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 SHARP & DOHME CORP., A SUBSIDIARY OF MERCK & CO., INC. MK-0822 odanacatib, Tablets osteoporosis	**CLINICAL STUDY REPORT SYNOPSIS**	#031

PROTOCOL TITLE/NO.: Phase III Randomized, Placebo-Controlled Study to Evaluate the Effect of Odanacatib (MK-0822) on Bone Mineral Density (BMD) and Overall Safety, and to Estimate the Effect of Odanacatib (MK-0822) on Bone Micro-architecture in Postmenopausal Women Treated with Vitamin D

INVESTIGATOR(S)/STUDY CENTER(S): Worldwide Multicenter 13 centers in the United States (3), France (3), Canada (2), Switzerland (2), Denmark, Australia, and Germany

PUBLICATION(S): [redacted]

PRIMARY THERAPY PERIOD: 02-Oct-2008 to 21-Mar-2011	**CLINICAL PHASE:** III

DURATION OF TREATMENT: 24 months

OBJECTIVE(S): OBJECTIVE(S):

Primary Objectives

Efficacy: To evaluate at 12 months the effect of treatment with odanacatib 50 mg once weekly (OW) on areal bone mineral density (aBMD) at the lumbar spine (assessed by dual-energy X-ray absorptiometry [DEXA]) compared to placebo.

Safety: To assess at 12 and 24 months the safety and tolerability of treatment with odanacatib 50 mg OW compared to placebo.

Secondary

In postmenopausal women with low BMD:

- To evaluate at 24 months the effect of treatment with odanacatib 50 mg OW on aBMD at the lumbar spine (assessed by DEXA) compared to placebo.
- To evaluate at 12 and 24 months the effect of treatment with odanacatib 50 mg OW on aBMD at the total hip, femoral neck, hip trochanter, and distal forearm (one-third distal and ultradistal sites, assessed by DEXA) compared to placebo.
- To estimate at 12 and 24 months the effect of treatment with odanacatib 50 mg OW on trabecular volumetric BMD (vBMD) at the lumbar spine (assessed by quantitative computed tomography [QCT]).
- To estimate at 12 and 24 months the effect of treatment with odanacatib 50 mg OW on biochemical markers of bone formation (serum N-terminal propeptide of Type 1 collagen [s-P1NP]) and bone resorption (serum C-telopeptides of Type I collagen [s-CTx]).

[redacted]

- [redacted]

STUDY DESIGN: This was a randomized, double-blind, 24-month study with a primary endpoint of aBMD at the lumbar spine at 12 months. 214 postmenopausal women 45-85 years of age, with low bone density (t-score ≤ -1.5 and > -3.5) at either the hip or lumbar spine, were recruited and randomized in a 1:1 ratio to receive either odanacatib 50 mg OW + Vitamin D_3 5600 IU OW or placebo OW + Vitamin D_3 5600 IU OW, for 24 months. Women were excluded if they had a hip fracture or a non-hip clinical fragility fracture within 24 months prior to randomization unless they were unable to or refused to take currently available osteoporosis therapies. All study patients received calcium supplementation as needed to ensure a total daily calcium intake of 1200 mg. aBMD was assessed by DEXA at the lumbar spine, hip (total hip, femoral neck, and hip trochanter) and distal forearm (one-third distal and ultradistal sites) at Screening and Months 6, 12, and 24. vBMD was assessed by QCT at the lumbar spine [redacted] at Randomization, Month 12 and Month 24, and in addition at the lumbar spine only at Month 6. [redacted]
Markers of bone turnover(s-CTx and s-P1NP) were measured at Randomization and at subsequent time points. Optional transilial bone biopsies were performed at Month 24 in those patients consenting to undergo the procedure.

