A Study to Test the Effect of MK0217A on Vitamin D Inadequacy in Postmenopausal Women With Osteoporosis (0217A-262)

This study has been completed.

Sponsor:
Merck Sharp & Dohme Corp.

Information provided by (Responsible Party):
Merck Sharp & Dohme Corp.

ClinicalTrials.gov Identifier:
NCT00692913

First received: June 4, 2008
Last updated: July 21, 2015
Last verified: July 2015
History of Changes

Purpose

A study designed to see if the study drug will increase blood levels of vitamin D, bone mineral density (BMD), improve biochemical markers of bone turnover, and reduce the number of falls as compared to women receiving standard care for osteoporosis.

Condition	Intervention	Phase
Osteoporosis	Drug: FOSAVANCE 5600 (Alendronate Sodium (+) cholecalciferol) Dietary Supplement: Calcium Supplement 500 mg Other: Referred-Care Model	Phase 3

Study Type: Interventional
Study Design: Allocation: Randomized
Endpoint Classification: Safety/Efficacy Study
Intervention Model: Parallel Assignment
Masking: Open Label
Primary Purpose: Treatment

Official Title: A Phase III (Phase V Program), Open-Label, Randomized, Referred-Care-Controlled, Clinical Trial to Evaluate the Efficacy and Safety of MK -0217A/Alendronate Sodium-70 mg/Vitamin D3 5600 I.U. Combination Tablet on Vitamin D Inadequacy in the Treatment of Osteoporosis in Postmenopausal Women

Resource links provided by NLM:

MedlinePlus related topics: Osteoporosis Vitamin D

Drug Information available for: Cholecalciferol Vitamin D Alendronate sodium

U.S. FDA Resources

Further study details as provided by Merck Sharp & Dohme Corp.:

Primary Outcome Measures:

- Percentage of Participants With Serum Levels of 25-hydroxyvitamin D Below 20 ng/mL at Week 26 [Time Frame: Week 26] [Designated as safety issue: No]

  Percentage of participants with serum levels of 25-hydroxyvitamin D below 20 nanograms/milliliter (ng/mL) after 26 weeks of treatment with FOSAVANCE 5600 once weekly versus Referred-Care in postmenopausal women with osteoporosis and at increased risk of falls.

Secondary Outcome Measures:

- Percent Change From Baseline at Week 26 in N-Telopeptides of Type 1 Collagen to Urine Creatinine Ratio [Time Frame: Baseline and Week 26] [Designated as safety issue: No]

  N-Telopeptides of Type 1 Collagen to Urine Creatinine Ratio (NTx) is a urine biochemical marker of bone resorption and measured in nanomoles (nmol) Bone Collagen Equivalents (BCE)/millimoles (mmol) creatinine. The percent change was calculated as: [100 * ((Week 26/Baseline)-1)]. The greater the percent decrease from baseline, the greater the response to therapy.

- Percent Change From Baseline at Week 26 in Bone-Specific Alkaline Phosphatase [Time Frame: Baseline and Week 26] [Designated as safety issue: No]

  Bone-Specific Alkaline Phosphatase (BSAP) is a serum biochemical marker of bone formation and measured in micrograms/Liter (mcg/L). The percent change was calculated as: [100 * ((Week 26/Baseline)-1)]. The greater the percent decrease from baseline, the greater the response to therapy.

- Percentage of Participants With Serum Levels of 25-hydroxyvitamin D Below 20 ng/mL at Week 52 [Time Frame: Week 52] [Designated as safety issue: No]

  Percentage of participants with serum levels of 25-hydroxyvitamin D below 20 ng/mL after 52 weeks of treatment (6 month extension study) with FOSAVANCE 5600 once weekly versus Referred-Care in postmenopausal women with osteoporosis and at increased risk of falls.

- Percent Change From Baseline in Lumbar Spine and Total Hip Bone Mineral Density [Time Frame: Baseline and Week 52] [Designated as safety issue: No]

  Bone Mineral Density (BMD) as measured by Dual Energy X-Ray Absorptiometry (DEXA) and measured in g/cm^2 was obtained at baseline (visit 1) and Week 52 (visit 13) or at early study discontinuation visit. The percent change was calculated as: [100 * ((Week 52/Baseline)-1)]. The greater the percent change from baseline, the greater the response to therapy.

- Falls Per Participant [Time Frame: Up to Week 52] [Designated as safety issue: No]

  Number of falls per participant was measured. The fall event rate during the study period was defined as the number of adjudicated falls during the study period divided by the total patient-years in the study. Each participant was to be in the study for approximately one year. In order to guide and standardize all procedures during the fall adjudication process, a Standard Operating Procedure for Fall Adjudication was created by the SPONSOR and served as a guideline to standardize operational procedures for fall adjudication.

- Percent Change From Baseline at Week 52 in N-Telopeptides of Type 1 Collagen to Urine Creatinine Ratio [Time Frame: Baseline and Week 52] [Designated as safety issue: No]

  NTx is a urine biochemical marker of bone resorption and measured in nanomoles (nmol) Bone Collagen Equivalents (BCE)/millimoles (mmol) creatinine. The percent change was calculated as: [100 * ((Week 52/Baseline)-1)]. The greater the percent decrease from baseline, the greater the response to therapy.

- Percent Change From Baseline at Week 52 in Bone-Specific Alkaline Phosphatase [Time Frame: Baseline and Week 52] [Designated as safety issue: No]

  BSAP is a serum biochemical marker of bone formation and measured in micrograms/Liter (mcg/L). The percent change was calculated as: [100 * ((Week 52/Baseline)-1)]. The greater the percent decrease from baseline, the greater the response to therapy.

