Supplemental Material Table of contents

Supplemental Table 1. The median interval (months) from starting denosumab therapy to each measurement.

Time points (Y)	N	Median interval, month (IQR)
-1	103	-12.9 (-13.8 - -12.4)
-0.5	95	-6.9 (-7.6 - -6.3)
Baseline	124	-0.7 (-1.5 - -0.3)
0.5	117	5.4 (4.6 - 6.1)
1	114	11.4 (10.4 - 12.0)
1.5	107	17.5 (16.7 - 18.1)
2	99	23.5 (22.7 - 24.2)
2.5	84	29.7 (28.9 - 30.5)
3	67	35.9 (34.9 - 36.7)
3.5	58	42.0 (41.4 - 42.7)
4	48	48.1 (47.3 - 49.4)
4.5	45	54.3 (53.6 - 55.0)
5	27	60.3 (59.4 - 60.9)

Abbreviations: Y, year; IQR, range from 25th to 75th percentile; M, month.

Supplemental Table 2 Baseline clinical and biochemical characteristics of 4 dialysis patients who developed hip fracture during studied period.

Patients number	1	2	3	4
Age (years)	66	73	70	63
Sex	Male	Male	Male	Female
Hemodialysis therapy	HD	HD	HD	HD
Dialysis vintage, (months)	79	233	103	137
Cause of Kidney Failure	BNS	CGN	BNS	BNS
Smoker	No	No	Yes	No
Diabetes mellitus	Yes	No	Yes	Yes
Bone mineral density (BMD)				
Total hip BMD, (g/cm^2)	0.84	0.76	0.78	0.59
Femoral neck BMD, (g/cm^2)	0.51	0.53	0.53	0.45
T-score, (SD)	-2.8	-2.6	-2.6	-3.1
Z-score, (SD)	-1.9	-1.3	-.18 -1.8	-1.4 -1.4
Circulating biomarkers (n=121)				
Albumin, (g/dL)	3.4	3.4	3.3	3.1
Calcium, (mg/dL)	8.5	9.6	8.8	7.8
Phosphate, (mg/dL)	5.6	5.6	5.6	6.2
i-PTH, (pg/mL)	221	183	123	333
Alkaline phosphatase, (U/L)	187	214	262	341
3D-DXA parameters and bone strength indices				
Trabecular volumetric BMD at total, (mg/cm^3)	80	113	100	95
Cortical volumetric BMD at total, (mg/cm^3)	750	745	795	644
Cortical Thickness at total, (mm)	1.76	1.64	1.63	1.49
Cortical surface BMD at total, (mg/cm^3)	132	122	130	96
Cross-sectional area at neck, (cm^2)	0.64	0.72	0.65	0.59
Cross-sectional moment of inertia at neck, (cm^4)	1.07	1.10	1.14	0.73
Section modulus at neck, (cm^3)	0.47	0.56	0.50	0.40
Buckling ratio at neck	13	13	15	11

Abbreviation: HD, hemodialysis; BNS, Benign nephrosclerosis; CGN, Chronic glomerulonephritis; i-PTH, intact-parathyroid hormone.

Supplemental Table 3 Linear mixed model of CKD-MBD parameters from baseline to a maximum of 5 years of denosumab therapy.

	Coefficient (95%CI) (for each additional year) year)	p-value
Calcium, (mg/dL)	0.20 (-0.01 - 0.05)	0.24
Phosphate, (mg/dL)	0.17 (-0.05 - 0.08)	0.61
i-PTH, (pg/mL)	-4.28 (-11.91 - 3.35)	0.28
ALP, (U/L)	-4.83 (-9.76 - 0.10)	0.06
Albumin-corrected calcium, (mg/dL)	0.003 (0.002- 0.005)	<0.001
Albumin, (g/dL)	0.49 (0.32- 0.65)	<0.001

Abbreviation: i-PTH, intact-parathyroid hormone; ALP, alkaline phosphatase.

Supplemental Table 4 Linear mixed model of medication doses from baseline to a maximum of 5 years of denosumab therapy.

