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-0822A cholecalciferol (+) L-001037536, oral Vitamin D Insufficiency	**CLINICAL STUDY REPORT SYNOPSIS**

PROTOCOL TITLE/NO.: A Randomized, Double-Blind, Placebo-Controlled, Multicenter, 16-Week Study to Assess the Effect of Vitamin D3 8400 IU Once Weekly on Body Sway and Neuromuscular Function in Men and Women Aged 70 Years and Older #009

INVESTIGATORS/STUDY CENTERS: Multi-center (12)

PUBLICATION(S):

PRIMARY THERAPY PERIOD: 13-Oct-2005 first dose of placebo run-in until 15-Jun-2006 when last dose of study drug was taken. **CLINICAL PHASE:** IIa

DURATION OF TREATMENT: 16 weeks

OBJECTIVES: In men and women aged 70 years or older: Primary: To compare change in mediolateral body sway (measured with eyes open using the AccuSway^{PLUS} platform) following administration of vitamin D3 8400 IU once-weekly for 16 weeks to that following administration of placebo. Secondary: 1. To evaluate the safety and tolerability of vitamin D3 8400 IU administered once-weekly for 16 weeks relative to placebo. 2. To compare the change in functional status assessed using the Short Physical Performance Battery (SPPB) following administration of vitamin D3 8400 IU once-weekly for 16 weeks to placebo. 3. To evaluate the mean serum 25-hydroxyvitamin D [25(OH)D], calcium, and phosphate levels following administration of vitamin D3 8400 IU once-weekly for 16 weeks relative to placebo. 4. If the response to treatment with vitamin D3 is not universal across subjects, to determine the baseline serum 25(OH)D concentration in the subgroup of subjects in whom body sway improved in response to 16 week treatment with vitamin D3 8400 IU once-weekly. Exploratory: 1. To compare the change in body sway from baseline (measured with eyes closed on an AccuSway^{PLUS} platform) following administration of vitamin D3 8400 IU once-weekly vs. placebo for 16 weeks. 2. To evaluate the correlation between serum 25(OH)D concentration and body sway following administration of vitamin D3 8400 IU or placebo once-weekly for 16 weeks. 3. To evaluate the correlation between changes in serum 25(OH)D and changes in body sway from baseline following administration of vitamin D3 8400 IU or placebo once-weekly for 16 weeks.

STUDY DESIGN: 16-Week randomized, double-blind, placebo-controlled, multi-center study.

SUBJECT/PATIENT DISPOSITION:

	Vitamin D3 8400 IU	Placebo	Total
SCREENING FAILURES:			
RANDOMIZED:	114 (70-94)	112 (70-99)	226 (70-99)
Male (age range)	36 (70-94)	31 (71-99)	67 (70-99)
Female (age range)	78 (70-93)	81 (70-94)	159 (70-94)
COMPLETED:	105	97	202
DISCONTINUED:	9	15	24
Clinical adverse experience	2	2	4
Laboratory adverse experience	0	0	0
Other	7	13	20

DOSAGE/FORMULATION NOS.: Weekly dosing of: Vitamin D3 8400 IU; Calcium Supplement (Oscal 500) 500 mg only in those subjects with a dietary calcium intake, at screening, <1000 mg/day.

DIAGNOSIS/INCLUSION CRITERIA: Subjects were either men or women 70 years or older in generally good health that had serum 25(OH)D level ≥6 ng/mL but ≤20 ng/mL at the time of consent. Subjects must not have been receiving, at screening or within 6 months of screening, vitamin D supplements in excess of 800 IU/day.

EVALUATION CRITERIA: Efficacy Measurements: The primary efficacy endpoint for this study was body sway. Other endpoints included SPPB and serum 25(OH)D, calcium and phosphate levels.

Safety Measurements: Clinical evaluations were performed at all study clinic visits. Serum 25(OH)D levels were also assessed at all study clinic visits and subjects with serum 25(OH)D levels <6 ng/mL were discontinued from blinded drug and treated for vitamin D deficiency. Adverse experiences were assessed prior to blinded study drug administration and throughout the study.

STATISTICAL PLANNING AND ANALYSIS:

EFFICACY: Average change from baseline over the 16 weeks of treatment in the mediolateral body sway with eyes open was analyzed. Statistical tests were performed using the analysis of covariance (ANCOVA) model with terms for baseline body sway, baseline stratum, and treatment group. A repeated measures analysis model including the terms for baseline body sway, baseline stratum, week, and treatment group was used to corroborate the results from the ANCOVA model. Treatment comparisons were based on testing specific contrasts using the ANCOVA model. All statistical tests for treatment comparisons were two-tailed at $\alpha = 0.05$ level.

