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
Osteoporosis

CLINICAL STUDY REPORT SYNOPSIS

PROTOCOL TITLE/NO.: A Phase IIa Randomized, Double-Blind, Placebo Controlled Study to Evaluate the Effects of Odanacatib (MK-0822) on Bone Mineral Density (BMD) and Overall Safety in the Treatment of Osteoporosis in Postmenopausal Women Previously Treated with Alendronate

INVESTIGATOR(S)/STUDY CENTER(S): Worldwide Multicenter (42 sites in United States, Czech Republic, Spain, India, South Africa, France, Norway, Poland, Taiwan, Belgium, Germany, and Jordan)

PRIMARY THERAPY PERIOD: 27 APR 2009-15 SEP 2011 | **CLINICAL PHASE:** IIa

DURATION OF TREATMENT: 24 months

OBJECTIVE(S):

Primary objective at the end of 24 months: to evaluate the effect of treatment with odanacatib 50 mg once weekly (OW) on bone mineral density (BMD) percent change from baseline at the femoral neck site assessed by dual-energy X-ray absorptiometry (DXA) compared to placebo at the end of 24 months in postmenopausal women previously treated with alendronate with low BMD. Hypothesis: Treatment with odanacatib 50 mg OW will increase BMD at the femoral neck compared to placebo at the end of 24 months.

The primary safety objective was to assess safety and tolerability of treatment with odanacatib 50 mg OW compared to placebo over 24 months in postmenopausal women previously treated with alendronate with low BMD.

Secondary objectives at the end of 12 and 24 months: to evaluate the effect of treatment with odanacatib 50 mg OW on BMD percent change from baseline (1) at the femoral neck site as assessed by DXA at the end of 24 months; Hypothesis: Treatment with odanacatib 50 mg OW will increase BMD at the femoral neck compared to baseline at the end of 24 months; (2) at the trochanter, total hip, lumbar spine, and one-third distal radius sites assessed by DXA compared to placebo, and within each treatment group, at the end of 12 and 24 months; and (3) at the femoral neck site as assessed by DXA compared to placebo, and within each treatment group at 12 months in postmenopausal women previously treated with alendronate with low BMD. Other secondary objectives included evaluation of biochemical markers of bone resorption (C-telopeptides of Type 1 collagen [s-CTx] and urine N-telopeptides of Type 1 collagen [u-NTx]); and biochemical markers of bone formation (serum bone specific alkaline phosphatase [s-BSAP] and serum N-terminal propeptide of Type 1 collagen [s-P1NP]) compared to placebo and within each treatment group at the end of 12 and 24 months.

STUDY DESIGN: This was a randomized, double-blind, placebo-controlled, 24-month study with a primary endpoint of percent change from baseline at Month 24 on BMD at the femoral neck, and an interim analysis at the end of Month 12. The purpose of this study was to evaluate the effects of odanacatib 50 mg OW on BMD, biochemical markers of bone turnover and indices of calcium and mineral homeostasis in patients previously treated with alendronate (10 mg daily or 70 mg OW) for at least 3 years. This study was to also assess the safety and tolerability of treatment with odanacatib 50 mg OW compared with placebo over 24 months in this target population.

SUBJECT/PATIENT DISPOSITION:

	ODN 50 mg OW		Placebo OW		Total	
	n	(%)	n	(%)	n	(%)
Not Randomized					202	
Patients in population	124		122		246	
Study Disposition						
COMPLETED	86	(69.4)	99	(81.1)	185	(75.2)
DISCONTINUED	38	(30.6)	23	(18.9)	61	(24.8)
ADVERSE EVENT	12	(9.7)	4	(3.3)	16	(6.5)
EXCESSIVE BONE LOSS	6	(4.8)	3	(2.5)	9	(3.7)
LOST TO FOLLOW-UP	2	(1.6)	1	(0.8)	3	(1.2)
PHYSICIAN DECISION	2	(1.6)	1	(0.8)	3	(1.2)
PROTOCOL VIOLATION	3	(2.4)	1	(0.8)	4	(1.6)
WITHDRAWAL BY SUBJECT	13	(10.5)	13	(10.7)	26	(10.6)
Each patient is counted once for Study Disposition based on the latest corresponding disposition record.						