	Coefficient (95%CI) (for each additional year)	p-value
Calcium carbonate, (mg/day)	-20 (-62 - 23)	0.37
Cinacalcet, (mg/day)	-0.5 (-1.5 – 0.6)	0.39
Alfaclcidol, (mg/day)	-0.04 (-0.05 - -0.03)	<0.001
Calcitriol, (mg/day)	-0.01 (-0.03 - -0.001)	<0.05

Supplemental Table 5. Linear mixed model of 3D DXA parameters from baseline to a maximum of 5 years of denosumab therapy.

	Coefficient (95%CI) (for each additional year)	p-value
Areal BMD, (g/cm^2)	0.04 (0.04- 0.05)	<0.001
Integral volumetric BMD, (mg/cm^3)	1.03 (0.60- 1.45)	<0.001
Trabecular volumetric BMD, (mg/cm^3)	0.55 (0.27- 0.83)	<0.001
Cortical volumetric BMD, (mg/cm^3)	1.58 (1.07- 2.09)	<0.001
Cortical Thickness, (mm)	0.003 (0.002- 0.005)	<0.001
Cortical surface BMD, (mg/cm^3)	0.49 (0.32- 0.65)	<0.001

Abbreviations: CI, confidence interval; BMD, bone mineral density.

Supplemental Table 6. Linear mixed model of bone strength indices at the neck region from baseline to a maximum of 5 years of denosumab therapy.

	Coefficient (95%CI)	p-value
Cross-sectional area	0.03 (0.02- 0.04)	<0.001
Cross-sectional moment of inertia	0.005 (0.001- 0.010)	<0.05
Section modulus	0.002 (0.001- 0.004)	<0.01
Buckling ratio	0.03 (0.01- 0.05)	<0.001

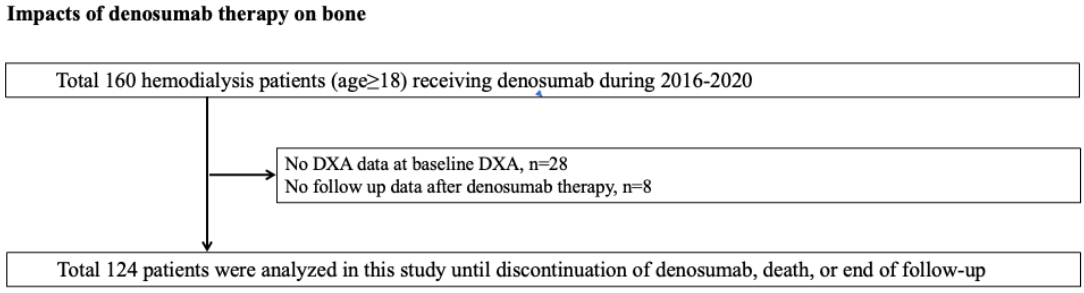
Abbreviations: CI, confidence interval.

Supplemental Table 7. Predictors of changes in areal BMD, trabecular volumetric BMD and cortical surface BMD from multivariable mixed analysis.

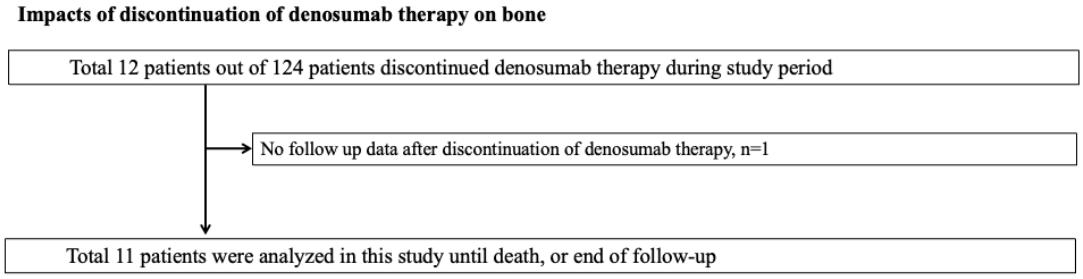
Baseline variables	Areal BMD		Trabecular volumetric BMD		Cortical surface BMD	
	Coefficient (95%CI)	**p value**	**Coefficient (95%CI)**	**p value**	**Coefficient (95%CI)**	**p value**
Calcium	-0.51 (-3.04-2.03)	0.69	-2.06 (-11.75-7.63)	0.67	-0.72 (-5.77-4.33)	0.78
Phosphate	-0.78 (-1.91-0.34)	0.17	-1.46 (-5.81-2.89)	0.51	-1.39 (-3.63-0.86)	0.22
i-PTH	0.002 (-0.009-0.014)	0.69	0.03 (-0.02-0.07)	0.26	0.019 (-0.003-0.043)	0.09
ALP	0.01 (0.004-0.023)	<0.01	0.01 (-0.03-0.05)	0.72	0.016 (-0.005-0.036)	0.13
Alb	2.37 (-1.07-5.82)	0.17	15.18 (0.83-29.53)	<0.05	5.29 (-2.32-12.90)	0.17
Calcium carbonate (yes vs. no)	0.32 (-2.26-2.91)	0.80	-1.26 (-11.14-8.62)	0.80	0.40 (-4.74-5.55)	0.88
[a]VDRA (yes vs. no)	0.61 (-1.68-2.90)	0.60	1.46 (-7.30-10.22)	0.74	3.37 (-1.11-7.85)	0.14
Cinacalcet (yes vs. no)	0.35 (-1.87-2.57)	0.75	-4.34 (-12.77-4.09)	0.31	0.47 (-3.96-4.89)	0.83

