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

SPONSOR:	**Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.**	
COMPOUND NAME:	odanacatib 50 mg tablet	
INDICATION:	Exploratory study for the identification of biomarkers of age-related sarcopenia in women.	
PROTOCOL TITLE:	A Sub-Study to Explore Biomarkers of Physical Function in the Phase 3 Randomized, Placebo-Controlled Clinical Trial to Assess the Safety and Efficacy of Odanacatib (MK-0822) to Reduce the Risk of Fracture in Osteoporotic Postmenopausal Women Treated with Vitamin D and Calcium	
TRIAL IDENTIFIERS:	Protocol Number:	035
	Clinical Phase:	3
	EudraCT Number:	2008-005874-11
TRIAL CENTERS:	This sub-study was conducted at 34 centers: 7 in the United States; 4 sites each in Norway, Peru and South Africa; 3 sites each in Colombia, France and the Russian Federation; 2 sites each in New Zealand and the Philippines; and 1 site each in Brazil and Hong Kong.	

<table>
<tr><td>DESIGN:</td><td colspan="2">Protocol 035 was an exploratory sub-study of Protocol 018 to identify biomarkers of physical function.

Protocol 018 was a multicenter, randomized, double-blind, parallel-group, placebo-controlled, trial to assess the safety and efficacy of odanacatib in the treatment of osteoporotic postmenopausal women. Patients enrolled in Protocol 018 were women 65 years of age or older with osteoporosis with or without prior vertebral fracture. Eligible patients were randomized (1:1) to receive 50 mg odanacatib or matching placebo once weekly in Protocol 018. All patients also received open-label vitamin D_3 (5600 IU once weekly) and calcium supplements. Patients in the Protocol 035 sub-study were not dispensed additional study medication. Eligible patients already enrolled in Protocol 018 and who consented to this sub-study, were enrolled. The original purpose of this exploratory sub-study was to identify a molecular signature of sarcopenia and the progression of sarcopenia using DNA and RNA biomarkers in the blood. The progression of sarcopenia was assessed using appendicular lean body mass (aLBM) as measured by total body DXA, and physical function as measured by the Short Physical Performance Battery (SPPB) and gait speed (a component of the SPBB summary score). Due to the much smaller than originally planned sample size (556 enrolled compared with the planned 2000 patients), along with an unequal distribution of sarcopenic vs. non-sarcopenic patients (more than 80% of the patients were sarcopenic), analysis of the biomarker data (DNA and RNA) was not performed. Between-treatment group differences in aLBM and the SPPB and its components were explored.</td></tr>
<tr><td></td><td>Planned duration of main phase:</td><td>This sub-study was conducted in parallel with the Protocol 018 base study. Study duration was 43 months, from March 2009 to October 2012.</td></tr>
<tr><td></td><td>Planned duration of run-in phase:</td><td>Not applicable</td></tr>
<tr><td></td><td>Planned duration of extension phase:</td><td>Not applicable</td></tr>
</table>

Primary Objectives	(1A) To evaluate the phenotypic distribution of aLBM, SPPB, and gait speed in the study population. Specifically to determine if, at baseline, measured traits (aLBM, SPPB and/or gait speed) form an appropriate distribution. (1B) To identify biomarkers of sarcopenia by evaluating low aLBM, low SPPB, and low gait speed, separately and in combination, by examining DNA and RNA in circulating blood. (2A) To determine if there is a measurable change in aLBM, SPPB, and gait speed over time within the duration of the study. Specifically to determine if the rate-of-change in the measured traits (aLBM, SPPB and/or gait speed) form an appropriate distribution. (2B) To identify biomarkers of rate-of-change (fast vs slow) of aLBM, SPPB, and gait speed, separately or in combination, by examining DNA and RNA in circulating blood. [redacted] 1. [redacted]	
Hypotheses	This was an exploratory study, therefore, there were no hypotheses.	
Treatments groups	Odanacatib	odanacatib, 50 mg tablet, once weekly 279 subjects enrolled (278 received study medication)
	Placebo	matching placebo, 50 mg tablet, once weekly 277 subjects enrolled and received study medication