Enrollment:	515
Study Start Date:	June 2008
Study Completion Date:	July 2010
Primary Completion Date:	July 2010 (Final data collection date for primary outcome measure)

Arms	Assigned Interventions

Experimental: FOSAVANCE 5600 alendronate sodium (+) cholecalciferol	Drug: FOSAVANCE 5600 (Alendronate Sodium (+) cholecalciferol) FOSAVANCE 5600 international units (IU)(Alendronate Sodium 70 mg/Vitamin D 5600 IU) combination tablet once weekly for 6 months (Week 26) during the base period and an additional 6-month extension period (Week 52). Dietary Supplement: Calcium Supplement 500 mg Calcium supplied locally by the investigator (containing 500 mg calcium supplement) daily for 52 weeks (unless the patient's dietary intake of calcium exceeds 1000 mg per day).
Referred-Care Model Usual treatment for osteoporosis chosen and prescribed by patients' own physicians.	Other: Referred-Care Model Usual treatment for osteoporosis chosen and prescribed by patients' own physicians for 6 months (Week 26) during the base period and an additional 6-month extension period (Week 52).

Eligibility

Ages Eligible for Study: 65 Years and older
Genders Eligible for Study: Female
Accepts Healthy Volunteers: No

Criteria

Inclusion Criteria:

- Female
- 65 years or older
- Diagnosed with osteoporosis (Bone Mineral Density (BMD) T-score <= -2.5 at spine or hip) or prior fragility fracture BMD T-score <=-1.5 in at least one of the anatomic sites including lumbar spine, total hip, and femoral neck sites
- Postmenopausal
- Low levels of vitamin D as measured 25-hydroxyvitamin D
- Has fallen at least once within the past 12 months

Exclusion Criteria:

- Unable to stand or sit upright for at least 30 minutes
- Has a bone disorder other than osteoporosis
- Contraindication to the use of FOSAVANCE

Contacts and Locations

Choosing to participate in a study is an important personal decision. Talk with your doctor and family members or friends about deciding to join a study. To learn more about this study, you or your doctor may contact the study research staff using the Contacts provided below. For general information, see Learn About Clinical Studies.

Please refer to this study by its ClinicalTrials.gov identifier: NCT00692913

Sponsors and Collaborators

Merck Sharp & Dohme Corp.

Investigators

Study Director: Medical Monitor Merck Sharp & Dohme Corp.

More Information

Publications:

Ralston SH, Binkley N, Boonen S, Kiel DP, Reginster JY, Roux C, Chen L, Rosenberg E, Santora A; FOCUS-D (FOSAVANCE vs. Standard Care-

Use and Study of Vitamin D) Trial. Randomized trial of alendronate plus vitamin D3 versus standard care in osteoporotic postmenopausal women with vitamin D insufficiency. Calcif Tissue Int. 2011 Jun;88(6):485-94. doi: 10.1007/s00223-011-9482-4. Epub 2011 Apr 11.

Responsible Party:	Merck Sharp & Dohme Corp.
ClinicalTrials.gov Identifier:	NCT00692913 History of Changes
Other Study ID Numbers:	0217A-262 2007_653
Study First Received:	June 4, 2008
Results First Received:	July 20, 2011
Last Updated:	July 21, 2015
Health Authority:	United States: Food and Drug Administration

Additional relevant MeSH terms:

Osteoporosis	Bone Density Conservation Agents
Bone Diseases	Growth Substances
Bone Diseases, Metabolic	Micronutrients
Musculoskeletal Diseases	Pharmacologic Actions
Alendronate	Physiological Effects of Drugs
Cholecalciferol	Vitamins
Vitamin D	

ClinicalTrials.gov processed this record on April 13, 2016

TO TOP

For Patients and Families | For Researchers | For Study Record Managers

HOME RSS FEEDS SITE MAP TERMS AND CONDITIONS DISCLAIMER CONTACT NLM HELP DESK

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First received: June 4, 2008
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History of Changes

Results First Received: July 20, 2011

Study Type:	Interventional
Study Design:	Allocation: Randomized; Endpoint Classification: Safety/Efficacy Study; Intervention Model: Parallel Assignment; Masking: Open Label; Primary Purpose: Treatment
Condition:	Osteoporosis
Interventions:	Drug: FOSAVANCE 5600 (Alendronate Sodium (+) cholecalciferol) Dietary Supplement: Calcium Supplement 500 mg Other: Referred-Care Model

Participant Flow

Hide Participant Flow

Recruitment Details

Key information relevant to the recruitment process for the overall study, such as dates of the recruitment period and locations
No text entered.

Pre-Assignment Details

Significant events and approaches for the overall study following participant enrollment, but prior to group assignment
No text entered.

Reporting Groups

	Description
FOSAVANCE 5600	Alendronate Sodium 70 mg/Vitamin D 5600 I.U. combination tablet once weekly plus a daily 500 mg elemental calcium supplement.
Referred-Care	Usual treatment for osteoporosis chosen and prescribed by patients' own physicians.

Participant Flow: Overall Study

	FOSAVANCE 5600	Referred-Care
STARTED	257	258
COMPLETED	228	228
NOT COMPLETED	29	30
Adverse Event	8	4
Lost to Follow-up	3	5
Physician Decision	2	0
Protocol Violation	1	1
Withdrawal by Subject	15	20

Baseline Characteristics

Hide Baseline Characteristics

Population Description

Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.
No text entered.

