Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

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Supplementary Appendix

Romosozumab or Alendronate for Fracture Prevention in Women with Osteoporosis

Kenneth G Saag, Jeffrey Petersen, Maria Luisa Brandi, Andrew C Karaplis, Mattias Lorentzon, Thierry Thomas, Judy Maddox, Michelle Fan, Paul D Meisner, Andreas Grauer

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Principal Investigators

Argentina: A Alvarisqueta, F Massari, O Messina, MB Oliveri, MR Ulla, BJ Zamora; *Australia*: T Diamond, J Eisman, C Gilfillan, M Kotowicz, E Seeman, C White; *Austria*: E Boschitsch, A Fahrleitner-Pammer, R Leikermoser, H Resch; *Belgium*: E Gielen, S Goemaere, J-Y Reginster, R Witvrouw; *Brazil*: M Castro, S Cezar Radominski, JL Cunha Borges, LH de Gregorio, C Moreira, C Pitanga Calil Salim, LG Oliveira, CAdF Zerbini; *Bulgaria*: D Bichovska, M Boyanov, D Georgiev, M Pavlova, D Penev, R Rashkov, A Shinkov, R Velev, S Zaharieva; *Canada*: J Brown, A Cheung, S Kaiser, A Karaplis, D Kendler, R Kremer, F Morin, G Tsoukas; *Chile*: VA Saavedra Gajardo; *Colombia*: MR Chalem Choueka, CA Cure Cure, M Diaz Jimenez, JJ Jaller Raad, JF Molina Restrepo, WJ Otero Escalante, J Restrepo, MA Terront Lozano, PJ Velez Sanchez, H Yupanqui Lozno; *Czech Republic*: E Dokoupilova, T Hala, M Machkova, T Mareth, L Pavlikova, R Pikner, V Smajstrla, O Smejkalova, V Vyskocil, V Zikan; *Denmark*: P Alexandersen, P Hermann, L Hyldstrup, B Langdahl, A Saetre Lihn, U Schmidt, P Schwarz; *Dominican Republic*: AR Bencosme Bencosme, DM Mejia de la Cruz, MC Velazco Espaillat; *Estonia*: K Maasalu, I Valter; *Finland*: A-M Koski, H Kröger, M Välimäki; *France*: R Chapurlat, B Cortet, M Laroche, S Lassoued, E Lespessailles, N Mehsen-Cetre, T Thomas, G Weryha; *Germany*: C Contzen, L Ezechieli, I Frieling, A-A Himpel-Bönninghoff, L Hofbauer, F Jakob, O Maus, C Niedhart, J Stössel, U Stumpf, F Thomasius; *Greece*: A Anastasilakis, A Bountis, M Daniilidis, T Karachalios, I Kyrkos, P Makras, K Mistakidou, A Pastroudis; *Guatemala*: NN Chavez Perez, RA Gonzalez Orellana, MZ Lopez Gutierrez, MD Palencia Pineda, C Robles Torres, BA Sandoval Sanchez, LM Rodas Acevedo, EO Turcios Juarez; *Hong Kong*: EMC Lau, P-C Leung, CT Sy, Y-C Woo; *Hungary*: T Balazs, E Drescher, K Horvath, E Kanakaridu, I Kiss, P Lakatos, M Nagy, E Peterfai, P Somogyi, EA Toth; *Israel*: J Foldes, M Hirsch, E Segal; *Italy*: F Bertoldo, G Bianchi, ML Brandi, O Di Munno, B Frediani, GC Isaia, N Malavolta, S Minisola, R Nuti, S Ortolani, M Rossini; *Latvia*: D Andersone, A Medne, M Zambrans; *Lithuania*: M Tamulaitiene, Z Visockiene; *Mexico*: FF Cons Molina, LJ Elizondo Alanis, PA Garcia Hernandez, JLA Morales Torres, RA Pascacio Perez, FA Rosas Lopez, JA Tamayo y Orozco, BE Zazueta Montiel; *The Netherlands*: N Appelman-Dijkstra, J van den Bergh, M Zillikens; *New Zealand*: N Gilchrist, I Reid; *Norway*: A Høiseth, HO Hoivik, P Norheim; *Peru*: AA Calvo Quiroz, EJ Carcausto Huamani, MG Leon Portocarrero; *Poland*: K Antkowiak-Piatyszek, E Blach, T Blicharski, M Cesarz, E Czerwinski, M Dabrowska, S Daniluk, E Franek, K Gruszecka, S Jeka, B Jendrych, M Korkosz, R Lorenc, R Plebanski, W Pluskiewicz, E Sewerynek, A Sidorowicz-Bialynicka, J Supronik, D Szyska-Skrobot; *Romania*: D Grigorie, RA Ionescu, IM Mircea, S Mustatea; *Russia*: A Belova, A Dimitrienko, O Ershova, O Lesnyak, S Mazurenko, O Nazarova, S Rodionova, L Rozhinskaya, R Sardinov, I Skripnikova, M Stanislav, N Vezikova, T Zykova; *Slovakia*: M Fabianova, H Halmova, Z Killinger, Z Kmecova, E Stenova, S Tomkova; *South Africa*: M Conradie, TJ De Villiers, A de Weerd, G Ellis, S Lipschitz, T Vally; *South Korea*: Y-S Chung, SB Han, S Lee, S-K Lim, BW Min, C-S Shin; *Spain*: AV Balsa Criado, FJ Blanco Garcia, M-D Cerda Gabaroi, R Garcia de Vicuña Pinedo, J Gonzalez-Macias, MJ Miranda Garcia, M Muñoz Torres, FX Nogues Solan; *Sweden*: M Lorentzon, P Nordström, M Palmer, A Spångéus; *Taiwan*: C-H Wu; *Turkey*: G Akyuz, R Guzel, S Tuzun; *United Kingdom*: I Arif, V Chalam, A Elshashai, S Eyre, G Fiore, U Kurup, A Mathew, S Ralston, H Thomas, P Walukiewicz, D Weeraratne; *United States*: M Baker, R Bernstein, P Camacho, R Civitelli, W Cottrell, G Crickard, M Christiansen, D El-Maouche, J Finkelstein, S Greenspan, P Miller, A Moore, S Nakhle, M Peacock, C Recknor, K Saag, J Schechtman, J Tesser