[redacted]

Endpoints and definitions	Key endpoint	Change from baseline in aLBM	Change from baseline in aLBM (as measured by total body DXA) at each post-randomization timepoints (months 12, 24, 36 and 48).
	Other endpoints	Change from baseline in scores	Change from baseline in scores at months 12, 24, 36 and 48 for the following tests were considered other efficacy endpoints: 1) SPPB - summary score, 2) gait speed test, 3) total balance test, and 4) chair stand test. [redacted]
Database lock	18-JAN-2013	Trial status	05-MAR-2009 (first subject first visit) 18-OCT-2012 (last subject last visit)

RESULTS AND ANALYSIS:	A total of 556 patients enrolled in Protocol 018 participated in this sub-study, of which 555 patients were included in the all-patients-treated population. One patient in the odanacatib group did not take trial medication and therefore was excluded from the all-patients-treated population. There were no clinically meaningful differences for the disposition status among the treatment groups. In general, there were no clinically meaningful differences observed between the two treatment groups with regard to baseline patient characteristics and baseline efficacy endpoints. However, there were more sarcopenic patients (85.6%) in the odanacatib group than in the placebo group (76.9%). This imbalance between treatment groups was taken into account in the analysis model. aLBM declined over time in both treatment groups. There were no differences between the odanacatib and placebo groups in aLBM at post-randomization timepoints. There was a small numerical increase in the SPPB summary score from baseline to Month 12 in the odanacatib treatment group, indicating improvement in physical function, followed by a small numerical decline and eventual stabilization at close to the baseline level. SPPB summary score declined over time in the placebo treatment group, indicating a worsenign of physical function. There were no clinically meaningful differences between the treatment groups in the SPPB summary score at all post-baseline timepoints. There were small numerical declines in gait speed in both treatment groups. There were no differences between the treatment groups in gait speed score (component of the SPPB score) at post-baseline timepoints. No between-treatment group differences were observed for the two other components of the SPPB score: the total balance and chair stand tests. [redacted]

Disposition of Patients
All-Patients-Treated Population

	ODN 50 mg OW		Placebo OW		Total	
	n	(%)	n	(%)	n	(%)
Patients in population	278		277		555	
Study Disposition						
Completed	236	(84.9)	220	(79.4)	456	(82.2)
Discontinued	42	(15.1)	57	(20.6)	99	(17.8)
Adverse Event	13	(4.7)	12	(4.3)	25	(4.5)
Lack Of Efficacy	0	(0.0)	2	(0.7)	2	(0.4)
Lost To Follow-Up	6	(2.2)	7	(2.5)	13	(2.3)
Other Protocol Specified Criteria	7	(2.5)	11	(4.0)	18	(3.2)
Physician Decision	1	(0.4)	2	(0.7)	3	(0.5)
Protocol Violation	1	(0.4)	1	(0.4)	2	(0.4)
Study Terminated By Sponsor	0	(0.0)	4	(1.4)	4	(0.7)
Withdrawal By Subject	14	(5.0)	18	(6.5)	32	(5.8)

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

Baseline Patient Characteristics by Treatment
All-Patients-Treated Population

	ODN 50 mg OW (N = 278)		Placebo OW (N = 277)		Total (N = 555)	
	n	(%)	n	(%)	n	(%)
Sex						
Female	278	(100)	277	(100)	555	(100)
Age (years)						
Below 70	73	(26.3)	81	(29.2)	154	(27.7)
70 and Over	205	(73.7)	196	(70.8)	401	(72.3)
N	278		277		555	
Mean	73.2		73.4		73.3	
SD	5.3		5.5		5.4	
Median	72.0		73.0		73.0	
Range	65.0 to 88.0		65.0 to 92.0		65.0 to 92.0	
Race						
American Indian or Alaska Native	1	(0.4)	3	(1.1)	4	(0.7)
Asian	29	(10.4)	44	(15.9)	73	(13.2)
Black or African American	2	(0.7)	0		2	(0.4)
Multi-racial	163	(58.6)	131	(47.3)	294	(53.0)
White	83	(29.9)	99	(35.7)	182	(32.8)
Region						
Americas	153	(55.0)	128	(46.2)	281	(50.6)
Asia Pacific	38	(13.7)	54	(19.5)	92	(16.6)
Europe †	87	(31.3)	95	(34.3)	182	(32.8)
Stratum						
Prior Vertebral Fracture	98	(35.3)	106	(38.3)	204	(36.8)
No Prior Vertebral Fracture	180	(64.7)	171	(61.7)	351	(63.2)