Reporting Groups

	Description
FOSAVANCE 5600	Alendronate Sodium 70 mg/Vitamin D 5600 I.U. combination tablet once weekly plus a daily 500 mg elemental calcium supplement.
Referred-Care	Usual treatment for osteoporosis chosen and prescribed by patients' own physicians.
Total	Total of all reporting groups

Baseline Measures

	FOSAVANCE 5600	Referred-Care	Total
Number of Participants [units: participants]	257	258	515
Age [units: years] Mean (Standard Deviation)	72.9 (5.3)	72.9 (5.9)	72.9 (5.6)
Gender [units: participants]			
Female	257	258	515

Male	**0**	**0**	**0**

Outcome Measures

Hide All Outcome Measures

1. Primary: Percentage of Participants With Serum Levels of 25-hydroxyvitamin D Below 20 ng/mL at Week 26 [Time Frame: Week 26]

Measure Type	Primary
Measure Title	Percentage of Participants With Serum Levels of 25-hydroxyvitamin D Below 20 ng/mL at Week 26
Measure Description	Percentage of participants with serum levels of 25-hydroxyvitamin D below 20 nanograms/milliliter (ng/mL) after 26 weeks of treatment with FOSAVANCE 5600 once weekly versus Referred-Care in postmenopausal women with osteoporosis and at increased risk of falls.
Time Frame	Week 26
Safety Issue	No

Population Description

Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.
Full Analysis Set Population (FAS) included participants who took at least one dose of study therapy during the entire treatment period of FOSAVANCE 5600 or who were assigned to receive regular care and had data reported at least once post-randomization during the entire study period, and had efficacy measurements during the entire study period.

Reporting Groups

	Description
FOSAVANCE 5600	Alendronate Sodium 70 mg/Vitamin D 5600 I.U. combination tablet once weekly plus a daily 500 mg elemental calcium supplement.
Referred-Care	Usual treatment for osteoporosis chosen and prescribed by patients' own physicians.

Measured Values

	FOSAVANCE 5600	**Referred-Care**
Number of Participants Analyzed [units: participants]	**221**	**216**
Percentage of Participants With Serum Levels of 25-hydroxyvitamin D Below 20 ng/mL at Week 26 [units: Percentage of Participants]	**8.6**	**31.0**

Statistical Analysis 1 for Percentage of Participants With Serum Levels of 25-hydroxyvitamin D Below 20 ng/mL at Week 26

Groups [1]	All groups
Method [2]	Regression, Logistic
P Value [3]	<0.001
Odds Ratio (OR) [4]	0.20

95% Confidence Interval	0.12 to 0.35

[1]	Additional details about the analysis, such as null hypothesis and power calculation:
	No text entered.
[2]	Other relevant method information, such as adjustments or degrees of freedom:
	The logistic regression model was adjusted by baseline 25-hydroxyvitamin D (25(OH)D) level stratum, age, and region.
[3]	Additional information, such as whether or not the p-value is adjusted for multiple comparisons and the a priori threshold for statistical significance:
	No text entered.
[4]	Other relevant estimation information:
	No text entered.

2. Secondary: Percent Change From Baseline at Week 26 in N-Telopeptides of Type 1 Collagen to Urine Creatinine Ratio [Time Frame: Baseline and Week 26]

Measure Type	Secondary
Measure Title	Percent Change From Baseline at Week 26 in N-Telopeptides of Type 1 Collagen to Urine Creatinine Ratio
Measure Description	N-Telopeptides of Type 1 Collagen to Urine Creatinine Ratio (NTx) is a urine biochemical marker of bone resorption and measured in nanomoles (nmol) Bone Collagen Equivalents (BCE)/millimoles (mmol) creatinine. The percent change was calculated as: [100 * ((Week 26/Baseline)-1)]. The greater the percent decrease from baseline, the greater the response to therapy.
Time Frame	Baseline and Week 26
Safety Issue	No

Population Description

Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.
Per-Protocol Population: excluded participants due to important deviations from the protocol that may substantially affect the results of the primary efficacy analysis.

Reporting Groups

	Description
FOSAVANCE 5600	Alendronate Sodium 70 mg/Vitamin D 5600 I.U. combination tablet once weekly plus a daily 500 mg elemental calcium supplement.
Referred-Care	Usual treatment for osteoporosis chosen and prescribed by patients' own physicians.

Measured Values

	FOSAVANCE 5600	**Referred-Care**
Number of Participants Analyzed [units: participants]	**216**	**226**
Percent Change From Baseline at Week 26 in N-Telopeptides of Type 1 Collagen to Urine Creatinine Ratio [units: Percent Change] Least Squares Mean (95% Confidence Interval)	**-57.06 (-60.19 to -53.68)**	**-47.36 (-51.23 to -43.18)**

Statistical Analysis 1 for Percent Change From Baseline at Week 26 in N-Telopeptides of Type 1 Collagen to Urine Creatinine Ratio

Groups [1]	All groups
Method [2]	Longitudinal Data Analysis Model
P Value [3]	<0.001
Difference in Least-squares means [4]	-9.70
95% Confidence Interval	-14.49 to -4.93

[1]	Additional details about the analysis, such as null hypothesis and power calculation:
	No text entered.
[2]	Other relevant method information, such as adjustments or degrees of freedom:
	The model was adjusted by baseline 25-hydroxyvitamin D level stratum, age, and region.
[3]	Additional information, such as whether or not the p-value is adjusted for multiple comparisons and the a priori threshold for statistical significance:
	No text entered.
[4]	Other relevant estimation information:
	No text entered.

3. Secondary: Percent Change From Baseline at Week 26 in Bone-Specific Alkaline Phosphatase [Time Frame: Baseline and Week 26]

Measure Type	Secondary
Measure Title	Percent Change From Baseline at Week 26 in Bone-Specific Alkaline Phosphatase
Measure Description	Bone-Specific Alkaline Phosphatase (BSAP) is a serum biochemical marker of bone formation and measured in micrograms/Liter (mcg/L). The percent change was calculated as: [100 * ((Week 26/Baseline)-1)]. The greater the percent decrease from baseline, the greater the response to therapy.
Time Frame	Baseline and Week 26
Safety Issue	No

Population Description

Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.
Per-Protocol Population: excluded participants due to important deviations from the protocol that may substantially affect the results of the primary efficacy analysis.