DOSAGE/FORMULATION NOS. (Lot Information for Investigational Medicinal Products):

Product Description	Potency Strength	ERP Bulk Item Master No.	ERP Bulk Lot No.
MK-0822	Placebo		
MK-0822	50 mg		
VitaminD3	2800 IU		
VitaminD3	2800 IU		
VitaminD3	2800 IU		
MK-0822	Placebo		
MK-0822	50 mg		

DIAGNOSIS/INCLUSION CRITERIA:

Postmenopausal osteoporotic women aged ≥ 60 years who have been on, or were on, an alendronate therapy for postmenopausal osteoporosis, either 10 mg daily or 70 mg OW, with or without vitamin D_3 combination, such as Fosamax Plus D® or Fosamax®, for ≥3 years prior to the screening visit (Visit 1) and have a BMD T-score at any hip site (femoral neck, trochanter, or total hip) of ≤-2.5 and >-3.5 as assessed by DXA (without a history of fragility fracture) or ≤-1.5 and >-3.5 at any hip site (with a history of fragility fracture [except hip fracture]). Patient must have suitable anatomy for DXA assessment including at least one femoral neck site at the hip without any sequelae or hardware and at least 3 evaluable vertebrae at the lumbar spine.

EVALUATION CRITERIA:

Efficacy Measurements: BMD and serum and urine biochemistry (biochemical markers of bone turnover and indices of calcium and mineral homeostasis).

Safety Measurements: clinical and laboratory adverse experiences, physical examination, stature (height), electrocardiogram (ECG), vital signs, body weight, laboratory safety measurements including serum chemistry, blood cell count, and urinalysis.

STATISTICAL PLANNING AND ANALYSIS:

Efficacy: The BMD percent change from baseline at the femoral neck at the end of 24 months compared with placebo was the primary efficacy endpoint. Analyses were performed using a constrained longitudinal data analysis (cLDA) method proposed by Liang and Zeger. Least-Squares means (LS means) and the associated 95% Confidence Intervals (CIs) for within- and between-treatment groups were tabulated to evaluate the treatment effect on the primary endpoint and tested further in the context of the cLDA model to assess the primary hypothesis on the between-group change, as well as the secondary hypothesis on the within-group change. Each of the secondary and exploratory endpoints was analyzed using a similar approach.

Approximately 80 patients per group were planned to be randomized into the study. Assuming an annual dropout rate of approximately 10%, the study enrollment was planned to allow for approximately 64 evaluable patients per group at the end of 24 months. With 64 patients per treatment group, there was 80% power to detect a between-group difference of 2% between odanacatib versus placebo, using a significance level of 5% and a two-sided test. This power calculation utilized an estimated standard deviation of 4% in the BMD percent change from baseline at the femoral neck site, based on the actual results of the odanacatib Phase IIb trial (PN 004).

Results from an interim analysis (performed after all patients completed their 12 month visit) were reviewed by a standing internal Data Monitoring Committee (siDMC).

Safety: Safety and tolerability were assessed by a clinical and statistical review of all safety data collected throughout the study, including adverse experiences (AEs), with special attention to skin disorders, respiratory disorders, fractures and dental disorders, vital signs, and laboratory evaluations. This analysis followed a multitiered approach. Tier 1 events included skin disorders, respiratory disorders, and dental disorders. P-values and 95% CIs for between-treatment differences in the percentage of patients with AEs were calculated using the Miettinen and Nurminen method.

RESULTS:

EFFICACY: In postmenopausal women previously treated with alendronate with low BMD, two years of treatment with odanacatib 50 mg:

- significantly increased BMD at the femoral neck site compared to placebo (p-value < 0.001) and compared to baseline (p-value = 0.003),
- significantly increased BMD at the trochanter, lumbar spine and total hip, compared to placebo (respective p-values = 0.002, < 0.001 and < 0.001) but not for the 1/3 distal forearm BMD,
- significantly increased BMD compared to baseline at the trochanter and lumbar spine (respective p-values = 0.016 and < 0.001) but not for the total hip BMD and 1/3 distal forearm BMD,
- significantly decreased u-NTx/Cr and increased s-P1NP compared to placebo (respective p-values < 0.001 and = 0.011) but no significant differences were observed in s-CTx and s-BSAP,
- significantly increased s-CTx, s-BSAP and s-P1NP compared to baseline (all p-values < 0.001) and significantly decreased u-NTx/Cr compared baseline (p-value = 0.004).