Countries in Respective Regions of Study

Listed in order of enrollment, from highest to lowest.

Central or Eastern Europe and Middle East: Poland, Czech Republic, Russian Federation, Hungary, Bulgaria, Estonia, Lithuania, Latvia, Austria, Romania, Slovakia, Turkey, and Israel; *Latin America (Central and South America)*: Colombia, Brazil, Peru, Mexico, Argentina, Guatemala, Dominican Republic, and Chile; *Western Europe, Australia, and New Zealand*: Italy, United Kingdom, Denmark, France, Germany, Spain, Norway, Greece, Belgium, Sweden, The Netherlands, Australia, Finland, and New Zealand; *Asia Pacific and South Africa*: Hong Kong, South Africa, Republic of Korea, and Taiwan; and *North America*: United States and Canada.

Methods

Fracture Assessment

Fracture assessment was performed by a central imaging vendor, BioClinica (formerly known as Synarc, Inc.). During image analysis, readers were blinded to treatment assignment. All images were checked visually for: appropriate anatomical coverage, correct subject positioning and subject side (left/right), follow-up scans consistent with baseline for subject positioning and subject side, scan mode selection correct and follow-up scans consistent with baseline, scanner consistent with baseline (same scanner used throughout study), presence of artifacts (metal, clothing, subject motion, etc.), proper use of film/screen combination and exposure parameters for hardcopy films, proper spatial and contrast resolution for digital images. If the scan quality was unacceptable and the problem could be corrected, a repeat examination to replace the rejected scan was requested.

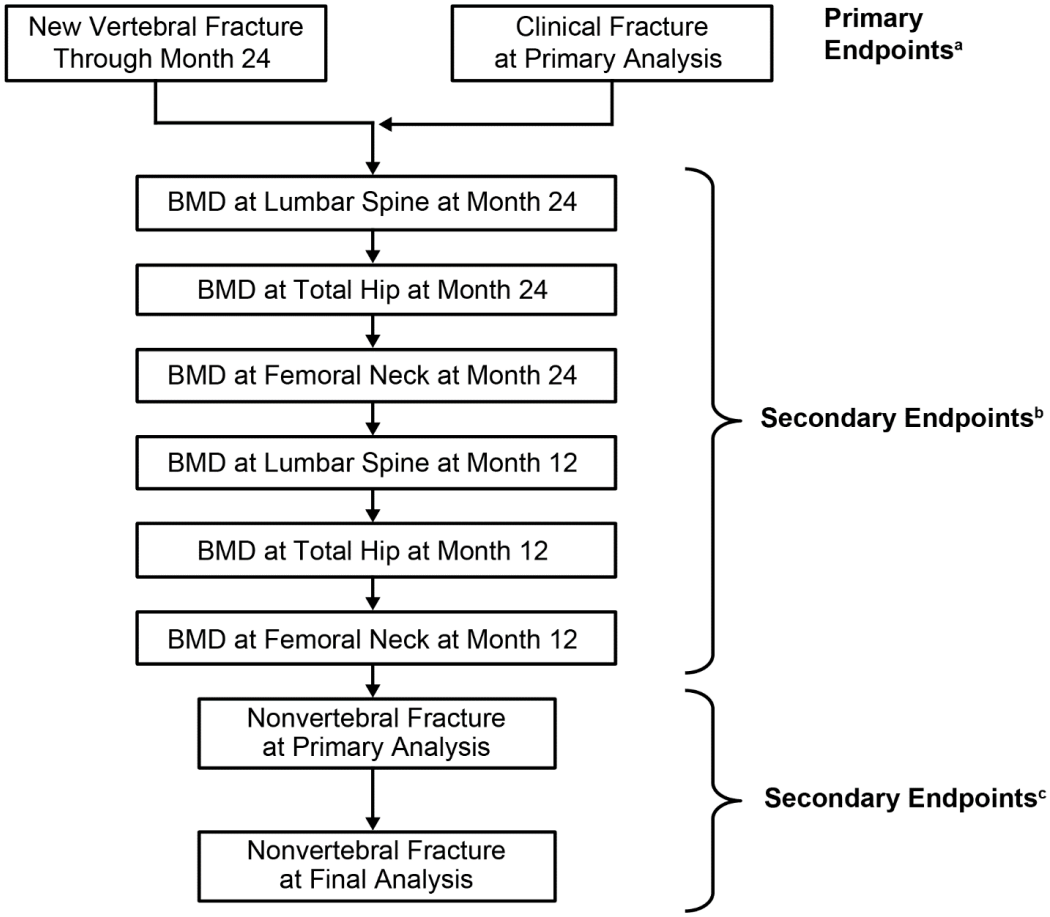
Vertebral Fracture Assessment – Lateral spinal radiographs were assessed for prevalent and incident fractures using the Genant Semiquantitative Scoring method.[1]
Grade 0 = No fracture
Grade 1 = mild fracture, 20%–25% reduction in vertebral height (anterior, middle, or posterior)
Grade 2 = moderate fracture, 25%–40% reduction in height
Grade 3 = severe fracture, greater than 40% reduction in height