Abbreviation: BMD, bone mineral density; i-PTH, intact-parathyroid hormone; ALP, alkaline phosphatase; VDRA vitamin D receptor activator. [a]VDRA, as sum of alfaclcidol and Calcitriol. Each baseline variables were adjusted for age (years), sex (male vs. female).

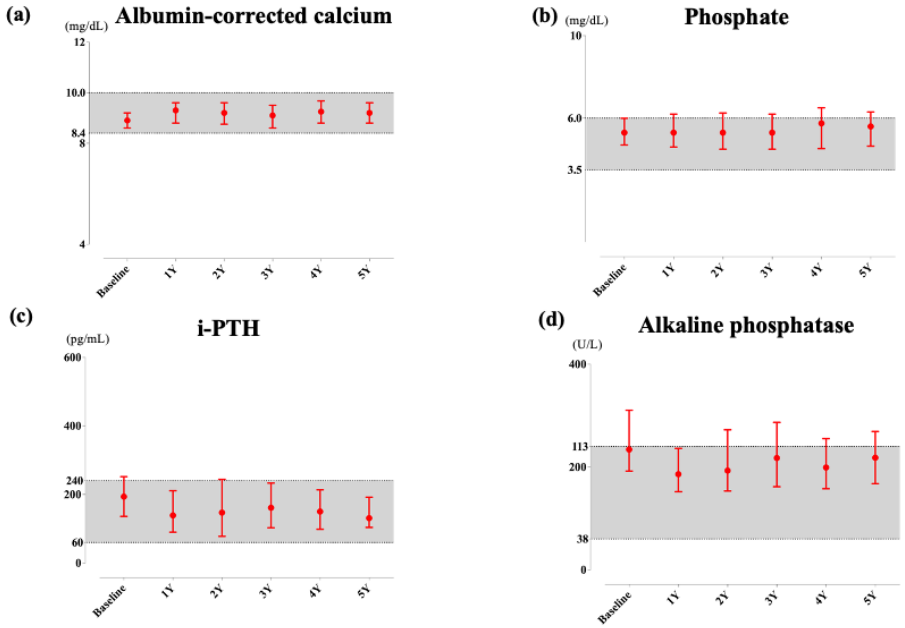
Supplemental Figure 1. Patient disposition