Baseline Patient Characteristics by Treatment
All-Patients-Treated Population

	ODN 50 mg OW (N = 278)		Placebo OW (N = 277)		Total (N = 555)	
	n	(%)	n	(%)	n	(%)
Stratification by SPPB and aLBM at Baseline						
Non-sarcopenic	40	(14.4)	64	(23.1)	104	(18.7)
Sarcopenic	238	(85.6)	213	(76.9)	451	(81.3)

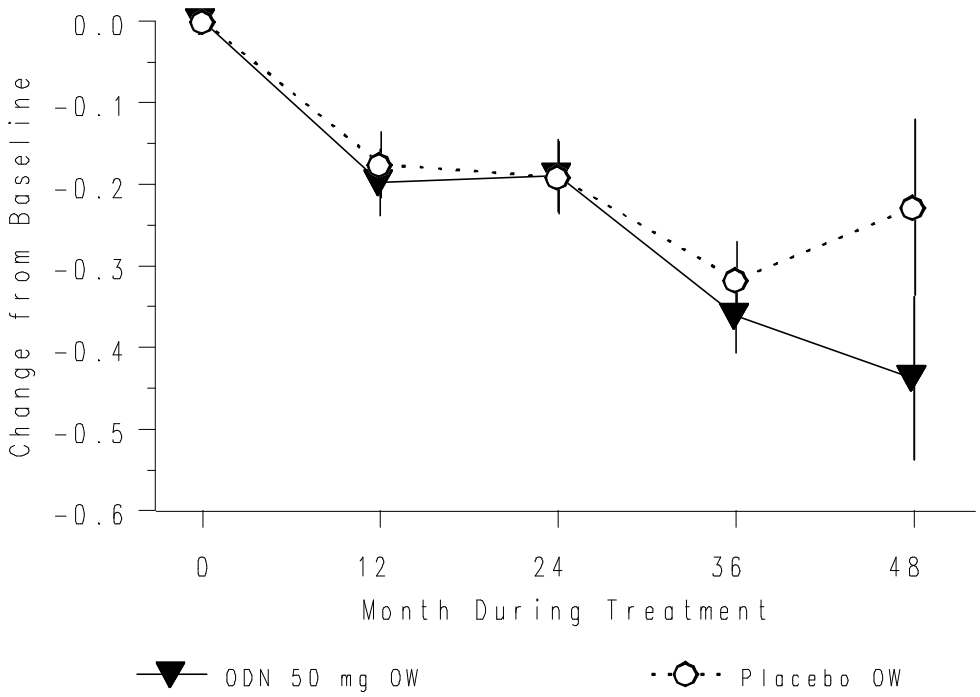
† South-Africa has been included in region Europe.
‡ Sarcopenic includes patients with SPPB score < 10 or appendicular lean body mass/height2 (aLBM/Ht2) >= 1 SD below peak. Non-Sarcopenic includes patients with SPPB score >= 10 and aLBM/Ht2 < 1 SD below peak.

Analysis description	**Primary Analysis**
Analysis population and time point description	A Full-Analysis-Set (FAS) population was used for all efficacy variables. Patients were included in the FAS population for the change from baseline at specific timepoints, which includes all randomized patients who took at least one dose of study medication and had the necessary baseline and on-treatment measurements available.
Summary	A longitudinal data analysis (LDA) model was used at Months 12, 24, 36 and 48 using the FAS population. In this model, the response vector included all post-baseline changes from baseline as response variables. The LDA model included terms for treatment, stratum (sarcopenia, non-sarcopenia), time, interaction between treatment and time, and interaction between treatment and stratum. Between and within treatment-group LS mean estimates and their 95% confidence intervals were provided from the LDA model specified. An unstructured covariance matrix was used to model the correlation among repeated measurements. Due to the exploratory nature of the efficacy endpoints, the analysis was restricted to a descriptive analysis; no formal statistical testing were conducted and only descriptive statistics were provided including estimates of the treatment difference and their 95% CIs. No formal statistical testing was performed as there were no hypotheses associated with the efficacy endpoints.

