Supplemental Material (Online only): ARCH QCT FEA Manuscript

Romosozumab Improves Lumbar Spine Bone Mass and Bone Strength Parameters Relative to Alendronate in Postmenopausal Women: Results From the Active-Controlled Fracture Study in Postmenopausal Women With Osteoporosis at High Risk (ARCH) Trial

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Supplemental Figure S1. ARCH study design overview.

Median (Q1, Q3) follow-up time through the primary analysis (double-blind + open-label) was 2.7 (2.2, 3.3) years. BMD was assessed by DXA at baseline and at Months 6, 12, 18, and 24 in a subset of patients in the imaging component of the ARCH substudy; n = 167. QCT images were obtained at baseline and at months 6, 12, and 24 for vBMD, bone volume, and BMC assessments and QCT-derived bone strength assessments in a subset of patients in the imaging component of the substudy; n = 90. Grey ovals indicate additional time points for DXA measurements for the imaging component of the substudy. aBMD, areal bone mineral density; Q1, Q3, first and third quartiles; QM, monthly; QW, weekly; vBMD, volumetric bone mineral density.
Supplemental Figure S2. CT scan with reconstructed section of the spine from mid-T12 to mid L4; L1 and L3 were analyzed as L2 was fractured.

Supplemental Figure S2 presents an example of a patient who had fractured the L2 vertebra more than 6 months before enrollment and had evaluable vertebrae (L1 and L3) in the region of interest for spine QCT scans. Left: axial slice through L3; right: sagittal reformation. Red: periosteal surface of vertebral body; green: endosteal surface of vertebral body; blue: peeled surface of trabecular bone. The integral VOI is bordered by the red surface, the cortical VOI by red and green surfaces, and the trabecular VOI by the blue surface. VOI, volume of interest.
**Supplemental Figure S3.** Anthropometric spine phantom (QSP: QRM Spine phantom) used for monitoring the stability of each CT scanner.

The QSP is always scanned on top of the BDC phantom, which is also used as in-scan calibration phantom for the patient scans. The QSP consists of 3 vertebrae of different densities. Left: CT scan including complete phantom; right: reconstructed section used for analysis. BDC, bone density calibration.
Supplemental Methods

Differences between MIAF and VirtuOst assessments of lumbar spine QCT scans

The MIAF and the VirtuOst analyses are independent of each other and use different segmentation approaches (as described in the Methods section of the manuscript). Briefly, while the VirtuOst approach uses a 2 mm homogenous peeling to define the cortical volume of interest (VOI), which is adequate for the strength analysis, MIAF uses a local adaptive segmentation to also capture the cortical thickness. This technique is more sensitive to sclerotic calcifications within the trabecular compartment and other degenerative changes. As such, a number of scans were excluded from the MIAF analysis but not from the VirtuOst analysis. Also, the scans of some patients were obtained without a calibration phantom. For the VirtuOst but not for the MIAF analysis an internal calibration procedure was applied. Furthermore, by default VirtuOst requires evaluation of only one vertebral body while MIAF requires two vertebrae. If one of the two vertebrae analyzed at baseline had an incident vertebral fracture then at follow-up only the remaining unfractured vertebra was analysed. MIAF results are average values of two vertebrae as long as the same vertebrae can be analyzed at all visits. In case of an incident vertebral fracture, only results of the remaining unfractured vertebra is used for all visits; i.e., in this case also the baseline results are only for the vertebra that remains unfractured during the study. Thus, results are comparable across visits. In general, evaluating results from two vertebrae improves precision and is advantageous compared with evaluating results from one vertebra.
Supplemental Figure S4. Patients in the ARCH study who enrolled in the QCT/FEA imaging substudy.