Supplemental Figure 2. Patient disposition for discontinuation analysis

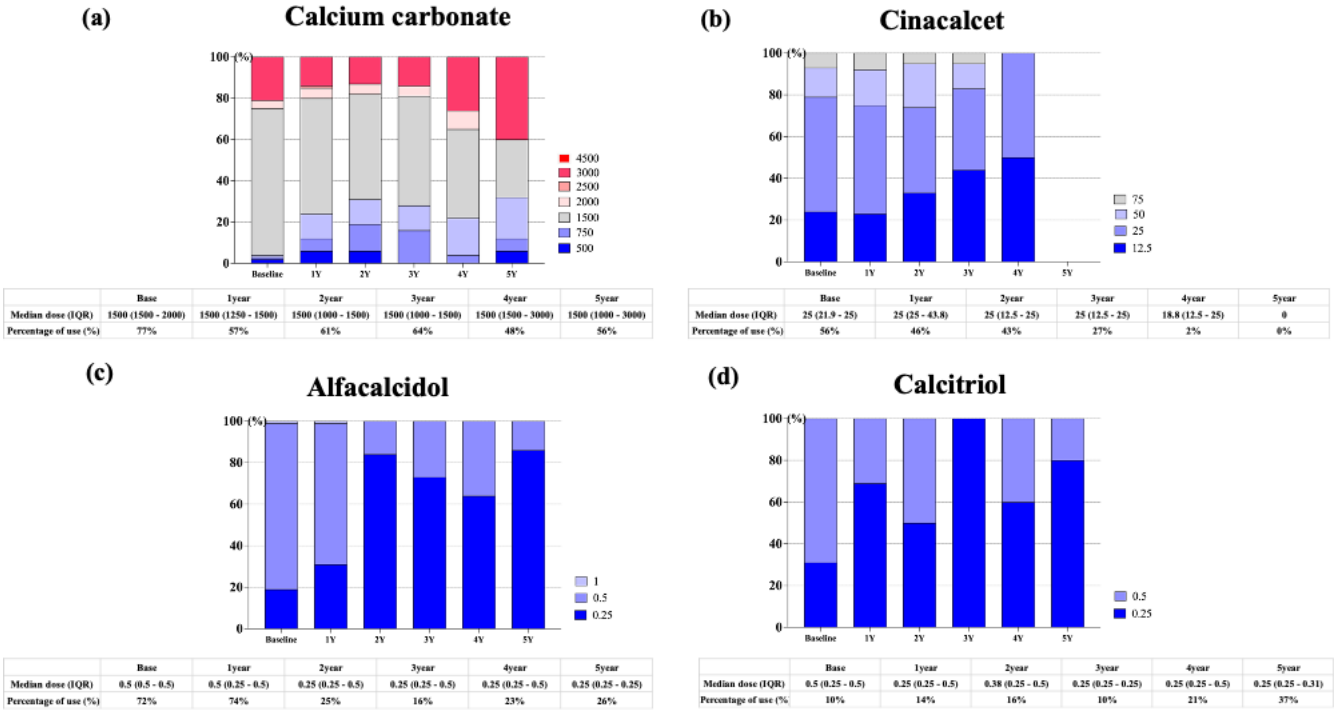


Supplemental Figure 3. Time courses of the CKD-MBD parameters from baseline to a maximum of 5 years of denosumab therapy.



Data represent the median (IQR). The gray shaded area represents the reference value (recommended by JSDT).
Abbreviation: i-PTH, intact-parathyroid hormone.

Supplemental Figure 4. Stacked bar chart of medication dose from baseline to a maximum of 5 years of denosumab therapy.



	Base	1year	2year	3year	4year	5year
Median dose (IQR)	1500 (1500 - 2000)	1500 (1250 - 1500)	1500 (1000 - 1500)	1500 (1000 - 1500)	1500 (1500 - 3000)	1500 (1000 - 3000)
Percentage of use (%)	77%	57%	61%	64%	48%	56%