Additional lateral spine x-rays were recommended to be obtained when a participant reported back pain, suggestive of a clinical vertebral fracture.

Nonvertebral Fracture Assessment – In the event of a clinical nonvertebral fracture, radiographs and/or translated local radiology or medical report were sent to BioClinica by the investigator site for central review. The BioClinica radiologist reviewed the radiograph(s), CT or MRI image(s) and/or local radiologist/medical report and confirmed the date of the x-ray exam, presence of the fracture, its location, and the number of fractures.

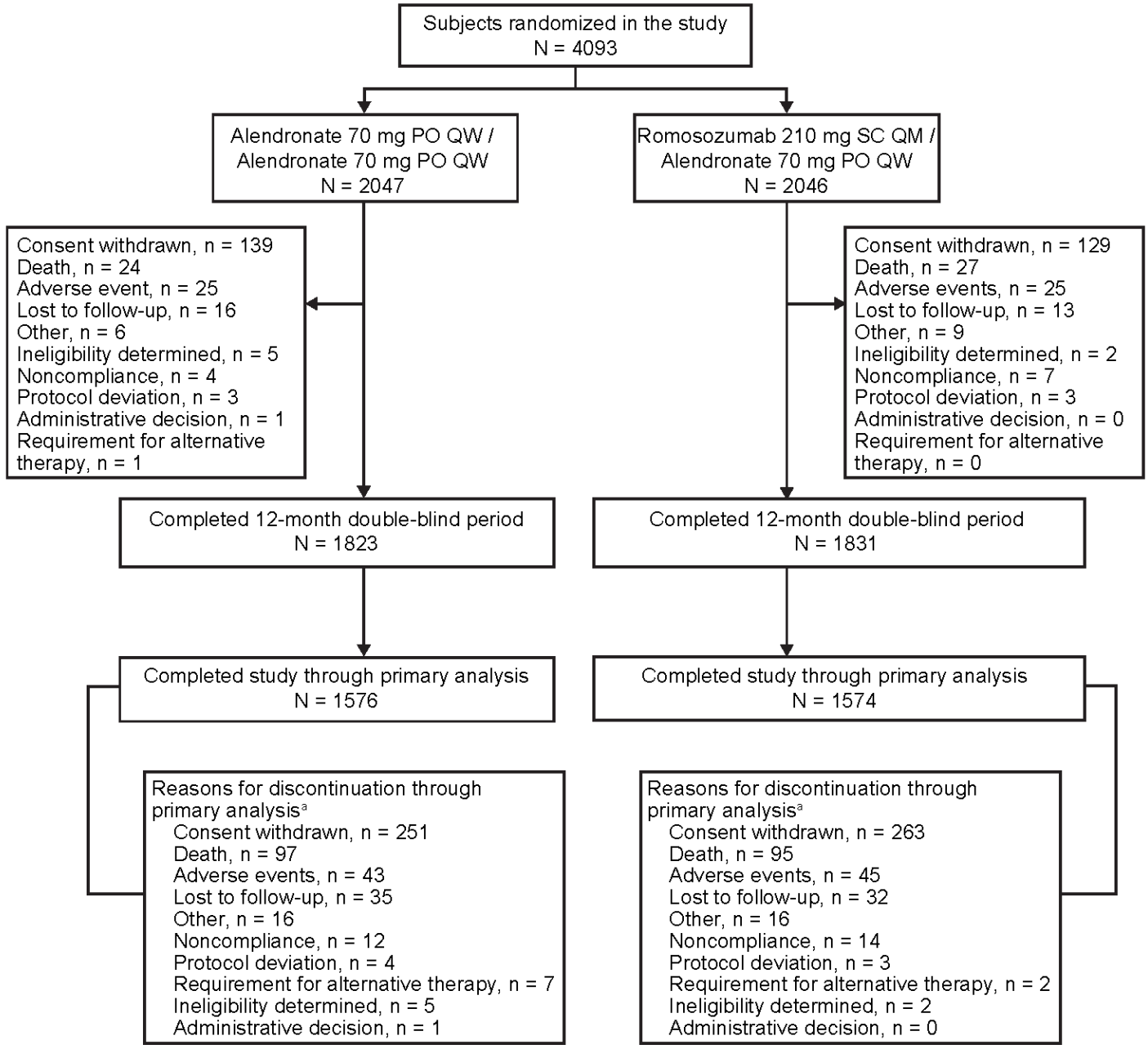
All subjects identified by the primary radiologist to have an incident vertebral fracture were read by a secondary radiologist using the Semiquantitative method with the second reading performed independent of the results of the first reading. If the secondary radiologist agreed with the primary radiologist on the presence, location, and severity of the incident fracture no additional reading was required. Adjudication of incident vertebral fracture discrepancies between the primary and secondary Semiquantitative radiologists were adjudicated by a third radiologist at BioClinica who was blinded to the results of the two Semiquantitative radiologists; the adjudicated result was the final result for analysis. For nonvertebral fracture events as well as QCT and DXA scans, there was a single reading of each subject's images/scans and therefore no adjudication.