- **Patients randomized in the study**
  - N = 4093

- **Romosozumab 210 mg s.c. QM / Alendronate 70 mg orally QW**
  - n = 2046
  - Did not enroll in the ARCH imaging substudy
    - n = 1960
  - Enrolled in the ARCH imaging substudy
    - n = 86
    - Did not enroll in the QCT/FEA component of the imaging substudy
      - n = 37
      - Enrolled in the QCT/FEA imaging component of the substudy
        - n = 49
        - Had scans analyzed by MIAF for vBMD/bone volume/BMC assessments; n = 40a
        - Had scans analyzed by VirtuOst software for bone strength assessments; n = 47b

- **Alendronate 70 mg orally QW / Alendronate 70 mg orally QW**
  - n = 2047
  - Did not enroll in the ARCH imaging substudy
    - n = 1965
  - Enrolled in the ARCH imaging substudy
    - n = 81
    - Did not enroll in the QCT/FEA component of the imaging substudy
      - n = 40
      - Enrolled in the QCT/FEA imaging component of the substudy
        - n = 41
        - Had scans analyzed by MIAF for vBMD/bone volume/BMC assessments; n = 36a
        - Had scans analyzed by VirtuOst software for bone strength assessments; n = 39b

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*Had baseline and ≥ 1 postbaseline vBMD/bone volume/BMC assessment derived from scans that could be analyzed by MIAF. Had baseline and ≥ 1 postbaseline FEA assessment derived from scans that could be analyzed by VirtuOst software. BMC, bone mineral content; BMD, bone mineral density; FEA, fine element assessment; MIAF, Medical Imaging Analysis Framework; QM, monthly; QW, weekly; vBMD, volumetric bone mineral density.*
**Supplemental Table S1.** Missing value imputation using last postbaseline observation carried forward in the QCT/FEA imaging component of the ARCH substudy.

| LOCF proportion – LOCF/available data (%) | Month 6 | Month 12 Romosozumab + Alendronate | Month 12 Alendronate | Month 12 Romosozumab | Month 24 |
|-------------------------------------------|---------|------------------------------------|----------------------|----------------------|----------|
| QCT integral BMD                          | 0/70 (0)| 11/74 (14.9)                      | 5/35 (14.3)          | 6/39 (15.4)          | 0/54 (0) |
| QCT trabecular BMD                        | 0/70 (0)| 11/74 (14.9)                      | 5/35 (14.3)          | 6/39 (15.4)          | 0/54 (0) |
| QCT FEA                                   | 0/81 (0)| 12/85 (14.1)                      | 4/38 (10.5)          | 8/47 (17.0)          | 0/50 (0) |

FEA, finite element analysis; LOCF, last observation carried forward.
**Supplemental Table S2.** Baseline QCT lumbar spine bone volume and BMC values for patients in the ARCH QCT/FEA substudy.

| Patients Included in the ARCH QCT/FEA Substudy | Romosozumab / Alendronate $n = 49$ | Alendronate / Alendronate $n = 41$ |
|---------------------------------------------|----------------------------------|----------------------------------|
| QCT lumbar spine bone volume, cm$^3$, mean (SD) |                                  |                                  |
| Integral                                    | 29.8 (5.3)                       | 29.0 (4.8)                       |
| Cortical                                    | 6.6 (1.3)                        | 6.2 (1.4)                        |
| Trabecular                                  | 17.8 (3.7)                       | 17.5 (3.1)                       |
| QCT lumbar spine BMC, mg, mean (SD)         |                                  |                                  |
| Integral                                    | 3845 (900)                       | 3505 (978)                       |
| Cortical                                    | 1907 (537)                       | 1729 (575)                       |
| Trabecular                                  | 1041 (333)                       | 930 (365)                        |

$n =$ number of randomized patients enrolled in the QCT/FEA imaging component of the ARCH substudy and with values at baseline and ≥ 1 postbaseline QCT visit.
**Supplemental Figure S5.** Observed areal BMD percentage change from baseline at the lumbar spine with romosozumab or alendronate treatment at months 6, 12, 18, and 24 by DXA.

Box plots show the 25th and 75th percentiles; horizontal bars = median values; x marks = mean values; error bars = minimum to maximum values, excluding any outliers; and circles = outliers defined by either larger than 1.5 IQR above the 75th percentile or smaller than 1.5 IQR below the 25th percentile. 