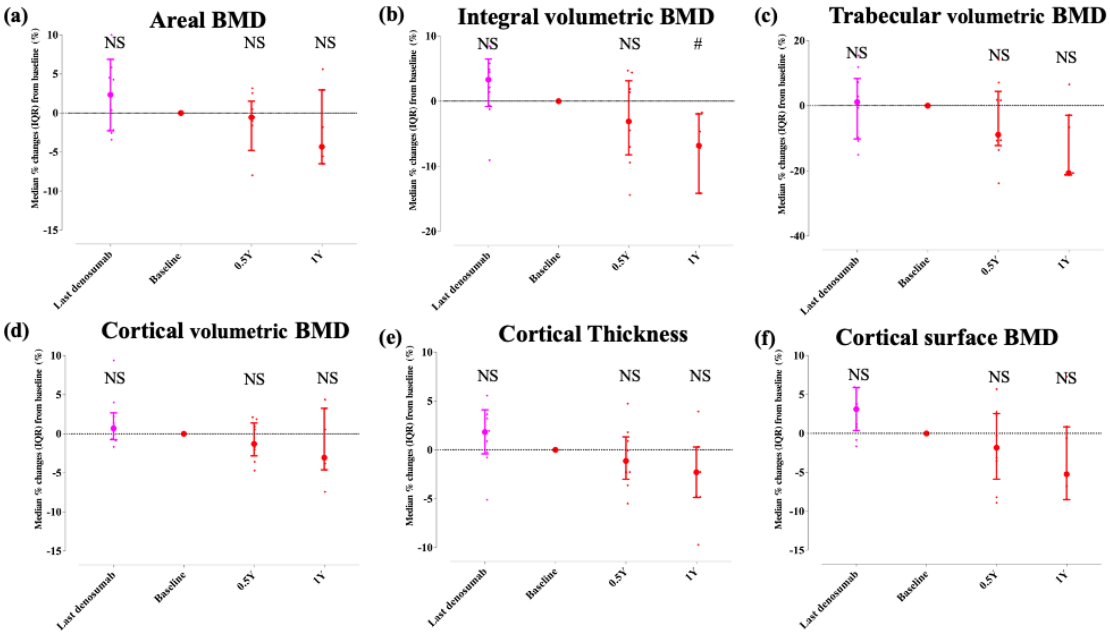
	Base	1year	2year	3year	4year	5year
Median dose (IQR)	25 (21.9 - 25)	25 (25 - 43.8)	25 (12.5 - 25)	25 (12.5 - 25)	18.8 (12.5 - 25)	0
Percentage of use (%)	56%	46%	43%	27%	2%	0%

	Base	1year	2year	3year	4year	5year
Median dose (IQR)	0.5 (0.5 - 0.5)	0.5 (0.25 - 0.5)	0.25 (0.25 - 0.5)	0.25 (0.25 - 0.5)	0.25 (0.25 - 0.5)	0.25 (0.25 - 0.25)
Percentage of use (%)	72%	74%	25%	16%	23%	26%

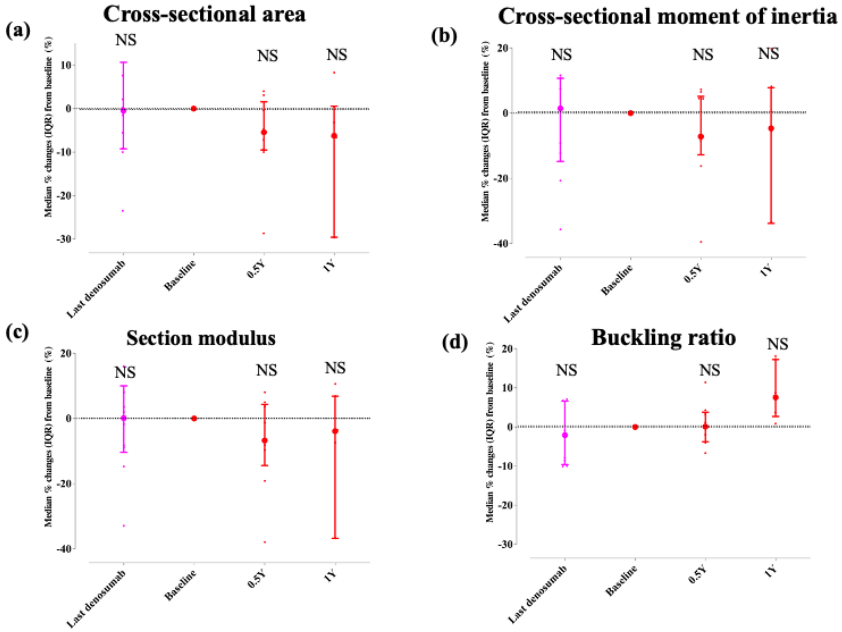
	Base	1year	2year	3year	4year	5year
Median dose (IQR)	0.5 (0.25 - 0.5)	0.25 (0.25 - 0.5)	0.38 (0.25 - 0.5)	0.25 (0.25 - 0.25)	0.25 (0.25 - 0.5)	0.25 (0.25 - 0.31)
Percentage of use (%	10%	14%	16%	10%	21%	37%

The table in the bottom row shows median doses (IQR) and percentage of medication use (%).

