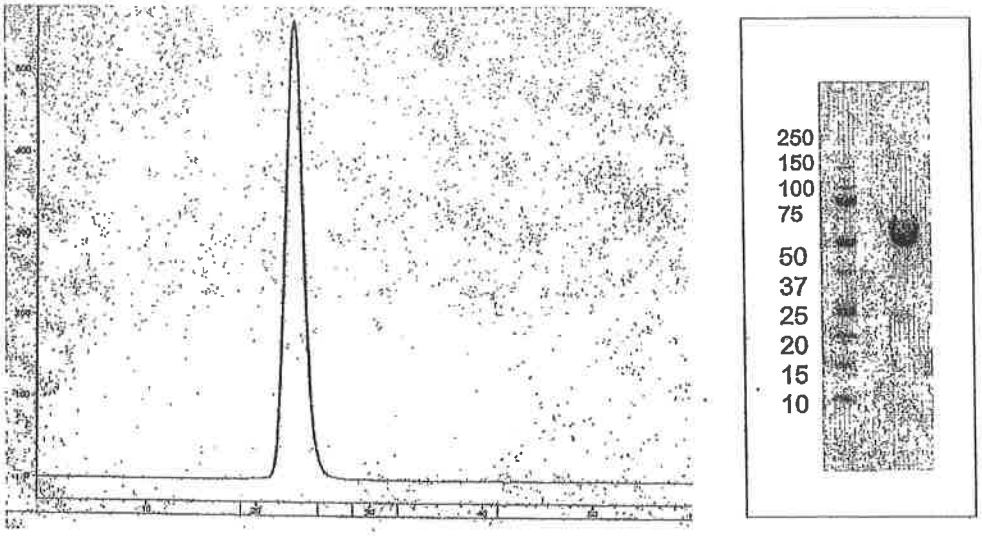


Figure 1

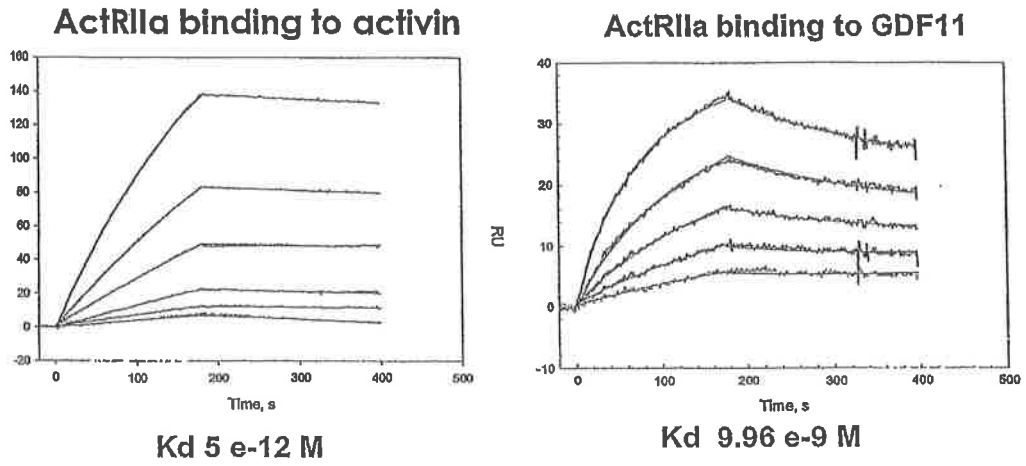

ActRIIa binding to activin
160
140
120
100
80
60
40
20
0
-20
0
100
200
300
400
500
Time, s
RU
Kd 5 e-12 M
ActRIIa binding to GDF11
40
30
20
10
0
-10
0
100
200
300
400
500
Time, s
Kd 9.96 e-9 M

Figure 2

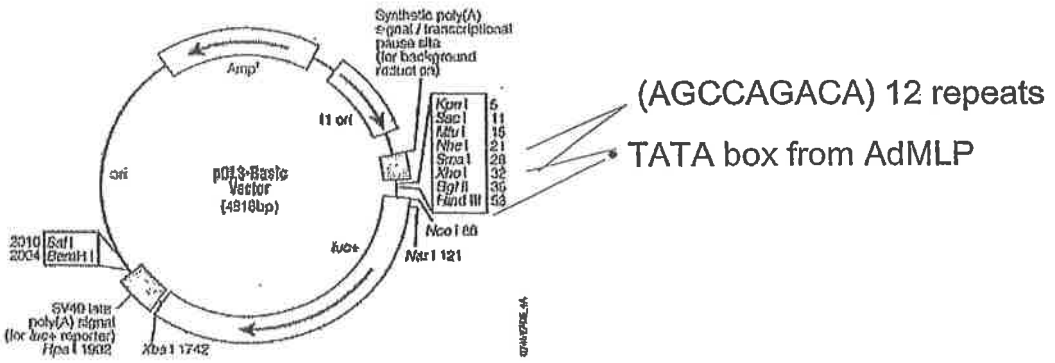

Synthetic poly(A) signal / transcriptional pause site (for background reduction)
Amp
f1 ori
ori
pGL3-Basic Vector (4818bp)
luc+
Kpn I 5
Sac I 11
Mlu I 15
Nhe I 21
Sma I 28
Xho I 32
Bgl II 35
Hind III 53
Nco I 66
Nde I 121
2010 Sal I
2004 BamH I
SV40 late poly(A) signal (for luc+ reporter)
Hpa I 1902
Xba I 1742
(AGCCAGACA) 12 repeats
TATA box from AdMLP

