Supplemental Data

Figure Legend:

Figure S1. Degradation of modulus in cortical beams loaded in bending fatigue. To compare change in modulus during fatigue loading, secant modulus (E) at a given cycle was normalized by E_i and plotted against normalized fatigue cycles (N/N_f). (a) Typical E/E_i history during fatigue loading of a beam illustrating the three distinct regions of response, and (b) E/E_i history of medial and lateral beams from the VEH, ALN0.2 and ALN1.0 groups tested at each of the six stress amplitudes. The lines represent polynomial fits to the pooled data for each group. According to the distinct transitions in E with cyclic loading, the responses were divided into three regions. Overall, beams from the drug-treated groups exhibited a faster reduction in E compared to those from the VEH. These differences were evident from the onset of fatigue loading, but were most pronounced towards the end of fatigue life, i.e., region III.

Tables:

	Cortex	VEH	ALN0.2	ALN1.0
# of beams	M	17	23	21
	L	12	9	10
# of beams reaching	M	3	10	8
2.5 mm limit	L	8	9	8
E_i (GPa)	M	11.0±1.2	10.3±1.4	8.8±1.1[a,b]
	L	7.2±1.4[c]	7.0±0.8[c]	6.0±0.9[c]
E_f (GPa)	M	6.2±1.9	5.1±1.4	4.3±1.7 [a]
	L	4.1±1.0[c]	3.8±0.8[c]	3.8±0.7
ΔE (GPa)	M	4.8±1.7	5.2±1.4	4.7±0.9
	L	3.1±1.4	3.2±1.0	2.3±1.1
ΔE (%)	M	44.1±14.7	50.7±12.5	54.1±9.1
	L	42.0±15.5	44.6±12.2	36.5±14.3[c]
On.Ar (%)	M	58.3±6.5	53.7±9.1	50.4±8.8[a]
	L	53.1±7.1	48.7±10.8	47.1±9.1
On.Dn (#/mm^2)	M	48.6±9.2	44.3±9.1	48.9±10.2
	L	45.8±9.7	39.9±8.8	44.8±8.0
On.Ar (x10^3 μm^2)	M	12.2±1.6	12.4±2.5	10.5±1.8[a]
	L	12.3±4.5	12.3±1.5	10.8±2.7
Ca.Ar (%)	M	2.0±0.5	2.4±0.5	2.3±0.6
	L	3.2±1.0[c]	3.0±1.0[c]	3.1±2.1
Ca.Ar (x10^3 μm^2)	M	0.41±0.11	0.51±0.16	0.46±0.18
	L	0.68±0.40[c]	0.74±0.45[c]	0.63±0.40

Table S1. Comparison of biomechanical and micro-architectural traits for beams machined from medial (M) and lateral (L) cortices. Data represented as mean ± SD were analyzed by ANOVA followed by Tukey HSD: vs. control (VEH), [a] $p<0.05$; vs. ALN0.2, [b] $p<0.05$; vs. M, [c] $p<0.05$. Only 2 (both VEH-treated, medial beams, see Figure 3) reached 250,000 cycles prior to failure.

σ_a (MPa)	Cortex	VEH	ALN0.2	ALN1.0
52	M	$7.77x10^4$	$6.06x10^4$	$1.95x10^4$
	L	$1.45x10^4$	$7.43x10^3$	$5.00x10^3$
60	M	$1.91x10^4$	$1.41x10^4$	$4.11x10^3$
	L	$2.65x10^3$	$6.00x10^2$	$1.03x10^3$
67	M	$6.48x10^3$	$4.56x10^3$	$1.24x10^3$
	L	$4.90x10^1$	$1.50x10^2$	$1.01x10^3$
75	M	$2.14x10^3$	$1.44x10^3$	$3.63x10^2$
	L	$5.60x10^1$	$3.29x10^2$	$8.35x10^1$
85	M	$6.28x10^2$	$4.03x10^2$	$9.32x10^1$
	L	$6.00x10^1$	$2.73x10^2$	$3.40x10^1$

Table S2. Average number of cycles to failure for a given applied stress (σ_a) for beams machined from medial (M) and lateral (L) cortices.

	VEH	ALN0.2	ALN1.0
Tb.Th (µm)	47±5	47±4	49±5
Tb.Sp (µm)	287±117	244±50	190±29[a,b]
Tb.N (mm^{-1})	3.3±0.9	3.5±0.6	4.3±0.6[a,b]
Tb.Pf (mm^{-1})	2.4±1.8	2.1±0.9	1.6±1.7
Tb.Ar/Ma.Ar (%)	15.3±4.6	16.5±3.6	20.5±1.9[a,b]
Tb.BMD (g/cm^3)	0.21±0.03	0.24±0.03	0.24±0.02

Table S3. Trabecular bone traits, as measured by X-ray micro-computed tomography of ribs (n=6/group). Data represented as mean ± SD were analyzed by ANOVA followed by Tukey HSD: vs. control (VEH), [a] $p<0.05$; vs. ALN0.2, [b] $p<0.05$.