Changes from baseline through Month 48 in aLBM, SPPB, and gait speed are presented below. As the number of patients with available data was markedly lower at Month 48 [redacted], results are summarized focusing on the Month 36 time point.

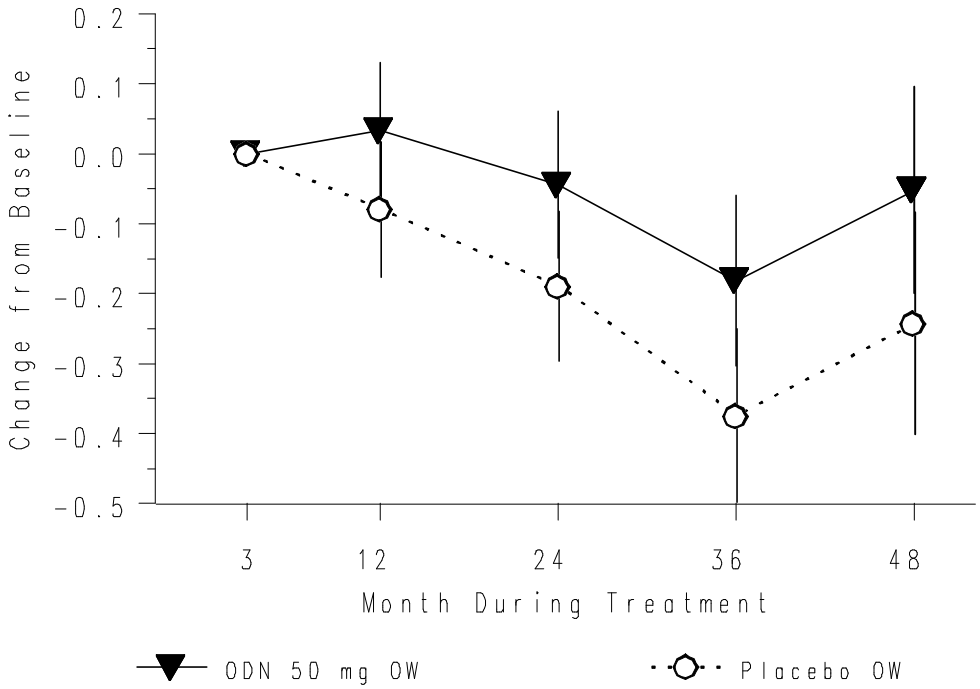
Mean decline from baseline in aLBM generally increased over time in both treatment groups. At Month 36, the mean decreases (95% CI) from baseline were 0.36 kg (-0.45, -0.27) and 0.32 kg (-0.41, -0.23) in the odanacatib (N=201) and placebo groups, respectively. There was no clinically meaningful between-treatment group difference in the mean change from baseline in aLBM over time.

Change from Baseline (LS Mean +/- SE) in Appendicular LBM (kg) by Time Point and Treatment
Full-Analysis-Set Population