Figure S1. Primary and Key Secondary Endpoint Sequential Testing Procedure
If both primary endpoints were significant under the Hochberg[2] procedure, a fixed-sequence testing procedure was to be used for bone mineral density endpoints, at months 12 and 24, at the 5% level (2-sided). If all preceding endpoints were significant, the nonvertebral fracture endpoint was to be tested using a group sequential approach at the primary analysis and the final analysis based on a 1-sided test (α=0.025). The Lan-DeMets alpha spending function[3] that approximates a Pocock boundary was to be used to determine the significance level at the time of the primary analysis.



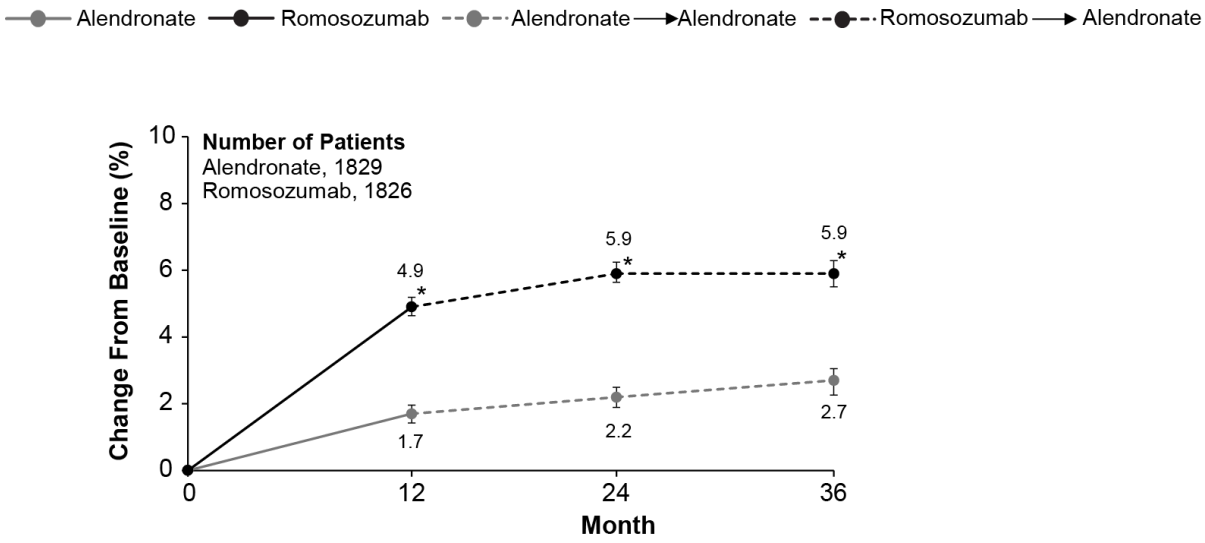
[a]Primary endpoints were tested at the 5% level (2-sided), accounting for multiplicity using the Hochberg procedure. If the larger of the 2 P-values is significant at the 0.05 level (2-sided), the statistical testing continued to the secondary endpoint in the testing sequence.
[b]A fixed-sequence testing procedure was used for bone mineral density endpoints at the 5% level (2-sided) if both the primary endpoints were significant at the 0.05 level (2-sided).
[c]The nonvertebral fracture endpoint was tested using a group sequential approach at the primary analysis and the final analysis based on a 1-sided test (overall α=0.025). The Lan-DeMets alpha spending function that approximates a Pocock boundary, 0.0233 (1-sided), was used to determine the statistical significance at the time of the primary analysis.

Figure S2. Patient Disposition



[a]Discontinuations through the primary analysis are cumulative.
PO=orally; QM=once monthly; QW=once weekly; SC=subcutaneously.

Figure S3. Percentage Change From Baseline in Bone Mineral Density at the Femoral Neck



Least-squares means percentage changes in bone mineral density at the femoral neck in patients who had a baseline measurement and at least one post-baseline visit at or before month 36. Error bars are pointwise 95% confidence intervals. Between-group comparisons for percentage change were analyzed using a repeated measures model adjusting for treatment, presence of severe vertebral fracture at baseline, visit, treatment-by-visit interaction, baseline bone mineral density value as fixed effects, with machine type and baseline bone mineral density value-by-machine type interaction as covariates, using an unstructured variance covariance structure; *P<0.001.