PATIENT DEMOGRAPHICS/DISPOSITION:

	Odanacatib 50 mg OW		Placebo OW		Total	
	n	(%)	n	(%)	n	(%)
Not Randomized					111	
Randomized Patients	109		105		214	
Patient Demographics						
SEX						
Female	109	(100)	105	(100)	214	(100)
AGE (years)						
Mean (SD)	63.9 (7.3)		64.0 (6.2)		64.0 (6.8)	
Median	63		63		63	
Range	46 to 81		45 to 83		45 to 83	
Study Disposition						
COMPLETED	84	(77.1)	90	(85.7)	174	(81.3)
DISCONTINUED	25	(22.9)	15	(14.3)	40	(18.7)
ADVERSE EVENT	11	(10.1)	5	(4.8)	16	(7.5)
LACK OF EFFICACY[§]	0	(0.0)	1	(1.0)	1	(0.5)
LOST TO FOLLOW-UP	3	(2.8)	1	(1.0)	4	(1.9)
PHYSICIAN DECISION	1	(0.9)	1	(1.0)	2	(0.9)
PROTOCOL VIOLATION	1	(0.9)	0	(0.0)	1	(0.5)
WITHDRAWAL BY SUBJECT	9	(8.3)	7	(6.7)	16	(7.5)

Each patient is counted once for Study Disposition based on the latest corresponding disposition record.

[§]One patient discontinued due to an AE of excessive bone loss but the actual reason for discontinuation was "lack of efficacy".

DOSAGE/FORMULATION NOS.:

Drug	Potency	Formulation No.	Dosage Form	Control No.
Placebo to match MK-0822 50 mg	Placebo	[redacted]	Oral Compressed Tablet (OCT)	[redacted]
MK-0822	50 mg		OCT	
Vitamin D3	2800 IU		OCT	

DIAGNOSIS/INCLUSION CRITERIA: Postmenopausal women aged 45-85 years with a BMD T-score at the total hip, hip trochanter, femoral neck or lumbar spine ≤–1.5 but >–3.5.

EVALUATION CRITERIA:

Efficacy Evaluation: Dual-Energy X-ray Absorptiometry (DEXA), Quantitative Computed Tomography (QCT), [redacted] Transilial Bone Biopsy, Biochemical Markers of Bone Turnover, Archival Serum and Urine Samples.

Safety Evaluation: Physical examinations, vital signs, laboratory evaluations, and assessment of adverse experiences (AEs).

STATISTICAL PLANNING AND ANALYSIS:

Efficacy:

Percent change from baseline in aBMD was summarized at Months 6, 12 and 24. A longitudinal analysis of covariance (ANCOVA) model was used to obtain an estimate of the between-treatment difference together with its 95% confidence interval. Table and graphical presentations were provided of the least squares (LS) means and the corresponding standard error of the percent change from baseline over time by treatment group.

Similar analyses were performed for the QCT, [redacted] measurements.

All these analyses were performed using the *Full-Analysis-Set population*.

Biochemical markers of bone turnover (s-CTX and s-P1NP) were analyzed similarly, using the log-transformed fraction from baseline. Summary statistics were obtained after back-transformation of the log-transformation (geometric mean percent change from baseline). Biomarkers were analyzed using the *Per-Protocol population*.

A step-down, closed-testing approach was used from the primary hypothesis to the secondary to account for multiple testing. Within the secondary endpoints (with associated hypothesis) a Hochberg approach was used. No multiplicity adjustment was applied for secondary or exploratory endpoints without hypotheses and many endpoints were tested; p-values should therefore be interpreted with caution.

Safety:

The analysis of safety results followed a tiered approach. The tiers are different with respect to the analyses that were performed. Safety parameters or AEs of special interest that were identified *a priori* constituted Tier 1 safety endpoints that would be subject to inferential testing for statistical significance with p-values and 95% CIs provided for between-group comparisons. Tier 1 AEs include skin AEs that were severe, serious, or suggestive of morphea/scleroderma, serious respiratory infections confirmed by adjudication, osteonecrosis of the jaw confirmed by adjudication, morphea/scleroderma confirmed by adjudication, and delayed fracture unions confirmed by adjudication. Other safety parameters would be considered Tier 2 or Tier 3. Tier 2 parameters were assessed via point estimates with 95% CIs provided for between-group comparisons. Only point estimates by treatment group are provided for Tier 3 safety parameters.

RESULTS:

Efficacy: The primary and key secondary BMD endpoints (by DEXA and QCT only) at Month 12 and Month 24 are presented below. [redacted]

Key DEXA Efficacy Endpoints

At Months 12 and 24, significant improvements in areal BMD by DEXA at the lumbar spine, total hip, femoral neck, and trochanter were observed for the odanacatib 50 mg treatment group in comparison to the placebo treatment group. The mean percent change of aBMD from baseline at the lumbar spine, total hips, femoral neck, and trochanter increased over time in the odanacatib 50 mg treatment group, while it either remained stable or slightly decreased in the placebo group. The total radius aBMD remained relatively stable in the odanacatib 50 mg treatment group, while it decreased in the placebo treatment group. The results at the radius were significant at 12 months (p=0.030); at 24 months odanacatib showed moderately significant gains compared to placebo (1.70 treatment difference, p<0.001).