Reporting Groups

	Description
FOSAVANCE 5600	Alendronate Sodium 70 mg/Vitamin D 5600 I.U. combination tablet once weekly plus a daily 500 mg elemental calcium supplement.
Referred-Care	Usual treatment for osteoporosis chosen and prescribed by patients' own physicians.

Measured Values

	FOSAVANCE 5600	**Referred-Care**

Number of Participants Analyzed [units: participants]	**223**	**237**
Percent Change From Baseline at Week 26 in Bone-Specific Alkaline Phosphatase [units: Percent Change] Least Squares Mean (95% Confidence Interval)	**-46.67 (-49.32 to -43.88)**	**-39.60 (-42.60 to -36.44)**

Statistical Analysis 1 for Percent Change From Baseline at Week 26 in Bone-Specific Alkaline Phosphatase

Groups [1]	All groups
Method [2]	Longitudinal Data Analysis Model
P Value [3]	<0.001
Difference in Least-squares mean [4]	-7.07
95% Confidence Interval	-10.95 to -3.20

[1]	Additional details about the analysis, such as null hypothesis and power calculation:
	No text entered.
[2]	Other relevant method information, such as adjustments or degrees of freedom:
	The model was adjusted by baseline 25-hydroxyvitamin D level stratum, age, and region.
[3]	Additional information, such as whether or not the p-value is adjusted for multiple comparisons and the a priori threshold for statistical significance:
	No text entered.
[4]	Other relevant estimation information:
	No text entered.

4. Secondary: Percentage of Participants With Serum Levels of 25-hydroxyvitamin D Below 20 ng/mL at Week 52 [Time Frame: Week 52]

Measure Type	Secondary
Measure Title	Percentage of Participants With Serum Levels of 25-hydroxyvitamin D Below 20 ng/mL at Week 52
Measure Description	Percentage of participants with serum levels of 25-hydroxyvitamin D below 20 ng/mL after 52 weeks of treatment (6 month extension study) with FOSAVANCE 5600 once weekly versus Referred-Care in postmenopausal women with osteoporosis and at increased risk of falls.
Time Frame	Week 52
Safety Issue	No

Population Description

Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.
The FAS population included participants who took at least one dose of study therapy during the entire treatment period of FOSAVANCE 5600 or who were assigned to receive regular care and had data reported at least once post-randomization during the entire study period, and had efficacy measurements during the entire study period.

Reporting Groups

	Description
FOSAVANCE 5600	Alendronate Sodium 70 mg/Vitamin D 5600 I.U. combination tablet once weekly plus a daily 500 mg elemental calcium supplement.
Referred-Care	Usual treatment for osteoporosis chosen and prescribed by patients' own physicians.

Measured Values

	FOSAVANCE 5600	Referred-Care
Number of Participants Analyzed [units: participants]	**212**	**203**
Percentage of Participants With Serum Levels of 25-hydroxyvitamin D Below 20 ng/mL at Week 52 [units: Percentage of Participants]	**11.3**	**36.9**

Statistical Analysis 1 for Percentage of Participants With Serum Levels of 25-hydroxyvitamin D Below 20 ng/mL at Week 52

Groups [1]	All groups
Method [2]	Regression, Logistic
P Value [3]	<0.001
Odds Ratio (OR) [4]	0.21
95% Confidence Interval	0.13 to 0.35

[1]	Additional details about the analysis, such as null hypothesis and power calculation:
	No text entered.
[2]	Other relevant method information, such as adjustments or degrees of freedom:
	The logistic regression model was adjusted by baseline 25-hydroxyvitamin D level stratum, age, and region.
[3]	Additional information, such as whether or not the p-value is adjusted for multiple comparisons and the a priori threshold for statistical significance:
	No text entered.
[4]	Other relevant estimation information:
	No text entered.

5. Secondary: Percent Change From Baseline in Lumbar Spine and Total Hip Bone Mineral Density [Time Frame: Baseline and Week 52]

Measure Type	Secondary
Measure Title	Percent Change From Baseline in Lumbar Spine and Total Hip Bone Mineral Density
Measure Description	Bone Mineral Density (BMD) as measured by Dual Energy X-Ray Absorptiometry (DEXA) and measured in g/cm^2 was obtained at baseline (visit 1) and Week 52 (visit 13) or at early study discontinuation visit. The percent change was calculated as: [100 * ((Week 52/Baseline)-1)]. The greater the percent change from baseline, the greater the response to therapy.
Time Frame	Baseline and Week 52

Safety Issue	No

Population Description

Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.
The FAS population included participants who took at least one dose of study therapy during the entire treatment period of FOSAVANCE 5600 or who were assigned to receive regular care and had data reported at least once post-randomization during the entire study period, and had efficacy measurements during the entire study period.

Reporting Groups

	Description
FOSAVANCE 5600	Alendronate Sodium 70 mg/Vitamin D 5600 I.U. combination tablet once weekly plus a daily 500 mg elemental calcium supplement.
Referred-Care	Usual treatment for osteoporosis chosen and prescribed by patients' own physicians.

Measured Values

	FOSAVANCE 5600	**Referred-Care**
Number of Participants Analyzed [units: participants]	**227**	**219**
Percent Change From Baseline in Lumbar Spine and Total Hip Bone Mineral Density [units: Percent Change] Least Squares Mean (95% Confidence Interval)		
Lumbar Spine (n= 226/ n=219)	**4.92 (4.17 to 5.66)**	**3.91 (3.16 to 4.66)**
Total Hip (n=227/ n=218)	**2.22 (1.65 to 2.79)**	**1.40 (0.83 to 1.97)**

Statistical Analysis 1 for Percent Change From Baseline in Lumbar Spine and Total Hip Bone Mineral Density

Groups [1]	All groups
Method [2]	Traditional Longitudinal data analysis
P Value [3]	0.047
Least Squares Mean Difference [4]	1.01
95% Confidence Interval	0.01 to 2.00

[1]	Additional details about the analysis, such as null hypothesis and power calculation:
	No text entered.
[2]	Other relevant method information, such as adjustments or degrees of freedom:
	The model was adjusted by baseline 25-hydroxyvitamin D level stratum, age, and region.
[3]	Additional information, such as whether or not the p-value is adjusted for multiple comparisons and the a priori threshold for statistical significance:
	No text entered.
[4]	Other relevant estimation information:

	FOSAVANCE minus Referred-Care. Analysis was for Lumbar Spine.