Table S1. Fracture Endpoints at Pre-Specified Timepoints

	Alendronate to Alendronate (N = 2047) % (n/N1)	Romosozumab to Alendronate (N = 2046) % (n/N1)	Risk Ratio or Hazard Ratio (95% CI)	Nominal *P* Value
		12 Month Double-Blind Period		
New vertebral fracture by multiple imputation[a]	6.3% (128/2047)	4.0% (82/2046)	0.63 (0.47, 0.85)	0.003
New vertebral fracture by LOCF[b]	5.0% (85/1703)	3.2% (55/1696)	0.64 (0.46, 0.89)	0.008
New or worsening vertebral fracture[b]	5.9% (101/1703)	4.0% (67/1696)	0.66 (0.49, 0.89)	0.006
Clinical vertebral fracture[c]	0.9% (18/2047)	0.5% (10/2046)	0.56 (0.26, 1.22)	0.14
Clinical fracture[c]	5.4% (110/2047)	3.9% (79/2046)	0.72 (0.54, 0.96)	0.027
Nonvertebral fracture[c,d]	4.6% (95/2047)	3.4% (70/2046)	0.74 (0.54, 1.01)	0.057
Major nonvertebral fracture[c,e]	4.3% (88/2047)	2.9% (59/2046)	0.67 (0.48, 0.94)	0.019
Hip fracture[c]	1.1% (22/2047)	0.7% (14/2046)	0.64 (0.33, 1.26)	0.19
Osteoporotic fracture[c,f]	9.2% (189/2047)	6.5% (134/2046)	0.71 (0.57, 0.88)	0.002
Major osteoporotic fracture[c,g]	4.2% (85/2047)	3.0% (61/2046)	0.72 (0.52, 1.01)	0.053
		Month 24		
New vertebral fracture by multiple imputation[a]	11.9% (243/2047)	6.2% (127/2046)	0.52 (0.40, 0.66)	<0.001
New vertebral fracture by LOCF[b,h]	8.0% (147/1834)	4.1% (74/1825)	0.50 (0.38, 0.66)	<0.001
New or worsening vertebral fracture[b]	9.2% (168/1834)	4.8% (87/1825)	0.52 (0.40, 0.66)	<0.001
Clinical vertebral fracture[c]	2.1% (44/2047)	0.9% (18/2046)	0.41 (0.24, 0.71)	<0.001
		Primary Analysis Period		
Clinical fracture[c,h]	13.0% (266/2047)	9.7% (198/2046)	0.73 (0.61, 0.88)	<0.001
Nonvertebral fracture[c,d]	10.6% (217/2047)	8.7% (178/2046)	0.81 (0.66, 0.99)	0.037
Major nonvertebral fracture[c,e]	9.6% (196/2047)	7.1% (146/2046)	0.73 (0.59, 0.90)	0.004
Hip fracture[c]	3.2% (66/2047)	2.0% (41/2046)	0.62 (0.42, 0.92)	0.015
Osteoporotic fracture[c,f]	19.1% (392/2047)	13.0% (266/2046)	0.65 (0.56, 0.76)	<0.001
Major osteoporotic fracture[c,g]	10.2% (209/2047)	7.1% (146/2046)	0.68 (0.55, 0.84)	<0.001

n/N1 = number of patients with fractures/number of patients in the analysis set.
[a]Missing fracture status is imputed by multiple imputation. The imputation model included treatment group and the following baseline variables: age, years since menopause, body mass index, number of prevalent vertebral fractures, worst vertebral fracture severity, and T score at the lumbar spine, total hip, and femoral neck. n and % are based on the average across 5 imputed datasets.
[b]Risk ratio based on Mantel-Haenszel method adjusted for age strata, baseline total hip bone mineral density T score (≤ -2.5, > -2.5), and presence of severe vertebral fracture at baseline; nominal P-values were based on a logistic regression model adjusting for age strata, baseline total hip bone mineral density T score, and presence of severe vertebral fracture at baseline; missing data handled using last-observation-carried-forward (LOCF).
[c]Hazard ratio and nominal P-values were based on a Cox proportional hazards model adjusting for age strata, baseline total hip bone mineral density T score and presence of severe vertebral fracture at baseline.
[d]Nonvertebral fractures excluded fractures of the skull, facial bones, metacarpals, fingers, and toes. Pathologic or high trauma fractures were also excluded.
[e]Major nonvertebral fracture included fractures of the pelvis, distal femur, proximal tibia, ribs, proximal humerus, forearm, and hip.
[f]Osteoporotic fractures include any osteoporotic nonvertebral fractures that are not associated with high trauma severity or pathologic fractures and new or worsening vertebral fractures regardless of trauma severity or pathologic fractures.
[g]Major osteoporotic fracture include fractures of the hip, forearm, and humerus that are not associated with a pathologic fracture regardless of trauma severity, and clinical vertebral fractures.
Note: All fracture types, including nonvertebral fractures, excluded severe trauma (except major osteoporotic fractures) or pathologic fractures. Severe trauma was defined as a fall from higher than the height of a stool, chair, first rung on a ladder or equivalent (>20 inches), or severe trauma other than a fall per investigator judgment.
[h]The nominal P-value for new vertebral fracture at Month 24 using the logistic regression model defined in footnote “b” was <0.001 and <0.001 for clinical fracture at primary analysis using the Cox proportional hazards model described in footnote “c”. The larger of the 2 P-values is less than 0.05, thus both endpoints were statistically significant using the Hochberg procedure and the statistical testing continued to the secondary endpoints in the testing sequence as defined in Figure S1.
CI = confidence interval.
For all analysis models, 11 subjects had missing or unreadable baseline skeletal x-rays, thus it was treated as absence of severe vertebral fracture, and one subject had had missing baseline data, which was imputed by the average of baseline total hip bone mineral density T score of those subjects who had DXA taken at the same side of the hip and measured by the same DXA machine.