Analysis of Percent Change From Baseline at Month 12
(Full-Analysis-Set Population)

		Percent Change From Baseline		Treatment Difference[‡]		
Treatment	N	LS Mean[†]	(95% CI)	LS Mean[†]	(95% CI)	p-Value
DEXA Lumbar Spine Areal BMD (gm/cm^2)						
ODN 50 mg OW	96	3.63	(3.04, 4.21)	3.49	(2.66, 4.32)	<0.001
Placebo OW	97	0.14	(-0.45, 0.72)			
DEXA Total Hip Areal BMD (gm/cm^2)						
ODN 50 mg OW	96	1.41	(0.92, 1.89)	1.57	(0.88, 2.25)	<0.001
Placebo OW	97	-0.16	(-0.64, 0.32)			
DEXA Femoral Neck Areal BMD (gm/cm^2)						
ODN 50 mg OW	96	1.03	(0.41, 1.65)	1.48	(0.60, 2.35)	0.001
Placebo OW	97	-0.45	(-1.07, 0.17)			
DEXA Hip Trochanter Areal BMD (gm/cm^2)						
ODN 50 mg OW	96	2.37	(1.59, 3.15)	2.19	(1.09, 3.29)	<0.001
Placebo OW	97	0.18	(-0.60, 0.95)			
DEXA Total Radius Areal BMD (gm/cm^2)						
ODN 50 mg OW	96	0.01	(-0.44, 0.47)	0.71	(0.07, 1.35)	0.030
Placebo OW	96	-0.70	(-1.15, -0.24)			

[†]Weighted LS mean, weighted for center size, based on analysis of variance with terms for treatment and study center.
PBO = Placebo once weekly, 50 mg = MK-0822 50 mg once weekly.
CI = Confidence Interval; LS Mean = Weighted Least Squares Mean.

Analysis of Percent Change From Baseline at Month 24 (Full-Analysis-Set Population)

		Percent Change From Baseline		Treatment Difference‡		
Treatment	N	LS Mean†	(95% CI)	LS Mean†	(95% CI)	p-Value
DEXA Lumbar Spine Areal BMD (gm/cm^2)						
ODN 50 mg OW	83	5.02	(4.28, 5.76)	5.39	(4.36, 6.42)	<0.001
Placebo OW	90	-0.38	(-1.09, 0.34)			
DEXA Total Hip Areal BMD (gm/cm^2)						
ODN 50 mg OW	82	2.43	(1.76, 3.10)	3.32	(2.39, 4.26)	<0.001
Placebo OW	90	-0.89	(-1.55, -0.24)			
DEXA Femoral Neck Areal BMD (gm/cm^2)						
ODN 50 mg OW	82	2.47	(1.67, 3.28)	3.81	(2.69, 4.93)	<0.001
Placebo OW	90	-1.33	(-2.11, -0.56)			
DEXA Hip Trochanter Areal BMD (gm/cm^2)						
ODN 50 mg OW	82	4.75	(3.75, 5.76)	5.48	(4.08, 6.89)	<0.001
Placebo OW	90	-0.73	(-1.71, 0.25)			
DEXA Total Radius Areal BMD (gm/cm^2)						
ODN 50 mg OW	82	-0.19	(-0.71, 0.34)	1.70	(0.97, 2.43)	<0.001
Placebo OW	90	-1.89	(-2.40, -1.38)			

†Weighted LS mean, weighted for center size, based on analysis of variance with terms for treatment and study center.
PBO = Placebo once weekly, 50 mg = MK-0822 50 mg once weekly.
CI = Confidence Interval; LS Mean = Weighted Least Squares Mean.

Biochemical markers of Bone Resorption and Bone Formation

There was a decrease (without multiplicity adjustment) from baseline in serum C-telopeptide of Type I collagen for the odanacatib 50 mg treatment group in comparison to the placebo treatment group. The geometric mean decreased sharply from baseline to Month 6 and then increased slightly from Month 6 to Month 24 (staying well below the placebo control which remained relatively stable over time).

