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
odanacatib, Tablet
Treatment of Women With Breast Cancer and MBD

CLINICAL STUDY REPORT SYNOPSIS

PROTOCOL TITLE/NO.: A Phase II Study to Assess the Safety, Tolerability, and Efficacy of MK-0822 (Cathepsin-K Inhibitor) in the Treatment of Women With Breast Cancer and Established Bone Metastases (MBD) — #016

INVESTIGATOR(S)/STUDY CENTER(S): Multicenter (15)

PRIMARY THERAPY PERIOD: 13-Dec-2006 to 05-Dec-2007. Last dose of study drug was taken on 20-Nov-2007. Last patient out was on 05-Dec-2007.

CLINICAL PHASE: IIa

DURATION OF TREATMENT: Four weeks of treatment.

OBJECTIVE(S): Primary: (1) To assess the effect of 4 weeks of treatment with MK-0822 5 mg daily on Urinary N-telopeptide of Type I collagen (OSTEOMARK™) (u-NTx), a biochemical index of bone resorption, relative to baseline. (2) To assess the safety and tolerability of 4 weeks of treatment with MK-0822 5 mg daily. Secondary: (1) To assess the effect of 4 weeks of treatment with MK-0822 5 mg daily on urinary deoxypyridinoline (u-DPD), another marker of bone resorption, on serum 1CTP, a biochemical index of collagen breakdown and cathepsin K activity, and on serum Bone Specific Alkaline Phosphatase (BSAP), a marker of bone formation. (2) To assess the pharmacokinetic profile of MK-0822 during 4 weeks of therapy.

STUDY DESIGN: This was a 4-week, randomized, double-blind, parallel-arm, active comparator-controlled multicenter study, in which women with breast cancer and MBD were randomized in a 2:1 ratio to receive treatment with either MK-0822 5 mg daily or IV Zoledronic Acid (ZA) 4 mg given once. The study examined the effects of MK-0822 5 mg daily on biochemical indices of bone turnover and evaluated drug safety and tolerability during 4 weeks of treatment.

SUBJECT/PATIENT DISPOSITION:

	IV ZA	MK-0822	Total
SCREENING FAILURES			36
RANDOMIZED:	14	29	43
Female (age range)[†]	48-82	36-76	36-82
COMPLETED:	14	26	40
DISCONTINUED:	0	3	3
Clinical adverse experience (disease progression)	0	1	1
Laboratory adverse experience	0	1	1
Other[‡]	0	1	1

[†] All patients were females.
[‡] One patient was discontinued by mistake.

DOSAGE/FORMULATION NOS.:

Drug	Potency	Formulation No.	Dosage Form	Control No.
Zoledronic Acid	4 mg/5 mL concentrate	[redacted]	Sterile Liquid	[redacted]
MK-0822	5 mg		OCT[†]	
Placebo to MK-0822	0 mg		OCT[†]	

[†] OCT = Oral Compressed Tablet.

DIAGNOSIS/INCLUSION CRITERIA: Female ≥18 years old with breast cancer and metastatic bone disease. Patients were excluded if they had bisphosphonate use within 3 months of screening, were not on a stable hormonal therapy for at least 3 months prior to screening, and were not on a stable chemotherapy for at least 1 month prior to screening.

EVALUATION CRITERIA:

EFFICACY MEASUREMENTS: Urinary NTx, urinary DPD, serum 1CTP, serum BSAP and plasma pharmacokinetic measurements. The Brief Pain Inventory (BPI) was also administered to assess pain.

SAFETY MEASUREMENTS: Physical examinations, vital signs, ECG, Eastern Cooperative Oncology Group (ECOG) Performance Scale, laboratory safety evaluations, and assessment of Adverse Experiences (AE). AEs were assessed according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0.

STATISTICAL PLANNING AND ANALYSIS:

EFFICACY: The log-transformed fraction of baseline value (calculated by dividing the on-treatment value by the baseline value and applying the natural log) was analyzed for the primary efficacy endpoint of urinary NTx. A longitudinal data analysis (LDA) model was used for the primary efficacy variable. The model included factors for baseline, treatment, time-by-baseline (time as categorical variable) and time-by-treatment interactions. Baseline value was also log-transformed in the above model for analysis. The assessment of treatment effect was focused on within-group change from baseline. Estimates of within-group change along with the associated 95% CI were provided. No formal hypothesis testing was performed. If the lower bound of the 95% CI for the average percent reduction of u-NTx from baseline at Week 4 in the MK-0822 group was greater than 50%, the criterion for a substantial suppression of u-NTx was considered met; If the upper bound of the 95% CI for the average percent reduction of u-NTx from baseline at Week 4 was <50%, criterion for a substantial suppression was NOT achieved at this MK-0822 dose. If the 95% CI included 50% suppression, criterion for a substantial suppression may be achieved. Secondary efficacy endpoints were assessed and evaluated for supportive evidence.