\( n = \) number of randomized patients enrolled in the QCT/FEA imaging component of the ARCH substudy with values at baseline and ≥ 1 postbaseline DXA visit at Month 6 or Month 18 and with values at baseline and ≥ 1 postbaseline QCT visit; 

\( n1 = \) number of patients with values at that time point. Month 6 and 12 measurements were during the double-blind period when patients received monthly s.c. romosozumab 210 mg or weekly oral alendronate 70 mg for 12 months; month 24 measurements were during the open-label period when patients received open-label weekly oral alendronate 70 mg for 12 months. aBMD, areal bone mineral density; ALN, alendronate; FEA, finite element analysis; IQR, interquartile range; Q1, Q3, first and third quartiles; ROMO, romosozumab.
Supplemental Figure S6. Observed vBMD percentage change from baseline at the lumbar spine with romosozumab or alendronate treatment at months 6, 12, and 24 by QCT: integral vBMD (Panel A), cortical vBMD (Panel B), and trabecular vBMD (Panel C).

Box plots show the 25th and 75th percentiles; horizontal bars = median values; x marks = mean values; error bars = minimum to maximum values, excluding any outliers; and circles = outliers defined by either larger than 1.5 IQR above the 75th percentile or smaller than 1.5 IQR below the 25th percentile. 

n = number of patients enrolled in the QCT/FEA imaging component of the ARCH substudy with values at baseline and ≥1 postbaseline visit; nl = number of patients with values at that time point. Month 6 and 12 measurements were during the double-blind period when patients received monthly s.c. romosozumab 210 mg or weekly oral alendronate 70 mg for 12 months; month 24 measurements were during the open-label period when patients received open-label weekly oral alendronate 70 mg for 12 months. ALN, alendronate; FEA, finite element analysis; IQR, interquartile range; Q1, Q3, first and third quartiles; ROMO, romosozumab; vBMD, volumetric bone mineral density.
### Supplemental Table S3. Least squares mean bone volume percentage change from baseline at the lumbar spine (integral, cortical, and trabecular) with romosozumab or alendronate treatment at months 6, 12, and 24.

| Month | Integral | Cortical | Trabecular | Difference (cortical minus trabecular) | p-Value for Difference |
|-------|----------|----------|------------|----------------------------------------|------------------------|
| **Month 6** | | | | | |
| Romosozumab / Alendronate | 0.3 (–0.9, 0.4)† | 8.2 (5.4, 10.9)* | –2.9 (–3.7, –2.0)* | 10.9 (7.8, 14.0) | p < 0.001 |
| Alendronate / Alendronate | 0.2 (–0.9, 0.5)† | 1.7 (–0.4, 3.7)† | –0.9 (–1.6, –0.1)§ | 2.6 (0.7, 4.6) | p = 0.007 |
| Difference (Romosozumab – Alendronate) | –0.1 (–1.1, 0.9) | 6.5 (3.0, 9.9) | –2.0 (–3.2, –0.8) | 8.3 (4.6, 11.9) | p = 0.001 |
| **Month 12** | | | | | |
| Romosozumab / Alendronate | 0.2 (–0.5, 0.9)† | 11.3 (8.2, 14.4)* | –3.2 (–4.3, –2.2)* | 14.4 (10.7, 18.1) | p < 0.001 |
| Alendronate / Alendronate | 0.4 (–0.2, 0.9)† | 2.7 (1.1, 4.3)** | –0.6 (–1.3, 0.1)† | 3.5 (1.8, 5.1) | p = 0.007 |
| Difference (Romosozumab – Alendronate) | –0.2 (–1.1, 0.7) | 8.6 (5.1, 12.1) | –2.6 (–3.9, –1.3) | 10.9 (6.9, 15.0) | p < 0.001 |
| **Month 24** | | | | | |
| Romosozumab / Alendronate | –0.3 (–1.2, 0.6)† | 8.1 (4.7, 11.6)* | –3.5 (–4.4, –2.7)* | 11.3 (7.9, 14.7) | p < 0.001 |
| Alendronate / Alendronate | 0.9 (0.3, 1.5)§ | 3.1 (1.2, 5.1)§ | –0.1 (–1.3, 1.0)† | 3.7 (1.3, 6.1) | p = 0.003 |
| Difference (Romosozumab – Alendronate) | –1.2 (–2.2, –0.1) | 5.0 (1.0, 9.0) | –3.4 (–4.9, –2.0) | 7.7 (3.5, 11.8) | p < 0.001 |