Table S2. Percentage Change from Baseline in Bone Mineral Density

		Repeated Measures Model[a]			ANCOVA Model Using LOCF[b]		
		Alendronate to Alendronate	Romosozumab to Alendronate	LS Mean Difference From Alendronate	Alendronate to Alendronate	Romosozumab to Alendronate	LS Mean Difference from Alendronate
Month 12	Lumbar Spine[c]	5.0 (4.69, 5.25)	13.7 (13.38, 13.95)	8.7* (8.31, 9.08)	5.0 (4.73, 5.21)	13.7 (13.36, 13.99)	8.7* (8.31, 9.09)
	Total Hip[d]	2.8 (2.61, 3.02)	6.2 (5.95, 6.36)	3.3* (3.05, 3.62)	2.8 (2.67, 3.02)	6.2 (5.94, 6.39)	3.3* (3.03, 3.60)
	Femoral Neck[d]	1.7 (1.42, 1.96)	4.9 (4.64, 5.19)	3.2* (2.91, 3.54)	1.7 (1.46, 1.98)	4.9 (4.65, 5.23)	3.2* (2.90, 3.54)
Month 24	Lumbar Spine[c]	7.1 (6.78, 7.48)	15.2 (14.82, 15.52)	8.0* (7.55, 8.52)	7.2 (6.90, 7.53)	15.3 (14.89, 15.69)	8.1* (7.58, 8.57)
	Total Hip[d]	3.4 (3.15, 3.63)	7.1 (6.88, 7.36)	3.7* (3.40, 4.06)	3.5 (3.23, 3.68)	7.2 (6.95, 7.48)	3.8* (3.42, 4.10)
	Femoral Neck[d]	2.2 (1.89, 2.49)	5.9 (5.64, 6.24)	3.8* (3.38, 4.12)	2.3 (1.96, 2.57)	6.0 (5.69, 6.37)	3.8* (3.40, 4.14)
Month 36	Lumbar Spine[c]	8.5 (8.01, 8.91)	14.9 (14.45, 15.35)	6.4* (5.81, 7.08)	7.8 (7.47, 8.13)	15.2 (14.73, 15.59)	7.4* (6.84, 7.89)
	Total Hip[d]	3.6 (3.28, 3.92)	7.0 (6.66, 7.31)	3.4* (2.93, 3.84)	3.5 (3.28, 3.75)	7.2 (6.89, 7.46)	3.7* (3.29, 4.02)
	Femoral Neck[d]	2.7 (2.26, 3.05)	5.9 (5.50, 6.29)	3.2* (2.73, 3.76)	2.4 (2.11, 2.77)	6.0 (5.66, 6.38)	3.6* (3.18, 3.97)

Data are least-squares (LS) means (95% confidence interval [CI]).

[a]Based on repeated measures model adjusting for treatment, age strata, presence of severe vertebral fracture at baseline, visit, treatment-by-visit interaction, baseline bone mineral density value as fixed effects, with machine type and baseline bone mineral density value-by-machine type interaction as covariates, using an unstructured variance covariance structure.

[b]Based on analysis of covariance model using last-observation-carried-forward (LOCF) adjusting for treatment, age strata, presence of severe vertebral fracture at baseline, baseline bone mineral density value, machine type, and baseline bone mineral density value-by-machine type interaction.

[c]Lumbar spine: number of subjects with values at baseline and at least one post-baseline visit at or before month 36, alendronate=1757 and romosozumab=1750

[d]Total hip and femoral neck: number of subjects with values at baseline and at least one post-baseline visit at or before month 36, alendronate=1829 and romosozumab=1826

*Nominal P<0.001.

Table S3. Percentage Change from Baseline in Bone Mineral Density in a Subset of Subjects from the Substudy