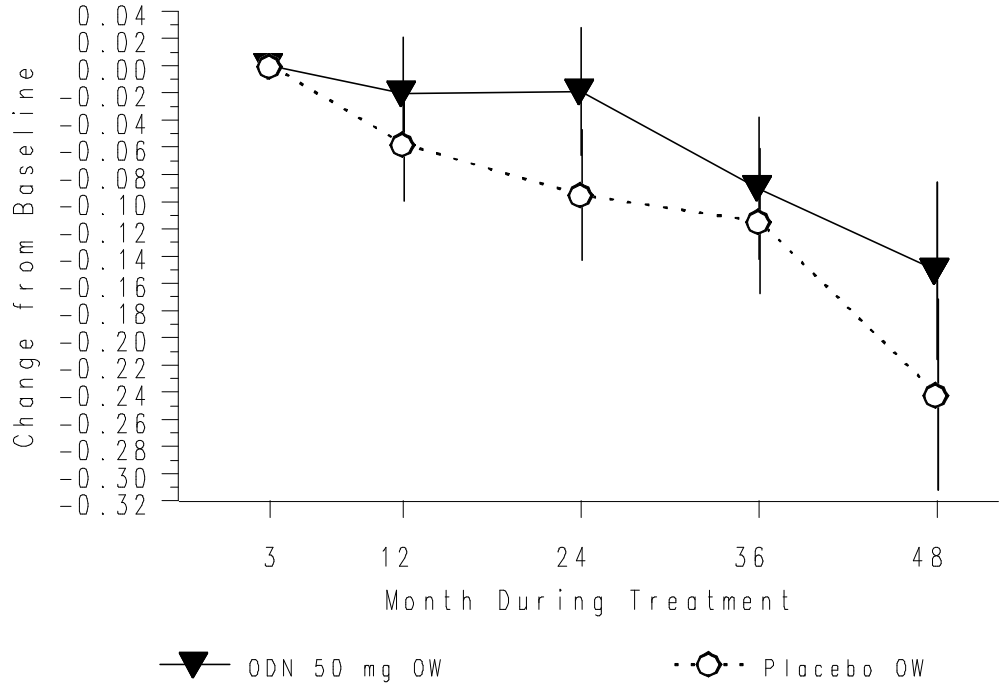
The mean changes from baseline in the SPPB summary score were numerically small, but appeared to be consistent with those seen with aging over a period of 3 to 4 years. At all post-baseline timepoints, the placebo group had a decrease from baseline in SPPB summary score, indicating worsening of physical function, whereas the odanacatib group had a small increase at Month 12, indicating an improvement in physical function, and small decreases from baseline at subsequent time points. At Month 36, the SPPB summary score decreased by 0.18 (95% CI -0.42, 0.06) in the odanacatib group, and by 0.37 (95% CI -0.62, -0.13) in the placebo group. The differences between the odanacatib and placebo groups were small and not considered to be clinically meaningful.

Change from Baseline (LS Mean +/- SE) in SPPB Summary Score by Time Point and Treatment
Full-Analysis-Set Population



The gait speed test was scored on a 0 to 4 scale (higher score represents faster gait speed). The mean changes from baseline in gait speed score were numerically small in both treatment groups. The gait speed score decreased over time in both the odanacatib and placebo groups. At Month 36, the gait speed score decreased by 0.09 (95% CI -0.19, 0.02) in the odanacatib arm, and by 0.11 (95% CI -0.22, -0.01) in the placebo arm. There was no clinically meaningful between-treatment group difference in the change from baseline in gait speed score over time.

Change from Baseline (LS Mean +/- SE) in Gait Speed Test Score by Time Point and Treatment
Full-Analysis-Set Population



Safety is being summarized in the context of Protocol 018; no additional safety analyses were performed for this sub-study. Refer to the Protocol 018 CSR for safety analyses.

CONCLUSIONS:	In a sub-population of the postmenopausal women with osteoporosis who participated in Protocol 018: • Primary Objective 1A – Most of the enrolled patients (over 80%) had sarcopenia, as defined by low aLBM (≥1 SD below the mean for young adult) and/or SPPB summary score <10. • Primary Objective 2A - Overall, there were small declines over time in aLBM, and SPPB summary score and the component score for gait speed. The decline in SPPB summary score was primarily in the patients without sarcopenia at baseline. The magnitude of the changes in the SPPB and the gait speed component score seem to be consistent with those seen with aging in a population of this age over a period of 3 to 4 years. • [redacted] [redacted] • There were no clinically meaningful differences between the odanacatib and placebo treatment groups in the mean change over time in aLBM, SPPB summary or component scores, or self-reported mobility-disability. • Analyses to support Primary Objectives 1B, 2B and [redacted] were not performed because the number of patients enrolled was much smaller than the 2000 originally targeted. The enrolled number of patients (556) was not sufficient to support these objectives.
REPORT DATE	**21-OCT-2015**