Statistical Analysis 2 for Percent Change From Baseline in Lumbar Spine and Total Hip Bone Mineral Density

Groups [1]	All groups
Method [2]	Traditional Longitudinal data analysis
P Value [3]	0.035
Least Squares Mean Difference [4]	0.82
95% Confidence Interval	0.06 to 1.58

[1]	Additional details about the analysis, such as null hypothesis and power calculation:
	No text entered.
[2]	Other relevant method information, such as adjustments or degrees of freedom:
	The model was adjusted by baseline 25-hydroxyvitamin D level stratum, age, and region.
[3]	Additional information, such as whether or not the p-value is adjusted for multiple comparisons and the a priori threshold for statistical significance:
	No text entered.
[4]	Other relevant estimation information:
	FOSAVANCE minus Referred-Care. Analysis was for Total Hip.

6. Secondary: Falls Per Participant [Time Frame: Up to Week 52]

Measure Type	Secondary
Measure Title	Falls Per Participant
Measure Description	Number of falls per participant was measured. The fall event rate during the study period was defined as the number of adjudicated falls during the study period divided by the total patient-years in the study. Each participant was to be in the study for approximately one year. In order to guide and standardize all procedures during the fall adjudication process, a Standard Operating Procedure for Fall Adjudication was created by the SPONSOR and served as a guideline to standardize operational procedures for fall adjudication.
Time Frame	Up to Week 52
Safety Issue	No

Population Description

Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.
Intent-to-Treat (ITT) population included all randomized participants within the treatment group to which they were randomized regardless of whether or not a participant may have dropped out in the base or continued into the extension study.

Reporting Groups

	Description
FOSAVANCE 5600	Alendronate Sodium 70 mg/Vitamin D 5600 I.U. combination tablet once weekly plus a daily 500 mg elemental calcium supplement.

Referred-Care	Usual treatment for osteoporosis chosen and prescribed by patients' own physicians.

Measured Values

	FOSAVANCE 5600	Referred-Care
Number of Participants Analyzed [units: participants]	**257**	**258**
Falls Per Participant [units: Number of Falls] Mean (Standard Deviation)	**0.51 (1.53)**	**0.45 (0.80)**

Statistical Analysis 1 for Falls Per Participant

Groups [1]	All groups
Method [2]	Zero-Inflated Poisson Regression
P Value [3]	0.675
Difference of falls (falls/patient-year) [4]	0.03
Standard Error of the mean	(0.08)
95% Confidence Interval	-0.12 to 0.19

[1]	Additional details about the analysis, such as null hypothesis and power calculation:
	No text entered.
[2]	Other relevant method information, such as adjustments or degrees of freedom:
	Adjusted by the terms for treatment, baseline 25(OH) D level stratum, age, and region and offset variable of log (total patient-years in the study).
[3]	Additional information, such as whether or not the p-value is adjusted for multiple comparisons and the a priori threshold for statistical significance:
	No text entered.
[4]	Other relevant estimation information:
	No text entered.

7. Secondary: Percent Change From Baseline at Week 52 in N-Telopeptides of Type 1 Collagen to Urine Creatinine Ratio [Time Frame: Baseline and Week 52]

Measure Type	Secondary
Measure Title	Percent Change From Baseline at Week 52 in N-Telopeptides of Type 1 Collagen to Urine Creatinine Ratio
Measure Description	NTx is a urine biochemical marker of bone resorption and measured in nanomoles (nmol) Bone Collagen Equivalents (BCE)/millimoles (mmol) creatinine. The percent change was calculated as: [100 * ((Week 52/Baseline)-1)]. The greater the percent decrease from baseline, the greater the response to therapy.
Time Frame	Baseline and Week 52
Safety Issue	No

Population Description

Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.
Per-Protocol Population: excluded patients due to important deviations from the protocol that may substantially affect the results of the primary efficacy analysis.

Reporting Groups

	Description
FOSAVANCE 5600	Alendronate Sodium 70 mg/Vitamin D 5600 I.U. combination tablet once weekly plus a daily 500 mg elemental calcium supplement.
Referred-Care	Usual treatment for osteoporosis chosen and prescribed by patients' own physicians.

Measured Values

	FOSAVANCE 5600	**Referred-Care**
Number of Participants Analyzed [units: participants]	**216**	**227**
Percent Change From Baseline at Week 52 in N-Telopeptides of Type 1 Collagen to Urine Creatinine Ratio [units: Percent Change] Least Squares Mean (95% Confidence Interval)	**-58.42 (-61.58 to -54.99)**	**-50.07 (-54.01 to -45.79)**

Statistical Analysis 1 for Percent Change From Baseline at Week 52 in N-Telopeptides of Type 1 Collagen to Urine Creatinine Ratio

Groups [1]	All groups
Method [2]	Longitudinal Data Analysis Model
P Value [3]	0.001
Difference in Least Squares Means [4]	-8.35
95% Confidence Interval	-13.19 to -3.54

[1]	Additional details about the analysis, such as null hypothesis and power calculation:
	No text entered.
[2]	Other relevant method information, such as adjustments or degrees of freedom:
	The model was adjusted by baseline 25-hydroxyvitamin D level stratum, age, and region.
[3]	Additional information, such as whether or not the p-value is adjusted for multiple comparisons and the a priori threshold for statistical significance:
	No text entered.
[4]	Other relevant estimation information:
	No text entered.