		Repeated Measures Model[a]			ANCOVA Model Using LOCF[b]		
		Alendronate to Alendronate	Romosozumab to Alendronate	LS Mean Difference from Alendronate	Alendronate to Alendronate	Romosozumab to Alendronate	LS Mean Difference from Alendronate
Month 6	Lumbar Spine[c]	3.8 (2.80, 4.85)	11.0 (9.95, 11.97)	7.1* (5.72, 8.55)	3.7 (2.85, 4.55)	11.3 (10.11, 12.50)	7.6* (6.16, 9.04)
	Total Hip[d]	2.3 (1.49, 3.14)	4.3 (3.53, 5.12)	2.0* (0.88, 3.14)	2.2 (1.49, 2.94)	4.5 (3.53, 5.39)	2.2* (1.09, 3.41)
	Femoral Neck[d]	1.2 (0.07, 2.42)	3.9 (2.73, 5.00)	2.6* (1.24, 4.00)	1.0 (-0.11, 2.09)	3.9 (2.63, 5.21)	2.9* (1.54, 4.32)
Month 12	Lumbar Spine[c]	5.1 (3.93, 6.20)	13.8 (12.70, 14.95)	8.8* (7.20, 10.33)	4.8 (3.93, 5.76)	13.7 (12.42, 15.03)	8.9* (7.33, 10.43)
	Total Hip[d]	2.6 (1.66, 3.52)	6.6 (5.66, 7.48)	4.0* (2.69, 5.27)	2.6 (1.66, 3.50)	6.3 (5.37, 7.25)	3.7* (2.44, 5.02)
	Femoral Neck[d]	1.8 (0.59, 2.92)	6.1 (4.96, 7.23)	4.3* (2.98, 5.71)	1.7 (0.53, 2.84)	5.8 (4.64, 6.99)	4.1* (2.79, 5.47)
Month 18	Lumbar Spine[c]	6.4 (5.15, 7.74)	15.7 (14.38, 16.94)	9.2* (7.42, 11.00)	6.7 (5.94, 7.94)	16.0 (14.54, 17.45)	9.3* (7.44, 11.12)
	Total Hip[d]	3.4 (2.39, 4.33)	7.5 (6.60, 8.50)	4.2* (2.84, 5.54)	3.5 (2.44, 4.55)	7.8 (6.82, 8.78)	4.3* (2.89, 5.72)
	Femoral Neck[d]	2.4 (1.09, 3.66)	7.8 (6.57, 9.07)	5.4* (3.88, 7.01)	2.3 (0.87, 3.80)	7.7 (6.26, 9.15)	5.4* (3.74, 7.02)
Month 24	Lumbar Spine[c]	7.4 (5.97, 8.83)	16.6 (15.17, 17.99)	9.2* (7.20, 11.17)	7.4 (6.14, 8.70)	16.9 (15.30, 18.44)	9.4* (7.47, 11.43)
	Total Hip[d]	2.9 (1.79, 3.99)	7.2 (6.08, 8.24)	4.3* (2.74, 5.79)	3.1 (1.83, 4.29)	7.4 (6.45, 8.35)	4.3* (2.80, 5.88)
	Femoral Neck[d]	2.1 (0.85, 3.38)	7.5 (6.24, 8.70)	5.4* (3.82, 6.89)	2.3 (0.83, 3.72)	7.6 (6.26, 8.92)	5.3* (3.76, 6.87)
Month 36	Lumbar Spine[c]	9.6 (5.92, 13.35)	15.7 (10.58, 20.74)	6.0 (-0.25, 12.32)	7.9 (6.49, 9.30)	16.9 (15.28, 18.47)	9.0* (6.90, 11.05)
	Total Hip[d]	4.6 (2.78, 6.50)	7.9 (5.64, 10.24)	3.3† (0.35, 6.25)	3.4 (2.15, 4.64)	7.5 (6.51, 8.46)	4.1* (2.53, 5.66)
	Femoral Neck[d]	3.6 (1.12, 6.04)	9.7 (6.54, 12.93)	6.2† (2.21, 10.11)	2.6 (1.15, 4.05)	7.9 (6.48, 9.27)	5.3* (3.69, 6.87)

Data are least-squares (LS) means (95% confidence interval [CI]). The substudy population was representative of the overall study (data not shown).

[a]Based on repeated measures model adjusting for treatment, presence of severe vertebral fracture at baseline, visit, treatment-by-visit interaction, baseline bone mineral density value as fixed effects, with machine type and baseline bone mineral density value-by-machine type interaction as covariates, using an unstructured variance covariance structure.

[b]Based on analysis of covariance model using last-observation-carried-forward (LOCF) adjusting for treatment, presence of severe vertebral fracture at baseline, baseline bone mineral density value, machine type, and baseline bone mineral density value-by-machine type interaction.
[c]Lumbar spine: number of subjects with values at baseline and at least one post-baseline visit at month 6 or month 18, alendronate=79 and romosozumab=84
[d]Total hip and femoral neck: number of subjects with values at baseline and at least one post-baseline visit at month 6 or month 18, alendronate=80 and romosozumab=85
*Nominal P<0.001; †Nominal P<0.05.

Table S4. Comparison of Cardiovascular Risk Factors in Patients With Positively Adjudicated Cardiovascular Serious Adverse Events

	Patients in Safety Analysis Set		Patients With Adjudicated Cardiovascular Serious Adverse Events in the Double-Blind Period	
	Alendronate N=2014	Romosozumab N=2040	Alendronate N=38	Romosozumab N=50
Age (years), mean ± SD	74.2 ± 7.5	74.4 ± 7.5	76.3 ± 7.7	76.3 ± 7.3
Age ≥75 years	1049 (52.1)	1070 (52.5)	22 (57.9)	33 (66.0)
Current/Former smoker	591 (29.3)	533 (26.1)	12 (31.6)	20 (40.0)
eGFR 30–<60 mL/min/1.73 m^2	476 (23.6)	508 (24.9)	12 (31.6)	17 (34.0)
eGFR 60–<90 mL/min/1.73 m^2	1189 (59.0)	1257 (61.6)	22 (57.9)	27 (54.0)
Cardiovascular risk score,[a] median (Q1, Q3)	4 (2, 7)	4 (2, 7)	7 (3, 10)	6.5 (3, 10)
Any history of cardiovascular risk factor	1607 (79.8)	1625 (79.7)	35 (92.1)	48 (96.0)
History of hypercholesterolemia	674 (33.5)	708 (34.7)	14 (36.8)	25 (50.0)
History of hypertension	1227 (60.9)	1248 (61.2)	32 (84.2)	42 (84.0)
History of diabetes	658 (32.7)	664 (32.5)	18 (47.4)	24 (48.0)
History of cardiovascular disease	1456 (72.3)	1497 (73.4)	34 (89.5)	46 (92.0)
History of central nervous system vascular disorder	183 (9.1)	147 (7.2)	6 (15.8)	7 (14.0)
Cardiovascular related medications				
Patients with cardiovascular-related baseline medications	1212 (60.2)	1229 (60.2)	30 (78.9)	39 (78.0)
Beta blockers	473 (23.5)	509 (25.0)	17 (44.7)	22 (44.0)
ACE inhibitors	489 (24.3)	528 (25.9)	15 (39.5)	20 (40.0)
Angiotensin II receptor antagonists	374 (18.6)	347 (17.0)	9 (23.7)	12 (24.0)
Anti-coagulants	537 (26.7)	563 (27.6)	17 (44.7)	23 (46.0)