There was an initial decrease (without multiplicity adjustment) from baseline for the serum PINP for the odanacatib 50 mg treatment group in comparison to the placebo treatment group. The geometric mean decreased sharply from baseline to Month 6 but then increased back towards baseline and by Month 24, there was no significant difference between odanacatib and placebo levels. Serum P1NP in placebo-treated patients remained relatively stable over the entire 24-month period.

QCT Efficacy Endpoints

At Months 12 and 24, a significant improvement (without multiplicity adjustment) for the odanacatib 50 mg treatment group was seen in comparison to the placebo treatment group in trabecular vBMD at the central section of spine (L1).

[redacted]

[redacted]

Analysis of Percent Change From Baseline at Month 12
(Full-Analysis-Set Population)

		Percent Change From Baseline		Treatment Difference‡		
Treatment	N	LS Mean†	(95% CI)	LS Mean†	(95% CI)	p-Value
QCT Spine (L1) Mid Cylinder Trabecular Volumetric BMD (mg/cm^3)						
ODN 50 mg OW	82	6.58	(5.17, 7.99)	8.01	(6.03, 9.99)	<0.001
Placebo OW	86	-1.43	(-2.81, -0.04)			

†Weighted LS mean, weighted for center size, based on analysis of variance with terms for treatment and study center.
PBO = Placebo once weekly, 50 mg = MK-0822 50 mg once weekly.
CI = Confidence Interval; LS Mean = Weighted Least Squares Mean.

Analysis of Percent Change From Baseline at Month 24
(Full-Analysis-Set Population)

		Percent Change From Baseline		Treatment Difference‡		
Treatment	N	LS Mean†	(95% CI)	LS Mean†	(95% CI)	p-Value
QCT Spine (L1) Mid Cylinder Trabecular Volumetric BMD (mg/cm^3)						
ODN 50 mg OW	72	6.44	(4.64, 8.24)	11.46	(8.96, 13.97)	<0.001
Placebo OW	79	-5.02	(-6.76, -3.28)			
[redacted]						

†Weighted LS mean, weighted for center size, based on analysis of variance with terms for treatment and study center.
PBO = Placebo once weekly, 50 mg = MK-0822 50 mg once weekly.
CI = Confidence Interval; LS Mean = Weighted Least Squares Mean.

[redacted]

Safety:

Of the 214 patients who entered the study, 109 patients received at least one dose of odanacatib 50 mg and 105 patients received at least one dose of matching placebo. The mean duration of the treatment was 20.7 months in the odanacatib group and 21.9 months in the placebo group.

	ODN 50 mg OW		Placebo OW	
	n	(%)	n	(%)
Patients in population	109		105	
with one or more adverse events	90	(82.6)	89	(84.8)
with no adverse event	19	(17.4)	16	(15.2)
with drug-related[†] adverse events	15	(13.8)	26	(24.8)
with serious adverse events	13	(11.9)	16	(15.2)
with serious drug-related adverse events	0	(0.0)	0	(0.0)
who died[§]	0	(0.0)	0	(0.0)
discontinued[‡] due to an adverse event	11	(10.1)	6	(5.7)
discontinued due to a drug-related adverse event	4	(3.7)	4	(3.8)
discontinued due to a serious adverse event	5	(4.6)	1	(1.0)
discontinued due to a serious drug-related adverse event	0	(0.0)	0	(0.0)

[†] Determined by the investigator to be related to the drug.

[§] There were no deaths listed during the double-blind treatment period [redacted]

[‡] Study medication withdrawn.

CONCLUSIONS:

1) At 12 and 24 months, treatment with odanacatib resulted in significantly higher aBMD at the lumbar spine relative to placebo. Odanacatib also significantly increased aBMD at the total hip, femoral neck, hip trochanter, and maintained the aBMD at the one-third distal forearm compared to placebo at 12 and 24 months.

2) The 12-month changes in biochemical markers of bone turnover show a significant reduction in both serum CTx and P1NP compared to placebo. At 24 months, however, CTx continued to be significantly reduced in the odanacatib-treated group while P1NP returned towards baseline resulting in a non-significant reduction P1NP compared to placebo.

[redacted]

4) The safety results from this two year clinical trial indicate that odanacatib is generally safe and well-tolerated.