n = number of randomized patients enrolled in the QCT/FEA imaging component of the ARCH substudy and with values at baseline and ≥ 1 post-baseline QCT visit. Month 6 and 12 measurements were during the double-blind period where patients received monthly s.c. romosozumab 210 mg or weekly oral alendronate 70 mg for 12 months; month 24 measurements were during the open-label period when patients received open-label weekly oral alendronate 70 mg for 12 months. Data based on ANCOVA model adjusting for treatment, presence of severe vertebral fracture at baseline, and baseline bone volume value. *p < 0.001 vs baseline; **p = 0.001 vs baseline; †p < 0.05 vs baseline; ‡p > 0.05 vs baseline. Missing values were imputed by carrying forward the last non-missing post-baseline value prior to the missing value and within the treatment period. ANCOVA, analysis of covariance; FEA, finite element analysis.
Supplemental Figure S7. Least squares mean BMC absolute change from baseline at the lumbar spine with romosozumab or alendronate treatment at months 6, 12, and 24 by QCT: integral BMC (Panel A), cortical BMC (Panel B), and trabecular BMC (Panel C).

\[ n \] = number of randomized patients enrolled in the QCT/FEA imaging component of the ARCH substudy and with values at baseline and \( \geq 1 \) postbaseline QCT visit. \( n_1 \) = number of patients with evaluable data at the timepoint of interest. Month 6 and 12 measurements were during the double-blind period when patients received monthly s.c. romosozumab 210 mg or weekly oral alendronate 70 mg for 12 months; month 24 measurements were during the open-label period when patients received open-label weekly oral alendronate 70 mg for 12 months. Data were based on ANCOVA model, adjusting for presence of severe vertebral fracture at baseline and baseline BMC value. Missing values were imputed by carrying forward the last non-missing postbaseline value prior to the missing value and within the treatment period. ANCOVA, analysis of covariance; FEA, finite element analysis.

*\( p < 0.001 \) vs baseline; \( *p < 0.001 \) vs baseline; \( **p = 0.044 \) vs baseline
**Supplemental Figure S8.** Observed BMC absolute change from baseline at the lumbar spine with romosozumab or alendronate treatment at months 6, 12, and 24 by QCT: integral BMC (Panel A), cortical BMC (Panel B), and trabecular BMC (Panel C).

Box plots show the 25th and 75th percentiles; horizontal bars = median values; x marks = mean values; error bars = minimum to maximum values, excluding any outliers; and circles = outliers defined by either larger than 1.5 IQR above the 75th percentile or smaller than 1.5 IQR below the 25th percentile. n = number of patients enrolled in the QCT/FEA imaging component of the ARCH substudy and with values at baseline and ≥ 1 postbaseline QCT visit. n1 = number of patients with evaluable data at the timepoint of interest. Month 6 and 12 measurements were during the double-blind period when patients received monthly s.c. romosozumab 210 mg or weekly oral alendronate 70 mg for 12 months; month 24 measurements were during the open-label period when patients received open-label weekly oral alendronate 70 mg for 12 months. FEA, finite element analysis; IQR, interquartile range; Q1, Q3, first and third quartiles.
**Supplemental Table S4.** Least squares mean BMC absolute and percentage change from baseline at the lumbar spine (integral, cortical, and trabecular) with romosozumab or alendronate treatment at months 6, 12, and 24.