8. Secondary: Percent Change From Baseline at Week 52 in Bone-Specific Alkaline Phosphatase [Time Frame: Baseline and Week 52]

Measure Type	Secondary

Measure Title	Percent Change From Baseline at Week 52 in Bone-Specific Alkaline Phosphatase
Measure Description	BSAP is a serum biochemical marker of bone formation and measured in micrograms/Liter (mcg/L). The percent change was calculated as: [100 * ((Week 52/Baseline)-1)]. The greater the percent decrease from baseline, the greater the response to therapy.
Time Frame	Baseline and Week 52
Safety Issue	No

Population Description

Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.
Per-Protocol Population: excluded patients due to important deviations from the protocol that may substantially affect the results of the primary efficacy analysis.

Reporting Groups

	Description
FOSAVANCE 5600	Alendronate Sodium 70 mg/Vitamin D 5600 I.U. combination tablet once weekly plus a daily 500 mg elemental calcium supplement.
Referred-Care	Usual treatment for osteoporosis chosen and prescribed by patients' own physicians.

Measured Values

	FOSAVANCE 5600	**Referred-Care**
Number of Participants Analyzed [units: participants]	**223**	**237**
Percent Change From Baseline at Week 52 in Bone-Specific Alkaline Phosphatase [units: Percent Change] Least Squares Mean (95% Confidence Interval)	**-51.21 (-53.79 to -48.48)**	**-43.13 (-46.18 to -39.91)**

Statistical Analysis 1 for Percent Change From Baseline at Week 52 in Bone-Specific Alkaline Phosphatase

Groups [1]	All groups
Method [2]	Longitudinal Data Analysis Model
P Value [3]	<0.001
Difference in Least Squares Mean [4]	-8.07
95% Confidence Interval	-11.94 to -4.21

[1]	Additional details about the analysis, such as null hypothesis and power calculation:
	No text entered.
[2]	Other relevant method information, such as adjustments or degrees of freedom:
	The model was adjusted by baseline 25-hydroxyvitamin D level stratum, age, and region.
[3]	Additional information, such as whether or not the p-value is adjusted for multiple comparisons and the a priori threshold for statistical significance:
	No text entered.
[4]	Other relevant estimation information:

No text entered.

Serious Adverse Events

Hide Serious Adverse Events

Time Frame	No text entered.
Additional Description	FOSAVANCE 5600 group: participants who took at least 1 dose were included (254 out of 257 patients). All patients randomized in the referred-care group were included regardless of whether they took 1 dose of therapy as prescribed by their physicians.

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	Description
FOSAVANCE 5600	Alendronate Sodium 70 mg/Vitamin D 5600 I.U. combination tablet once weekly plus a daily 500 mg elemental calcium supplement.
Referred-Care	Usual treatment for osteoporosis chosen and prescribed by patients' own physicians.

Serious Adverse Events

	FOSAVANCE 5600	Referred-Care
Total, serious adverse events		
# participants affected / at risk	**25/254 (9.84%)**	**29/258 (11.24%)**
Cardiac disorders		
Angina Unstable [1]		
# participants affected / at risk	**0/254 (0.00%)**	**1/258 (0.39%)**
# events	**0**	**1**
Atrial Fibrillation [1]		
# participants affected / at risk	**3/254 (1.18%)**	**1/258 (0.39%)**
# events	**3**	**2**
Cardiac Failure [1]		
# participants affected / at risk	**1/254 (0.39%)**	**0/258 (0.00%)**
# events	**1**	**0**
Coronary Artery Disease [1]		
# participants affected / at risk	**2/254 (0.79%)**	**0/258 (0.00%)**
# events	**2**	**0**
Electromechanical Dissociation [1]		
# participants affected / at risk	**1/254 (0.39%)**	**0/258 (0.00%)**
# events	**1**	**0**
Myocardial Infarction [1]		
# participants affected / at risk	**0/254 (0.00%)**	**1/258 (0.39%)**
# events	**0**	**1**
Sick Sinus Syndrome [1]		
# participants affected / at risk	**1/254 (0.39%)**	**0/258 (0.00%)**
# events	**1**	**0**

Eye disorders		
Eye Haemorrhage [1]		
# participants affected / at risk	**0/254 (0.00%)**	**1/258 (0.39%)**
# events	**0**	**1**
Gastrointestinal disorders		
Abdominal Pain Upper [1]		
# participants affected / at risk	**0/254 (0.00%)**	**1/258 (0.39%)**
# events	**0**	**1**
Diarrhoea [1]		
# participants affected / at risk	**1/254 (0.39%)**	**0/258 (0.00%)**
# events	**1**	**0**
Faecaloma [1]		
# participants affected / at risk	**0/254 (0.00%)**	**1/258 (0.39%)**
# events	**0**	**1**
Gastric Ulcer [1]		
# participants affected / at risk	**1/254 (0.39%)**	**0/258 (0.00%)**
# events	**1**	**0**
Gastroesophageal Reflux Disease [1]		
# participants affected / at risk	**1/254 (0.39%)**	**0/258 (0.00%)**
# events	**1**	**0**
Intestinal Obstruction [1]		
# participants affected / at risk	**0/254 (0.00%)**	**1/258 (0.39%)**
# events	**0**	**1**
Retroperitoneal Haemorrhage [1]		
# participants affected / at risk	**1/254 (0.39%)**	**0/258 (0.00%)**
# events	**1**	**0**
Vomiting [1]		
# participants affected / at risk	**0/254 (0.00%)**	**1/258 (0.39%)**
# events	**0**	**1**
General disorders		
Chest Pain [1]		
# participants affected / at risk	**1/254 (0.39%)**	**0/258 (0.00%)**
# events	**1**	**0**
Local Swelling [1]		
# participants affected / at risk	**0/254 (0.00%)**	**1/258 (0.39%)**
# events	**0**	**1**
Non-Cardiac Chest Pain [1]		
# participants affected / at risk	**1/254 (0.39%)**	**1/258 (0.39%)**
# events	**1**	**1**
Pyrexia [1]		
# participants affected / at risk	**1/254 (0.39%)**	**0/258 (0.00%)**
# events	**1**	**0**
Hepatobiliary disorders		
Cholelithiasis [1]		