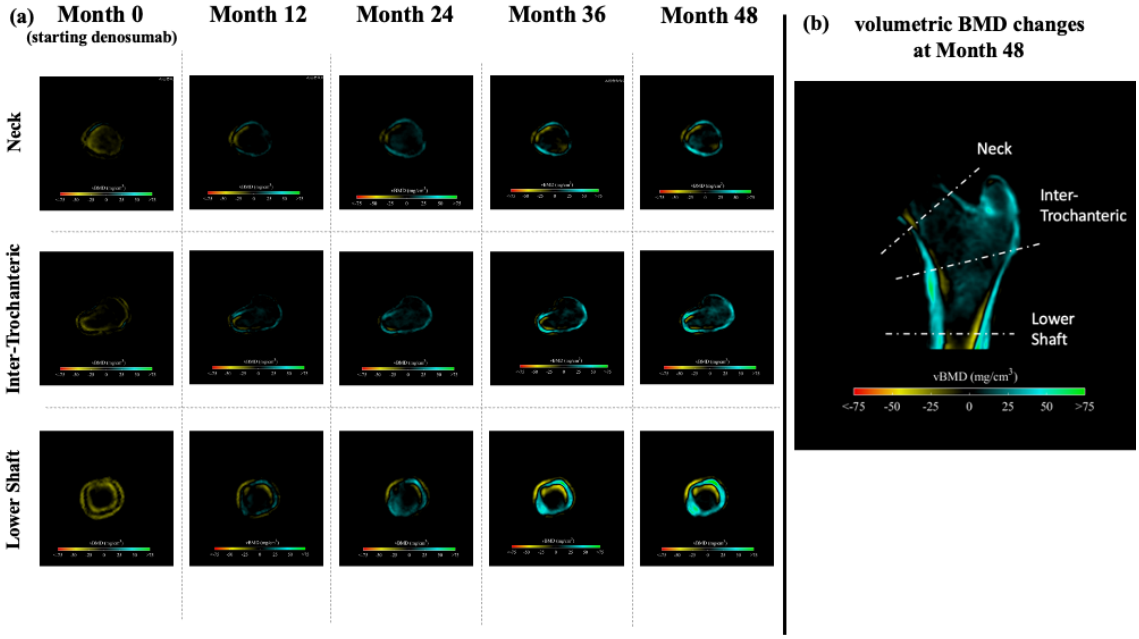
Supplemental Figure 5. Changes at the total hip region in areal BMD (a), integral volumetric BMD (b), trabecular volumetric BMD (c), cortical volumetric BMD (d), cortical thickness (e), and cortical surface BMD (f) after denosumab discontinuation in 11 dialysis patients.
Data represent the median (IQR). Abbreviations: Y, year; BMD, bone mineral density; DXA, dual-energy X-ray absorptiometry; IQR, interquartile range.
#p < 0.05 vs baseline (by Wilcoxon's signed-rank test).



Supplemental Figure 6. Changes at the neck region in cross-sectional area (a), cross-sectional moment of inertia (b), section modulus (c), and buckling ratio (d) after denosumab discontinuation in 11 dialysis patients.
Data represent the median (IQR). Abbreviations: Y, year; IQR, interquartile range.
NS vs baseline (by Wilcoxon's signed-rank test).



Supplemental Figure 7. Cross-sectional images showing the time course of the average changes in volumetric BMD from 1 year before to 4 years after denosumab initiation in 39 dialysis patients.
Data reflect the absolute volumetric BMD changes from baseline, with blue/green representing higher volumetric BMD, yellow/orange representing lower volumetric BMD, and black representing no change. Abbreviations: volumetric BMD, volumetric BMD.



Supplemental Figure 8. Cross-sectional images showing the time course of the average changes in volumetric BMD after denosumab discontinuation in 11 dialysis patients.
Data reflect absolute volumetric BMD changes from baseline, with blue/green representing higher volumetric BMD, yellow/orange representing lower volumetric BMD, and black representing no change. Abbreviations: volumetric BMD, volumetric BMD.