) the change in lower extremity muscle strength (bilateral isometric knee extension) and stair climbing power, (5) the change in levels of insulin-like growth factor-1 (IGF-1), and (6) the change in patient global assessment of improvement.

Exploratory: In patients who have recently experienced a hip fracture, following administration of MK-0677 (25-mg once daily) for 24 weeks, to determine which subgroups of patients show evidence of response to treatment based on the tools being utilized in this study, and to determine which tools best measure response to treatment.

STUDY DESIGN: This is a randomized, double-blind, placebo-controlled, multicenter study consisting of 24 weeks of treatment with study medication, followed by a 14-day post-treatment follow-up visit for safety.

SUBJECT/PATIENT DISPOSITION:

	MK-0677 25 mg	Placebo	Total
SCREENING FAILURES:			158
RANDOMIZED:	62	61	123
Male (age range)	66-92	65-92	65-92
Female (age range)	66-95	64-93	64-95
COMPLETED:	39	44	83
DISCONTINUED:	23	16	39
Clinical adverse experience	7	4	11
Site terminated	6	5	11
Other	10	7	17

DOSAGE/FORMULATION NOS.: Patients received one tablet of MK-0677 (ibutamoren mesylate), 25 mg, or matching placebo, daily for 24 weeks, starting the morning after Visit 2. The drug was taken orally each morning, with or without food. Patients who missed a dose in the morning should have taken the missed dose the same day in the afternoon or evening, but should not have taken 2 doses the next day.

DIAGNOSIS/INCLUSION CRITERIA: Ambulatory male or female patients ≥60 years old. Patients were enrolled if they had a recent unilateral hip fracture, with non-complicated surgical repair. Surgical repair of the fracture occurred no more than 4 days post hip fracture. Prior to starting the study medication, the patient was enrolled in a rehabilitation program (as an in-patient or as an out-patient), which provided a minimum of 10 hours of physical therapy over a 2 to 4-week period.

EVALUATION CRITERIA:

EFFICACY MEASUREMENTS: (1) Physical Function: PFP-10 total score and score for each of 5 domains (upper-body strength, lower-body strength, upper-body flexibility, balance and coordination, and endurance); SPPB (Short Physical Performance Battery); (2) Disability/Return to Independence: AM-PAC (Physical & Movement, and Personal Care & Instrumental domains), Patient Global Assessment of Improvement; (3) Biochemical: IGF-1; and (4) Lower Extremity Muscle Strength (bilateral knee extension and stair climbing power).

SAFETY MEASUREMENTS: Routine hematology, blood chemistry, and urinalysis, including monitoring of glucose indices (fasting glucose and hemoglobinA1C [HbA1C]), and lipid profile, physical examinations including vital signs, and monitoring of spontaneously reported adverse experiences.

STATISTICAL PLANNING AND ANALYSIS:

EFFICACY: The study was initially planned to have 130 patients per treatment group complete the study. The number was revised to 64 patients per group after a blinded validation analysis was conducted in February 2007 as pre-specified in the protocol. Based on the blinded validation analysis the primary endpoint was changed to stair-climbing power, and the PFP-10 became a secondary endpoint. It was also determined that 64 patients per treatment group completing the study would be needed in order to have 80% power to detect a clinically meaningful difference between groups (defined as ½ standard deviation of the blinded sample). The new primary endpoint and sample size was approved by Merck's internal committee in May, 2007, however the protocol did not get amended due to early termination of the study.

The study was terminated early due to a safety signal of congestive heart failure. After review of the unblinded data of these patients, the Merck internal Data Monitoring Committee recommended that this study be discontinued based on the pre-specified monitoring guidelines. Four out of the five episodes of congestive heart failure observed in this study were from MK-0677 group.

The analysis plan has been changed due to early termination of the study. Due to the resulting small sample size as compared to what was planned originally, the primary focus of the analysis was on estimation of the treatment effect. For all the efficacy endpoints, summary statistics (mean, SE, SD, and range) for each treatment group were provided at each visit; the between-group means and its 95% CIs were also provided.

The Full Analysis Set (FAS) population was used for the analysis of efficacy data. The FAS pupulation was a subset of all randomized patients with patients excluded for the following reasons: failure to receive at least one dose of study treatment, lack of any post-randomization endpoint data subsequent to at least one dose of study treatment, and lack of baseline data for those analyses that require baseline data. No missing data were imputed for the efficacy analyses.