SAFETY: Safety and tolerability were assessed by a review of all relevant safety parameters including clinical adverse experiences and laboratory values. As there was no predefined adverse experience of interest, no hypothesis was tested. But for the evaluation of adverse experiences and predefined limits of change in laboratory parameters, such as urine calcium and other safety aspects, only summary tabulations and 95% confidence intervals for between-group differences were provided.

RESULTS:

EFFICACY: The vitamin D3 8400 IU once-weekly for 16 week treatment group did not demonstrate statistically significant improvement relative to placebo in the primary endpoint, mediolateral body sway with eyes open. The subgroup analysis using the parametric ANCOVA model for patients with baseline mediolateral body sway ≥ 0.46 cm showed significant improvement (p-value = 0.047) in body sway for the vitamin D3 8400 IU group, although there were only 31 patients in this subgroup analysis. The other subgroup analyses based on baseline 25(OH)D level or nationality did not show treatment difference.

Analysis of Change from Baseline in Mediolateral Sway with Eyes Open at Week 16
(All-Patients-Treated Population)

		Patient Response		Change in Patient Response		
		Baseline	Week 16			LS Mean
Treatment	N	Mean (SD)	Mean (SD)	Median (SE)	Mean (SE)	(95% CI)
Vitamin D3 8400 IU	108	0.304 (0.122)	0.304 (0.126)	0.000 (0.009)	-0.000 (0.011)	-0.006 (-0.028, 0.016)
Placebo	102	0.350 (0.154)	0.353 (0.190)	0.006 (0.009)	0.003 (0.011)	0.005 (-0.017, 0.028)

Between-Treatment Comparison		
Treatment	LS Mean Difference (95% CI)	p-Value
Vitamin D3 8400 IU vs. Placebo	-0.012 (-0.043, 0.020)	0.463

Analysis of Main Effects	p-Value	RMSE
Treatment	0.463	0.11
Baseline Values	0.002	
Stratum	0.378	

IU = International Unit; SD=Standard Deviation; SE=Standard Error
CI = Confidence Interval; RMSE = Root Mean Squared Error; Computed From Main Effects Model

SAFETY: The overall incidence of clinical adverse experiences was similar in the vitamin D3 8400 IU treatment group and the placebo treatment group. Drug-related clinical adverse experiences were infrequent and similar in both treatment groups. The incidences of serious clinical adverse events were also low and similar in the two treatment groups (3 in each treatment group). However, no serious drug-related clinical adverse experience was reported in the study. There were 2 discontinuations in each treatment group for clinical adverse experiences. Laboratory adverse experiences were relatively infrequent (2 in the vitamin D3 8400 IU group and 9 in the placebo group) and no serious laboratory adverse experience were reported. However no drug-related laboratory adverse experience was reported. Some of the patients exceeded the upper limit of normal range for various laboratory parameters at week 16 as well as at baseline, and the proportion was comparable between the two treatment groups. No within-treatment percent changes and no between-treatment differences were observed for serum calcium, serum phosphate, serum creatinine, serum albumin, 24-hour urine creatinine and creatinine clearance after 16 weeks of treatment. Significant percent increases in 24-hour urine calcium for the vitamin D3 8400 IU group was observed and small non-significant percent increases were observed for the placebo group. The between-group difference reached borderline significance.

Clinical Adverse Experience Summary	Vitamin D3 8400 IU (N = 114)		Placebo (N = 112)	
	n	(%)	n	(%)
Number (%) of patients:				
With one or more adverse experiences	24	(21.1)	26	(23.2)
With no adverse experience	90	(78.9)	86	(76.8)
With drug-related adverse experiences[†]	1	(0.9)	4	(3.6)
With serious adverse experiences	3	(2.6)	3	(2.7)
With serious drug-related adverse experiences	0	(0.0)	0	(0.0)
Who died	1	(0.9)	0	(0.0)
Discontinued due to adverse experiences	2	(1.8)	2	(1.8)
Discontinued due to drug-related adverse experiences[†]	1	(0.9)	1	(0.9)
Discontinued due to serious adverse experiences	1	(0.9)	1	(0.9)
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	Vitamin D3 8400 IU (N = 114)		Placebo (N = 112)	
	n	(%)[‡]	n	(%)[‡]
Number (%) of patients:				
With at least one lab test postbaseline	111		110	
With one or more adverse experiences	2	(1.8)	9	(8.2)
With no adverse experience	109	(98.2)	101	(91.8)
With drug-related adverse experiences[†]	0	(0.0)	0	(0.0)
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	1	(0.9)	3	(2.7)
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 following the baseline visit.

CONCLUSION: Treatment with vitamin D3 8400 IU once weekly reduced body sway in subjects with elevated basal mediolateral sway, but it had no effect on body sway in subjects with normal basal mediolateral sway. Baseline 25(OH)D status did not interact with the effectiveness of vitamin D3 8400 IU once weekly on body sway. Administration of vitamin D3 8400 IU weekly for 16 weeks was well-tolerated in this study population.

AUTHORS: [redacted]