Summary of Main BMD/BIOC Results at Month 24

		Percent Change From Baseline		Difference‡		
Treatment	N	LS Mean†	(95% CI)	LS Mean†	(95% CI)	p-Value
Femoral Neck BMD (gm/cm^2)						
ODN 50 mg OW	83	1.73*	(0.61, 2.85)	2.67*	(1.17, 4.17)	<0.001
Placebo OW	95	-0.94	(-1.98, 0.10)			
Trochanter BMD (gm/cm^2)						
ODN 50 mg OW	83	1.83*	(0.34, 3.32)	3.18*	(1.19, 5.17)	0.002
Placebo OW	95	-1.35	(-2.73, 0.03)			
Total Hip BMD (gm/cm^2)						
ODN 50 mg OW	83	0.83	(-0.13, 1.80)	2.70*	(1.41, 4.00)	<0.001
Placebo OW	95	-1.87	(-2.77, -0.97)			
Lumbar Spine BMD (gm/cm^2)						
ODN 50 mg OW	80	2.28*	(1.30, 3.25)	2.57*	(1.26, 3.89)	<0.001
Placebo OW	89	-0.30	(-1.21, 0.62)			
1/3 Distal Forearm BMD (gm/cm^2)						
ODN 50 mg OW	80	-0.92	(-1.99, 0.15)	0.22	(-1.23, 1.67)	0.763
Placebo OW	86	-1.14	(-2.16, -0.13)			
u-NTx/Cr (nmol/mmol)						
ODN 50 mg OW	80	-15.55*	(-24.57, -5.47)	-47.04*	(-62.40, -31.67)	<0.001
Placebo OW	77	31.48	(17.60, 47.01)			
s-CTx (ng/mL)						
ODN 50 mg OW	80	93.86*	(69.42, 121.82)	10.16	(-19.39, 39.72)	0.500
Placebo OW	79	83.70	(61.06, 109.52)			
s-BSAP (ng/mL)						
ODN 50 mg OW	83	51.62*	(39.49, 64.79)	10.96	(-5.29, 27.22)	0.186
Placebo OW	83	40.65	(29.82, 52.39)			
s-P1NP (ng/mL)						
ODN 50 mg OW	82	90.70*	(70.43, 113.38)	31.17*	(7.13, 55.21)	0.011
Placebo OW	85	59.53	(43.10, 77.84)			

†LS mean based on the cLDA model including the baseline measurement and all post-baseline percent changes from baseline in the response vector, with fixed effects for treatment, time, duration of prior alendronate use, geographic region, machine type, treatment-by-time interaction and the time-factor interactions. * = significantly different from 0 (multiplicity strategy)

‡ Difference between odanacatib and placebo

CI = Confidence Interval; LS Mean = Least Squares Mean.

SAFETY:

Clinical adverse experiences were reported by 172 (69.9%) of the 243 treated patients. The overall incidence of clinical AEs was comparable in the odanacatib 50 mg treatment group (83 [68.0%]) and the placebo group (89 [73.6%]), though the incidence of discontinuations due to an AE was numerically higher in the odanacatib 50 mg treatment group compared to that observed in the placebo group (11 [9.0%] versus 4 [3.3%]). In general, there were no clinically meaningful differences in the incidence of skin, respiratory or dental AEs between the odanacatib 50 mg treatment group and the placebo group. The incidence of fractures was smaller in the odanacatib 50 mg treatment group (4.9%) compared to placebo (13.2%). The overall incidence of laboratory AEs and discontinuations due to laboratory AEs was similar between the odanacatib 50 mg treatment group and the placebo group.

Analysis of Adverse Event Summary
Clinical Adverse Events - (All-Patients-as-Treated Population)

	ODN 50 mg OW		Placebo OW		Difference in % vs Placebo OW
	n	(%)	n	(%)	Estimate (95% CI)[†]
Patients in population	122		121		
with one or more adverse events	83	(68.0)	89	(73.6)	-5.5 (-16.9, 6.0)
with no adverse events	39	(32.0)	32	(26.4)	
with drug-related[‡] adverse events	8	(6.6)	8	(6.6)	-0.1 (-6.8, 6.7)
with serious adverse events	18	(14.8)	20	(16.5)	-1.8 (-11.1, 7.5)
with serious drug-related adverse events	0	(0.0)	0	(0.0)	
who died	1	(0.8)	2	(1.7)	
discontinued[§] due to an adverse event	11	(9.0)	4	(3.3)	5.7 (-0.4, 12.6)
discontinued due to a drug-related adverse event	3	(2.5)	0	(0.0)	
discontinued due to a serious adverse event	5	(4.1)	3	(2.5)	
discontinued due to a serious drug-related adverse event	0	(0.0)	0	(0.0)	

[†] Based on Miettinen & Nurminen method.
[‡] Determined by the investigator to be related to the drug.
[§] Study medication withdrawn. [redacted]
Estimated differences and confidence intervals are provided in accordance with the statistical analysis plan.

CONCLUSIONS: In this study of post-menopausal women previously treated with alendronate with low BMD:

1. Two years of odanacatib 50 mg OW increased femoral neck BMD compared to placebo and compared to start of treatment.
2. Two years of odanacatib 50 mg OW increased trochanter, total hip, and lumbar spine BMD compared to placebo; and increased trochanter and lumbar spine compared to start of treatment.
3. Analyses of biochemical markers of bone metabolism suggest that odanacatib decreases bone resorption while preserving bone formation.
4. Incremental improvement in BMD at all anatomic sites studied occurred mostly in the second year of odanacatib treatment.
5. Odanacatib was generally safe and well-tolerated compared to placebo.