SAFETY: Safety and tolerability were assessed by a statistical and clinical review of all safety parameters, including adverse experiences, laboratory values, and vital signs. For all the clinical and laboratory AEs, events were listed and summarized by frequency of occurrence, only the counts and percentages were tabulated by treatment group. The predefined limits of changes (PDLCs) were provided on selected lab safety parameters and vital signs, the 95% CI were displayed on the between-group differences. Ninety-five percent CIs of between-treatment differences in percentages were derived using Wilson's score method. Vital signs and selected laboratory tests were also summarized.

The All Patients as Treated (APaT) population was used for the analysis of safety data in this study. The APaT population consisted of all randomized patients who received at least one dose of study treatment. At least one laboratory or vital sign measurement obtained subsequent to at least one dose of study treatment was required for inclusion in the analysis of each specific parameter. To assess change from baseline, a baseline measurement was also required.

RESULTS:

EFFICACY: A summary for the magnitude of treatment effect expressed in means for the primary and secondary efficacy endpoints are provided in Table below. Results should be interpreted with caution because of the small sample size which is a result of the early termination of the study.

Greater numerical improvements in stair climbing power, SPPB gait speed test, and SPPB total score were observed in the MK-0677 group compared to placebo (greater SPPB score was mainly driven by the Gait Speed); A greater increase in IGF-1 was observed in the MK-0677 group compared to placebo.

The MK-0677 group had similar treatment effects compared to placebo on the SPPB balance test, SPPB chair stand test, AM-PAC, lower extremity muscle strength, PFP-10 and SF-36.

The MK-0677 group had fewer falls during the treatment period compared to placebo and smaller number of patients who had any falls (about 50% reduction). The summary statistics for the number of falls are provided in Section 11.

Summary Statistics for the Primary and Secondary Efficacy Endpoints at Week 24
Full Analysis Set

Treatment	N	Observed Value	Change from Baseline				Comparison with Placebo in Change from Baseline	
		Mean(SD)	Mean(SD)	Median	SE	Range	Difference in Mean	95% CI
Stair Climbing Power (watts)								
MK-0677 25 mg	26	121.9(36.2)	70.2(40.3)	71.4	7.9	-26.6 , 162.2	12.5	(-10.95, 35.88)
Placebo	35	113.9(57.1)	57.7(48.6)	47.9	8.2	-26.3 , 174.8	--	--
AM-PAC Physical Movement								
MK-0677 25 mg	40	61.2(8.7)	13.9(9.2)	13.1	1.5	-2.0 , 41.4	-0.1	(-3.63, 3.43)
Placebo	44	63.0(9.2)	14.0(7.1)	12.9	1.1	-4.1 , 29.0	--	--
SPPB Balance Test								
MK-0677 25 mg	37	3.7(0.8)	1.0(1.3)	1.0	0.2	-1.0 , 4.0	0.4	(-0.16, 1.00)
Placebo	46	3.5(1.2)	0.6(1.4)	0.0	0.2	-2.0 , 4.0	--	--
SPPB Gait Speed Test								
MK-0677 25 mg	35	3.5(0.8)	2.0(1.1)	2.0	0.2	0.0 , 4.0	0.7	(0.17, 1.28)
Placebo	46	3.3(1.0)	1.3(1.3)	1.0	0.2	-1.0 , 4.0	--	--
SPPB Chair Stand Test								
MK-0677 25 mg	36	1.8(1.4)	1.5(1.4)	1.0	0.2	0.0 , 4.0	0.1	(-0.52, 0.65)
Placebo	44	2.1(1.2)	1.4(1.2)	1.5	0.2	-1.0 , 4.0	--	--
SPPB Total								
MK-0677 25 mg	34	9.1(2.2)	4.5(2.2)	5.0	0.4	0.0 , 8.0	1.2	(0.05, 2.33)
Placebo	44	8.9(2.6)	3.3(2.7)	3.0	0.4	-1.0 , 9.0	--	--
Lower Extremity Strength (kg) Affected Side								
MK-0677 25 mg	28	19.5(7.4)	8.6(6.5)	7.5	1.2	-10.0 , 22.0	0.1	(-2.76, 3.04)
Placebo	38	19.8(9.1)	8.5(5.3)	6.0	0.9	0.0 , 21.0	--	--
SF-36 Total Score								
MK-0677 25 mg	43	579.3(139.7)	188.2(129.3)	187.8	19.7	-64.5 , 492.8	3.1	(-49.06, 55.32)
Placebo	47	605.1(160.6)	185.0(120.3)	178.3	17.5	-73.8 , 438.5	--	--
PFP-10 Total								
MK-0677 25 mg	40	28.1(18.7)	19.7(15.5)	16.3	2.4	-22.2 , 59.7	0.0	(-6.12, 6.15)
Placebo	46	32.6(20.2)	19.7(13.2)	18.0	1.9	0.6 , 60.6	--	--
IGF-1 (ng/mL)								
MK-0677 25 mg	40	140.8(59.8)	59.0(53.8)	52.0	8.5	-55.0 , 227.0	51.4	(34.42, 68.44)
Placebo	47	81.8(24.6)	7.5(22.0)	4.0	3.2	-37.0 , 46.0	--	--

N = Number of patients with a baseline and treatment value.
SE = Standard Error of the Mean
Note: Although PFP-10 was described as a primary endpoint in protocol but subsequent to protocol finalization, stair climbing was changed to the primary endpoint based on the blinded validation analysis.