SAFETY: Safety and tolerability were assessed by a review of all relevant safety parameters including clinical AEs and laboratory values. The analysis of AEs followed a multi-tiered approach. For Tier 1 clinical AEs, inferential testing provided statistical significance levels for between-group comparisons. Tier 1 AEs included fracture and bone pain. Comparisons of proportions of patients were performed using Fisher's exact test and confidence intervals for between-group differences using Wilson's method were provided. For non-tier 1 AEs and predefined limits of change in laboratory variables, estimates of effects on safety were provided.

RESULTS:

EFFICACY: The primary efficacy endpoint is urinary NTx at Week 4 in the MK-0822 group, with a target of greater than 50% reduction in the average. The study results showed a substantial uNTx reduction of 77% in the MK-0822 group at Week 4, with the lower bound of the 95% confidence interval (71%) exceeding the minimum of 50% prespecified for a positive study. The reduction was comparable to that observed in the control group (73%). For the secondary efficacy endpoint of urinary DPD, there were substantial reductions in both treatment groups. The reduction was 30% in the MK-0822 group and 52% in the control group, at Week 4. For the secondary efficacy endpoint of serum BSAP, there was a reduction of 9% in BSAP in the MK-0822 group ($p<0.05$). The change in the control group was not significant. For the secondary efficacy endpoint of serum 1CTP, there was an increase of 93% in 1CTP in the MK-822 treatment group ($p<0.05$). There was essentially no change in the control group.

[redacted]

SAFETY: MK-0822 was generally well tolerated. One or more adverse experiences were reported by 9 (64%) patients in the IV ZA group and 20 (69%) patients in the MK-0822 group. The most common clinical adverse experiences were headache, vomiting, nausea, and bone pain The only notable difference was between the drug related adverse experiences, with a higher percentage in IV ZA treatment group (specifically gastrointestinal disorders). There were no serious drug-related adverse experiences or deaths that occurred after randomization. Laboratory experiences were reported by 12 (28%) patients in the IV ZA group and 8 (28%) patients in the MK-0822 group. There were 10 (23%) patients with laboratory adverse experiences of decreased lymphocytes, however, none were drug related. Overall, no clinically meaningful patters were observed for laboratory adverse experiences between treatment groups.

Clinical Adverse Experience Summary

	IV ZA (N = 14)		MK-0822 (N = 29)		Total (N = 43)	
	n	(%)	n	(%)	n	(%)
Number (%) of patients:						
With one or more adverse experiences	9	(64.3)	20	(69.0)	29	(67.4)
With no adverse experience	5	(35.7)	9	(31.0)	14	(32.6)
With drug-related adverse experiences†	6	(42.9)	6	(20.7)	12	(27.9)
With serious adverse experiences	2	(14.3)	4	(13.8)	6	(14.0)
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)	1	(3.4)	1	(2.3)
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)	1	(3.4)	1	(2.3)
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.

Laboratory Adverse Experience Summary

	IV ZA (N = 14)		MK-0822 (N = 29)		Total (N = 43)	
	n	(%)	n	(%)	n	(%)
Number (%) of patients:						
With at least one lab test postbaseline	14		29		43	
With one or more adverse experiences	4	(28.6)	8	(27.6)	12	(27.9)
With no adverse experience	10	(71.4)	21	(72.4)	31	(72.1)
With drug-related adverse experiences†	1	(7.1)	0	(0.0)	1	(2.3)
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)	1	(3.4)	1	(2.3)
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: In women with breast cancer and bone metastases, MK-0822 5 mg daily: 1) Substantially suppressed bone resorption, as shown by a significant change in urinary NTx and change in urinary DPD; 2) Produced a small but nominally significant decrease in serum BSAP, a marker of bone formation; 3) Produced a nominally significant increase in serum 1CTP, consistent with suppression of Cathepsin-K activity; 4) Was generally safe and well tolerated.

AUTHORS: [redacted]