Anti-platelet therapy	455 (22.6)	471 (23.1)	11 (28.9)	16 (32.0)
Aspirin	421 (20.9)	437 (21.4)	11 (28.9)	15 (30.0)
Statins	474 (23.5)	495 (24.3)	10 (26.3)	17 (34.0)

Data are n (%) unless otherwise noted.
[a]Modified after Samelson et al.[4] The score was determined as follows: ischemic heart disease or central nervous system hemorrhages and cerebrovascular conditions (4 points), diabetes mellitus (3 points), age ≥70 years (2 points), age 65 to 69 years (1 point), current/former smoker (1 point), hypertension (1 point), and hyperlipidemia (1 point); if positive for all three criteria: smoking, hypertension, and hyperlipidemia,1 extra point was added (ie, total of 4 points).
eGFR= estimated glomerular filtration rate; Q1=25th percentile; Q3=75th percentile; SD=standard deviation.

Table S5. Percentage Change from Baseline in Bone Mineral Density by Anti-Romosozumab Antibody

	Anti-romosozumab Antibody Status Through Month 18		
	All Negative	**Any Binding Positive**	**Any Neutralizing Positive**
Lumbar Spine	N=1450	N=289	N=11
Month 12	13.7 ± 7.2	13.8 ± 7.1	13.8 ± 8.5
Month 24	15.4 ± 8.4	14.8 ± 8.7	14.0 ± 7.6
Month 36	15.1 ± 9.4	14.5 ± 9.5	18.1 ± 7.1
Total Hip	N=1508	N=307	N=12
Month 12	6.2 ± 5.3	6.3 ± 5.0	6.3 ± 4.5
Month 24	7.2 ± 5.8	7.5 ± 5.7	6.9 ± 4.8
Month 36	7.5 ± 6.9	7.0 ± 6.1	9.3 ± 3.8
Femoral Neck	N=1508	N=307	N=12
Month 12	5.3 ± 5.5	5.3 ± 5.4	7.9 ± 6.4
Month 24	6.3 ± 6.1	6.6 ± 5.4	7.5 ± 4.2
Month 36	6.1 ± 6.7	6.5 ± 5.6	9.5 ± 5.6

Data are mean ± SD.
N=Number of subjects randomized to romosozumab, with bone mineral density values at baseline and at least one post-baseline visit at or before month 36 and with at least one post-baseline anti-romosozumab antibody data through month 18.

Table S6. Patient Incidence of Treatment-Emergent Autoimmune Disorders, Injection Site Reactions, and Hypersensitivity in the 12-month Double-Blind Period by Anti-Romosozumab Antibody Status in Patients Randomized to Romosozumab

		Romosozumab		
	Alendronate N=2014	Antibody Negative N=1639	Developing Binding Positive N=310	Developing Neutralizing Positive N=12
Event, n (%)				
Autoimmune disorders	35 (1.7)	23 (1.4)	1 (0.3)	0 (0)
Hypersensitivity	118 (5.9)	104 (6.3)	17 (5.5)	0 (0)
Injection-site reactions	53 (2.6)	68 (4.1)	16 (5.2)	1 (8.3)

N (alendronate)=Number patients who received at least one dose of alendronate during the double-blind period.
N (romosozumab)=Number of patients who received at least one dose of romosozumab and with at least one postbaseline anti-romosozumab antibody assessment. Anti-romosozumab antibodies were assessed through month 18 and were not tested in patients randomized to alendronate.
Adverse events were coded using Medical Dictionary for Regulatory Activities (MedDRA) version 19.1. Autoimmune disorder includes only treatment-emergent adverse events from the MedDRA high level group term of Autoimmune disorders. Hypersensitivity included treatment-emergent events as a result of a narrow search/scope in standardized MedDRA queries. Injection-site reactions defined by prespecified event of interest MedDRA search strategy. Binding and neutralizing antibodies are reported here for patients who had negative or no results at baseline. Neutralizing antibodies were tested in patients in whom binding antibodies were detected.

Clinical Trial Registration

When the study was initiated, trial registration followed the FDA guidance for registration within 21 days of first patient enrolled. The first patient was enrolled on May 4, 2012 and trial registration was completed on May 24, 2012. One patient out of 4093 enrolled between study initiation and registration.

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