SAFETY: One or more adverse experiences were reported by forty-eight (77%) patients in the MK-0677 group, compared to 33 (55%) in the placebo group. There was no difference in drug related AEs between groups. Fifteen (24%) patients in the MK-0677 group experienced serious AEs, compared to 8 (13%) in the placebo group. One (1) patient in the MK-0677 treatment group died during the study due to serious adverse experience of sepsis and pneumonia. These adverse experiences were severe in intensity, however were not considered by the investigator to be related to the study drug. Seven (11.3%) patients in the MK-0677 group discontinued due to AEs compared to 4 (6.7%) in the placebo group. Four patients experienced congestive hear failure in the MK-0677 group vs. one patient in the placebo group. In addition, both systolic and diastolic blood pressure was elevated in the MK-0677 group compared to the placebo group by week 4 and remained elevated throughout the study. Mean body weight increased in the MK-0677 group gradually during the study, while it decreased in the placebo group.

Clinical Adverse Experience Summary

	MK-0677 25mg (N = 62)		Placebo (N = 60)		Total (N = 122)	
	n	(%)	n	(%)	n	(%)
Number (%) of patients:						
With one or more adverse experiences	48	(77.4)	33	(55.0)	81	(66.4)
With no adverse experience	14	(22.6)	27	(45.0)	41	(33.6)
With drug-related adverse experiences†	9	(14.5)	9	(15.0)	18	(14.8)
With serious adverse experiences	15	(24.2)	8	(13.3)	23	(18.9)
With serious drug-related adverse experiences	3	(4.8)	1	(1.7)	4	(3.3)
Who died	1	(1.6)	0	(0.0)	1	(0.8)
Discontinued due to adverse experiences	7	(11.3)	4	(6.7)	11	(9.0)
Discontinued due to drug-related adverse experiences	2	(3.2)	1	(1.7)	3	(2.5)
Discontinued due to serious adverse experiences	4	(6.5)	4	(6.7)	8	(6.6)
Discontinued due to serious drug-related adverse experiences	2	(3.2)	1	(1.7)	3	(2.5)

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

Laboratory adverse experiences were reported by 10 (17.2%) patients in the MK-0677 group vs. 4 (6.9%) in the placebo group. The incidence of drug-related laboratory adverse experiences was higher in the MK-0677 group as compared to placebo group: 6 (10.3%) vs. 3 (5.2%) respectively. Four patients in the MK-0677 group were reported with increased blood glucose as an AE, compared to one patient in the placebo group. Three (3) patients in the MK-0677 group were reported with increased HbA_{1c}; none in the placebo group.

Laboratory Adverse Experience Summary

	MK-0677 25mg (N = 62)		Placebo (N = 60)		Total (N = 122)	
	n	(%)	n	(%)	n	(%)
Number (%) of patients:						
With at least one lab test postbaseline	58		58		116	
With one or more adverse experiences	10	(17.2)	4	(6.9)	14	(12.1)
With no adverse experience	48	(82.8)	54	(93.1)	102	(87.9)
With drug-related adverse experiences†	6	(10.3)	3	(5.2)	9	(7.8)
With serious adverse experiences	1	(1.7)	0	(0.0)	1	(0.9)
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: The results of this study indicate that there might be a positive effect of MK-0677 in muscle strength (assessed by stair-climbing power, SPPB, and gait speed) in patients recovering from hip fracture surgery. However, the effects were not consistent across endpoints, and responder analyses. Furthermore, there was no evidence of improvement in physical function (assessed by the AM-PAC, SF-36, and PFP-10). The lower incidence of falls and the smaller number of patients who experienced falls during the 6 months of the study suggest that there may be a functional benefit of treatment with MK-0677 in these patients. Nevertheless, due to the early termination of the study, no firm conclusions can be drawn regarding the efficacy of MK-0677 in improving or accelerating the recovery of patients following surgery for hip fracture repair.

The adverse events of increased blood glucose and HbA1c, myalgias, arthralgias, and congestive heart failure are possibly mechanism-based.

AUTHORS: [redacted]