|                  | Least Squares Mean BMC Absolute Change From Baseline | Least Squares Mean BMC Percentage Change From Baseline |
|------------------|-----------------------------------------------------|------------------------------------------------------|
|                  | Romosozumab / Alendronate | Alendronate / Alendronate | Difference (romosozumab – alendronate) | Romosozumab / Alendronate | Alendronate / Alendronate | Difference (romosozumab – alendronate) | p-value for difference |
|                  | $n = 40$ | $n = 36$ | mg (95% CI) | mg (95% CI) | % (95% CI) | % (95% CI) | % (95% CI) |
| **Month 6**      |         |         |          |          |         |          |          |
| Integral         | 618.7 (493.3, 744.2)* | 181.9 (114.4, 249.5)* | 436.8 (293.9, 579.7) | 17.2 (13.7, 20.6)* | 5.4 (13.2, 7.6)* | 11.8 (7.7, 15.9) | $p < 0.001$ |
| Cortical         | 388.6 (313.7, 463.5)* | 103.9 (64.4, 143.5)* | 284.7 (199.8, 369.6) | 22.3 (18.2, 26.5)* | 6.1 (3.4, 8.8)* | 16.3 (11.3, 21.2) | $p < 0.001$ |
| Trabecular       | 165.8 (112.0, 219.6)* | 50.9 (14.0, 87.8)$^\dagger$ | 114.9 (49.6, 180.4) | 17.3 (11.5, 23.1)* | 3.3 (–4.1, 10.8)$^\dagger$ | 14.0 (4.5, 23.5) | $p = 0.005$ |
| Difference (cortical minus trabecular) | $p < 0.001$ | $p = 0.038$ | $p < 0.001$ | 4.8 (0.2, 9.5) | 3.0 (–5.0, 11.0) | 1.9 (–7.4, 11.1) | $p = 0.690$ |
| **Month 12**     |         |         |          |          |         |          |          |
| Integral         | 800.5 (680.3, 920.7)* | 261.6 (183.3, 339.9)* | 538.9 (394.6, 683.2) | 21.8 (18.6, 25.0)* | 7.4 (5.0, 9.7)* | 14.5 (10.5, 18.5) | $p < 0.001$ |
| Cortical         | 515.8 (433.1, 598.6)* | 144.4 (104.2, 184.5)* | 371.5 (279.2, 463.8) | 28.6 (24.4, 32.9)* | 8.2 (5.6, 10.7)* | 20.5 (15.5, 25.4) | $p < 0.001$ |
| Trabecular       | 204.7 (147.5, 261.9)* | 72.8 (29.4, 116.1)* | 131.9 (59.8, 204.1) | 21.3 (15.2, 27.5)* | 5.6 (–2.2, 13.4)$^\dagger$ | 15.6 (5.7, 25.6) | $p = 0.003$ |
| Difference (cortical minus trabecular) | $p < 0.001$ | $p = 0.007$ | $p < 0.001$ | 7.4 (0.9, 13.9) | 2.6 (–5.4, 10.5) | 4.8 (–5.4, 15.1) | $p = 0.350$ |
| **Month 24**     |         |         |          |          |         |          |          |
| Integral         | 761.4 (622.6, 900.2)* | 293.4 (166.4, 420.3)* | 468.0 (278.2, 657.8) | 20.2 (16.6, 23.7)* | 7.9 (4.4, 11.5)* | 12.2 (7.2, 17.3) | $p < 0.001$ |
| Cortical         | 491.6 (396.0, 587.2)* | 135.6 (63.8, 207.4)* | 356.0 (235.5, 476.5) | 26.0 (21.5, 30.5)* | 7.8 (4.1, 11.6)* | 18.2 (12.3, 24.1) | $p < 0.001$ |
| Trabecular       | 178.4 (116.4, 240.3)* | 80.9 (2.4, 159.4)$^{**}$ | 97.5 (–3.2, 198.1) | 17.8 (11.4, 24.2)* | 3.2 (–10.3, 16.7)$^{\ddagger}$ | 14.6 (–0.4, 29.7) | $p = 0.056$ |
| Difference (cortical minus trabecular) | $p < 0.001$ | $p = 0.270$ | $p < 0.001$ | 8.0 (2.0, 14.0) | 4.9 (–9.3, 19.0) | 3.1 (–12.3, 18.5) | $p = 0.690$ |