# participants affected / at risk	0/254 (0.00%)	1/258 (0.39%)
# events	0	1
Infections and infestations		
Bacterial Diarrhoea [1]		
# participants affected / at risk	0/254 (0.00%)	1/258 (0.39%)
# events	0	1
Bronchitis [1]		
# participants affected / at risk	1/254 (0.39%)	0/258 (0.00%)
# events	1	0
Diverticulitis [1]		
# participants affected / at risk	0/254 (0.00%)	1/258 (0.39%)
# events	0	1
Enterovirus Infection [1]		
# participants affected / at risk	0/254 (0.00%)	1/258 (0.39%)
# events	0	1
Gastroenteritis Viral [1]		
# participants affected / at risk	1/254 (0.39%)	0/258 (0.00%)
# events	1	0
Malaria [1]		
# participants affected / at risk	1/254 (0.39%)	0/258 (0.00%)
# events	1	0
Peritonsillar Abscess [1]		
# participants affected / at risk	1/254 (0.39%)	0/258 (0.00%)
# events	1	0
Pneumonia [1]		
# participants affected / at risk	0/254 (0.00%)	1/258 (0.39%)
# events	0	1
Sepsis [1]		
# participants affected / at risk	1/254 (0.39%)	0/258 (0.00%)
# events	1	0
Subacute Endocarditis [1]		
# participants affected / at risk	1/254 (0.39%)	0/258 (0.00%)
# events	1	0
Urinary Tract Infection [1]		
# participants affected / at risk	1/254 (0.39%)	0/258 (0.00%)
# events	1	0
Injury, poisoning and procedural complications		
Ankle Fracture [1]		
# participants affected / at risk	1/254 (0.39%)	0/258 (0.00%)
# events	1	0
Contusion [1]		
# participants affected / at risk	0/254 (0.00%)	2/258 (0.78%)
# events	0	2
Hip Fracture [1]		
# participants affected / at risk	0/254 (0.00%)	2/258 (0.78%)

# events	0	2
Meniscus Lesion [1]		
# participants affected / at risk	0/254 (0.00%)	1/258 (0.39%)
# events	0	1
Pubis Fracture [1]		
# participants affected / at risk	0/254 (0.00%)	1/258 (0.39%)
# events	0	1
Metabolism and nutrition disorders		
Dehydration [1]		
# participants affected / at risk	0/254 (0.00%)	1/258 (0.39%)
# events	0	1
Musculoskeletal and connective tissue disorders		
Back Pain [1]		
# participants affected / at risk	1/254 (0.39%)	1/258 (0.39%)
# events	1	1
Intervertebral Disc Protrusion [1]		
# participants affected / at risk	0/254 (0.00%)	1/258 (0.39%)
# events	0	1
Lumbar Spinal Stenosis [1]		
# participants affected / at risk	0/254 (0.00%)	1/258 (0.39%)
# events	0	1
Osteoarthritis [1]		
# participants affected / at risk	0/254 (0.00%)	1/258 (0.39%)
# events	0	1
Spinal Column Stenosis [1]		
# participants affected / at risk	1/254 (0.39%)	1/258 (0.39%)
# events	1	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		
Basal Cell Carcinoma [1]		
# participants affected / at risk	1/254 (0.39%)	2/258 (0.78%)
# events	1	3
Colon Cancer [1]		
# participants affected / at risk	0/254 (0.00%)	1/258 (0.39%)
# events	0	1
Oesophageal Squamous Cell Carcinoma [1]		
# participants affected / at risk	1/254 (0.39%)	0/258 (0.00%)
# events	1	0
Ovarian Epithelial Cancer [1]		
# participants affected / at risk	1/254 (0.39%)	0/258 (0.00%)
# events	1	0
Pancreatic Carcinoma [1]		
# participants affected / at risk	1/254 (0.39%)	0/258 (0.00%)
# events	1	0
Uterine Cancer [1]		

# participants affected / at risk	1/254 (0.39%)	0/258 (0.00%)
# events	1	0
Nervous system disorders		
Carotid Artery Stenosis [1]		
# participants affected / at risk	0/254 (0.00%)	1/258 (0.39%)
# events	0	1
Cerebral Ischaemia [1]		
# participants affected / at risk	1/254 (0.39%)	0/258 (0.00%)
# events	1	0
Cerebrovascular Accident [1]		
# participants affected / at risk	1/254 (0.39%)	0/258 (0.00%)
# events	1	0
Facial Palsy [1]		
# participants affected / at risk	0/254 (0.00%)	1/258 (0.39%)
# events	0	1
Radiculopathy [1]		
# participants affected / at risk	1/254 (0.39%)	0/258 (0.00%)
# events	1	0
Transient Ischaemic Attack [1]		
# participants affected / at risk	0/254 (0.00%)	1/258 (0.39%)
# events	0	1
Unresponsive to Stimuli [1]		
# participants affected / at risk	1/254 (0.39%)	0/258 (0.00%)
# events	1	0
Vascular Dementia [1]		
# participants affected / at risk	0/254 (0.00%)	1/258 (0.39%)
# events	0	1
Renal and urinary disorders		
Haematuria [1]		
# participants affected / at risk	0/254 (0.00%)	1/258 (0.39%)
# events	0	1
Nephrolithiasis [1]		
# participants affected / at risk	0/254 (0.00%)	1/258 (0.39%)
# events	0	1
Renal Artery Stenosis [1]		
# participants affected / at risk	0/254 (0.00%)	1/258 (0.39%)
# events	0	1
Renal Failure Acute [1]		
# participants affected / at risk	1/254 (0.39%)	0/258 (0.00%)
# events	1	0
Respiratory, thoracic and mediastinal disorders		
Acute Respiratory Failure [1]		
# participants affected / at risk	1/254 (0.39%)	0/258 (0.00%)
# events	1	0
Dyspnoea [1]		