$n =$ Number of randomized patients enrolled in the QCT/FEA imaging component of the ARCH substudy and with values at baseline and ≥ 1 post-baseline QCT visit. Month 6 and 12 measurements were during the double-blind period where patients received monthly s.c. romosozumab 210 mg or weekly oral alendronate 70 mg for 12 months; month 24 measurements were during the open-label period when patients received open-label weekly oral alendronate 70 mg for 12 months. Data based on ANCOVA model adjusting for treatment, presence of severe vertebral fracture at baseline, and baseline BMC value. *$p < 0.001$ vs baseline; $^\ddagger p = 0.008$ vs baseline; $^{**}p = 0.044$ vs baseline; $^\dagger p = 0.16$ vs baseline; $^{\ddagger}p = 0.38$ vs baseline; $^\ddagger\ddagger p = 0.64$ vs baseline. Missing values were imputed by carrying forward the last non-missing post-baseline value prior to the missing value and within the treatment period. ANCOVA, analysis of covariance; BMC, bone mineral content; FEA, finite element analysis; LS, least squares.
Supplemental Figure S9. Observed bone strength percentage change from baseline at the lumbar spine with romosozumab or alendronate treatment at months 6, 12, and 24 by FEA: integral bone strength (Panel A), cortical bone strength (Panel B), and trabecular bone strength (Panel C).

Box plots show the 25th and 75th percentiles; horizontal bars = median values; x marks = mean values; error bars = minimum to maximum values, excluding any outliers; and circles = outliers defined by either larger than 1.5 IQR above the 75th percentile or smaller than 1.5 IQR below the 25th percentile. n = number of patients enrolled in the QCT/FEA imaging component of the ARCH substudy with values at baseline and ≥1 postbaseline visit; n1 = number of patients with values at that time point. Month 6 and 12 measurements were during the double-blind period where patients received monthly s.c. romosozumab 210 mg or weekly oral alendronate 70 mg for 12 months; and month 24 measurements were during the open-label period when patients received open-label weekly oral alendronate 70 mg for 12 months. ALN, alendronate; FEA, finite element analysis; IQR, interquartile range; Q1, Q3, first and third quartiles; ROMO, romosozumab.
Supplemental Figure S10, Supplemental Video 1. Illustration of internal tissue failure during virtual loading at baseline and at months 6, 12, and 24 for two representative patients (one from each treatment group) with similar baseline characteristics (including baseline bone strength and density values) and showing a typical response to each therapy.

Internal Tissue Failure During Virtual Loading at Baseline and At Months 6, 12, and 24

Sectioned 3D models are in grayscale with darker colors = lower bone density and brighter colors = higher bone density; light blue = top and bottom layers of bone cement; yellow-red colormap = regions of failed tissue. ALN, alendronate; ROMO, romosozumab.
Supplemental Figure S11. Correlation of postbaseline absolute changes in integral FEA bone strength and postbaseline absolute changes in integral QCT BMC at the lumbar spine for romosozumab-to-alendronate and alendronate-to-alendronate groups through month 24.

Includes randomized patients enrolled in the QCT/FEA imaging component of the ARCH substudy with baseline and ≥ 1 postbaseline reported result for the parameters of interest. \( n \) = number of evaluable measurements, with ≥ 1 measurements per patient. Month 6 and 12 measurements were during the double-blind period where patients received monthly s.c. romosozumab 210 mg or weekly oral alendronate 70 mg for 12 months; month 24 measurements were during the open-label period when patients received open-label weekly oral alendronate 70 mg for 12 months. ALN, alendronate; BMC, bone mineral content; FEA, finite element analysis; \( R \), Spearman’s correlation coefficient; ROMO = romosozumab.
Supplemental Table S5. Characteristics of patients in the alendronate-to-alendronate group who developed new vertebral fractures