# participants affected / at risk	1/254 (0.39%)	0/258 (0.00%)
# events	2	0
Pulmonary Congestion [1]		
# participants affected / at risk	1/254 (0.39%)	0/258 (0.00%)
# events	1	0
Respiratory Failure [1]		
# participants affected / at risk	1/254 (0.39%)	0/258 (0.00%)
# events	1	0
Vascular disorders		
Orthostatic Hypotension [1]		
# participants affected / at risk	0/254 (0.00%)	1/258 (0.39%)
# events	0	1
Peripheral Arterial Occlusive disease [1]		
# participants affected / at risk	0/254 (0.00%)	1/258 (0.39%)
# events	0	1
Thrombophlebitis Superficial [1]		
# participants affected / at risk	1/254 (0.39%)	0/258 (0.00%)
# events	1	0

1 Term from vocabulary, MedDRA (13.0)

Other Adverse Events

Hide Other Adverse Events

Time Frame	No text entered.
Additional Description	FOSAVANCE 5600 group: participants who took at least 1 dose were included (254 out of 257 patients). All patients randomized in the referred-care group were included regardless of whether they took 1 dose of therapy as prescribed by their physicians.

Frequency Threshold

Threshold above which other adverse events are reported	5%

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Other Adverse Events

	FOSAVANCE 5600	Referred-Care
Total, other (not including serious) adverse events		
# participants affected / at risk	61/254 (24.02%)	70/258 (27.13%)

Gastrointestinal disorders		
Diarrhoea [1]		
# participants affected / at risk	**8/254 (3.15%)**	**13/258 (5.04%)**
# events	**9**	**14**
Infections and infestations		
Urinary Tract Infection [1]		
# participants affected / at risk	**12/254 (4.72%)**	**14/258 (5.43%)**
# events	**12**	**18**
Injury, poisoning and procedural complications		
Contusion [1]		
# participants affected / at risk	**13/254 (5.12%)**	**14/258 (5.43%)**
# events	**21**	**19**
Musculoskeletal and connective tissue disorders		
Arthralgia [1]		
# participants affected / at risk	**20/254 (7.87%)**	**21/258 (8.14%)**
# events	**24**	**23**
Back Pain [1]		
# participants affected / at risk	**12/254 (4.72%)**	**21/258 (8.14%)**
# events	**14**	**22**
Nervous system disorders		
Dizziness [1]		
# participants affected / at risk	**9/254 (3.54%)**	**13/258 (5.04%)**
# events	**10**	**17**

1 Term from vocabulary, MedDRA (13.0)

Limitations and Caveats

Hide Limitations and Caveats

Limitations of the study, such as early termination leading to small numbers of participants analyzed and technical problems with measurement leading to unreliable or uninterpretable data

No text entered.

More Information

Hide More Information

Certain Agreements:

Principal Investigators are **NOT** employed by the organization sponsoring the study.

There **IS** an agreement between Principal Investigators and the Sponsor (or its agents) that restricts the PI's rights to discuss or publish trial results after the trial is completed.

The agreement is:

☐ The only disclosure restriction on the PI is that the sponsor can review results communications prior to public release and can embargo communications regarding trial results for a period that is **less than or equal to 60 days**. The sponsor cannot require changes to the communication and cannot extend the embargo.

The only disclosure restriction on the PI is that the sponsor can review results communications prior to public release and can embargo

☐ communications regarding trial results for a period that is **more than 60 days but less than or equal to 180 days**. The sponsor cannot require changes to the communication and cannot extend the embargo.

Other disclosure agreement that restricts the right of the PI to discuss or publish trial results after the trial is completed.

☑ **Restriction Description:** The SPONSOR must have the opportunity to review all proposed abstracts, manuscripts,or presentations regarding this study 60 days prior to submission for publication/presentation. Any information identified by the SPONSOR as confidential must be deleted prior to submission. SPONSOR review can be expedited to meet publication guidelines.

Results Point of Contact:

Name/Title: Senior Vice President, Global Clinical Development
Organization: Merck Sharp & Dohme Corp
e-mail: ClinicalTrialsDisclosure@merck.com

Publications:

Ralston SH, Binkley N, Boonen S, Kiel DP, Reginster JY, Roux C, Chen L, Rosenberg E, Santora A; FOCUS-D (FOSAVANCE vs. Standard Care-Use and Study of Vitamin D) Trial. Randomized trial of alendronate plus vitamin D3 versus standard care in osteoporotic postmenopausal women with vitamin D insufficiency. Calcif Tissue Int. 2011 Jun;88(6):485-94. doi: 10.1007/s00223-011-9482-4. Epub 2011 Apr 11.

Responsible Party:	Merck Sharp & Dohme Corp.
ClinicalTrials.gov Identifier:	NCT00692913 History of Changes
Other Study ID Numbers:	0217A-262 2007_653
Study First Received:	June 4, 2008
Results First Received:	July 20, 2011
Last Updated:	July 21, 2015
Health Authority:	United States: Food and Drug Administration

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For Patients and Families | For Researchers | For Study Record Managers

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