| Patient Number / Analysis Visit (Visit Number) | Location of Measurement | QCT | FEA | Fracture Image Study Day | Location of Vertebrae Assessed for Fracture (Grade) | New Verterbral Fracture | New or Worsening Verterbral Fracture | Multiple New or Worsening Verterbral Fracture | Clinical New or Worsening Verterbral Fracture | Integral Lumbar Spine |
|-----------------------------------------------|-------------------------|-----|-----|--------------------------|-----------------------------------------------|------------------------|--------------------------------------|-----------------------------------------------|-----------------------------------------------|---------------------|
| Patient 3                                     |                         |     |     |                          |                                               |                        |                                      |                                               |                                               |                     |
| Baseline (1)                                  |                         |     |     | –27                      | T₁₂ (3), L₁ (3), L₄ (1)                        | N                     | N                                    | N                              | N                              | 0.9                 | ND                  | ND                  | ND                  | 2630                |
| Month 12 (14)                                 |                         |     |     | 371                      | T₁₂ (3), L₁ (3), L₄ (1)                        | N                     | N                                    | N                              | N                              | 1.0                 | ND                  | ND                  | ND                  | 2910                |
| Month 24 (18)                                 |                         | NM  | NM  | 720                      | T₁₂ (3), L₁ (3), L₂ (2), L₄ (1)                | Y                     | Y                                    | Y                              | N                              | 1.0                 | NM                  | NM                  | NM                  |                     |
| Patient 4                                     |                         |     |     |                          |                                               |                        |                                      |                                               |                                               |                     |
| Baseline (1)                                  |                         | L₁  | L₁  | –21                      | L₁ (3), L₄ (1)                                 | N                     | N                                    | N                              | N                              | 0.8                 | 95.1                | 33.9                | 3227                | 2660                |
| Month 12 (14)                                 |                         | L₁  | L₂  | 363                      | L₁ (3), L₄ (1)                                 | N                     | N                                    | N                              | N                              | 0.8                 | 104.1               | 34.7                | 3617                | 2790                |
| Month 24 (18)                                 |                         | NM  | NM  | 722                      | T₄ (3), T₅ (2), L₁ (3), L₄ (1)                  | Y                     | Y                                    | Y                              | Y                              | 0.8                 | NM                  | NM                  | NM                  |                     |
| Patient 5                                     |                         |     |     |                          |                                               |                        |                                      |                                               |                                               |                     |
| Baseline (1)                                  |                         | T₁₂ | L₁  | –52                      | L₂ (3), L₁ (1)                                 | N                     | N                                    | N                              | N                              | 0.8                 | 92.3                | 27.4                | 2526                | 2300                |
| Month 12 (14)                                 |                         | T₁₂ | L₁  | 365                      | L₂ (3), L₁ (1)                                 | N                     | N                                    | N                              | N                              | 0.9                 | 107.6               | 27.5                | 2959                | 2870                |
| Month 24 (18)                                 |                         | T₁₂ | L₁  | 750                      | L₂ (3), L₁ (1)                                 | N                     | N                                    | N                              | N                              | 1.0                 | 108.2               | 28.5                | 3014                | 2710                |
| Month 36 (20)                                 |                         | NM  | NM  | 1110                     | L₄ (3), L₂ (3), L₃ (1)                          | Y                     | Y                                    | N                              | Y                              | 0.9                 | NM                  | NM                  | NM                  |                     |
| Patient 6                                     |                         |     |     |                          |                                               |                        |                                      |                                               |                                               |                     |
| Baseline (1)                                  |                         | L₂  | L₃  | –52                      | T₃ (3)                                          | 0.9                   | 125.9                                | 33.1                           | 4171                           | 3780                |
| Month 12 (14)                                 |                         | L₂  | L₃  | 372                      | T₃ (3)                                          | N                     | N                                    | N                              | N                              | 0.9                 | 125.7               | 33.0                | 4146                | 3800                |
| Month 24 (18)                                 |                         | L₂  | L₃  | 743                      | T₃ (3)                                          | N                     | N                                    | N                              | N                              | 0.9                 | 130.6               | 33.1                | 4239                | 3850                |
| Month 36 (20)                                 |                         | NM  | NM  | 848                      | T₃ (3), T₄ (3)                                  | Y                     | Y                                    | N                              | Y                              | 0.9                 | NM                  | NM                  | NM                  |                     |

Only includes randomized patients enrolled in the substudy and with values at baseline and ≥ 1 post-baseline QCT visit. Analysis visit is based on the analytical window defined in the statistical analysis plan (SAP) and visit number is the planned study visit according to the protocol schedule of assessments. All clinical new or worsening vertebral fractures are considered clinical fractures. Only include subjects with ≥ 1 on-study new or worsening vertebral fracture. aData presented only for vertebrae for measuring QCT lumbar spine integral BMD, BMC, bone volume and FEA vertebral strength. bBold font
indicates vertebrae with on-study fracture. aBMD, areal bone mineral density; FEA, finite element analysis; N, no; ND, not detectable; NM, not measured; vBMD, volumetric bone mineral density; Y, yes.