Figure 3

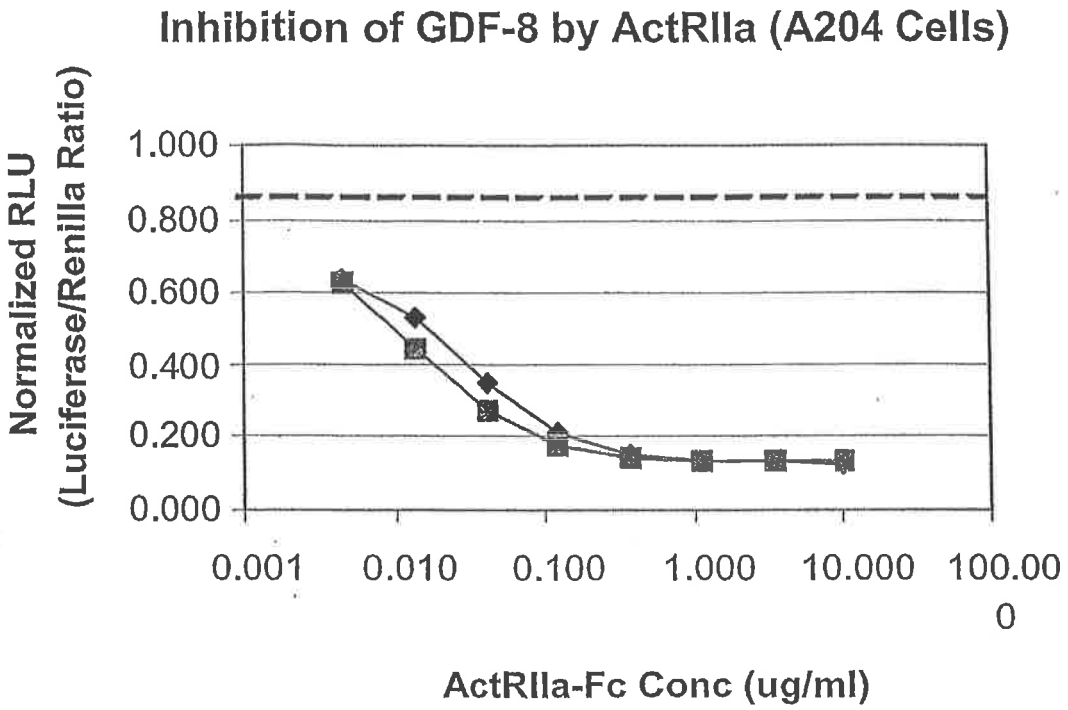

Inhibition of GDF-8 by ActRIIa (A204 Cells)
Normalized RLU
(Luciferase/Renilla Ratio)
1.000
0.800
0.600
0.400
0.200
0.000
0.001
0.010
0.100
1.000
10.000
100.000
ActRIIa-Fc Conc (ug/ml)

Figure 4

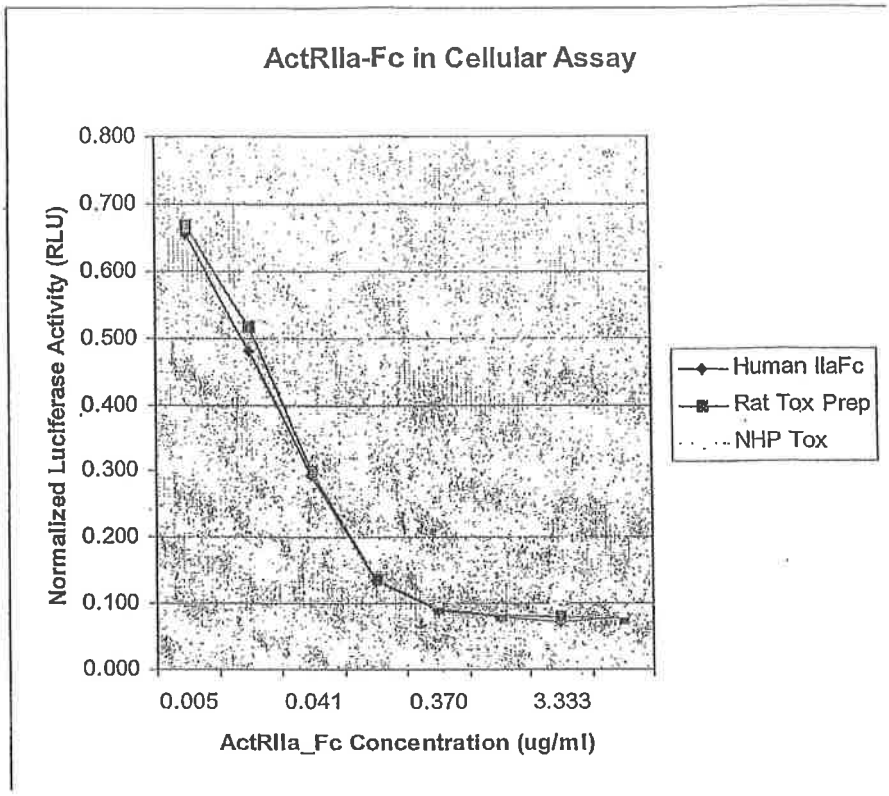

ActRIIa-Fc in Cellular Assay
Normalized Luciferase Activity (RLU)
0.800
0.700
0.600
0.500
0.400
0.300
0.200
0.100
0.000
0.005
0.041
0.370
3.333
ActRIIa_Fc Concentration (ug/ml)
Human IIaFc
Rat Tox Prep
NHP Tox

Figure 5

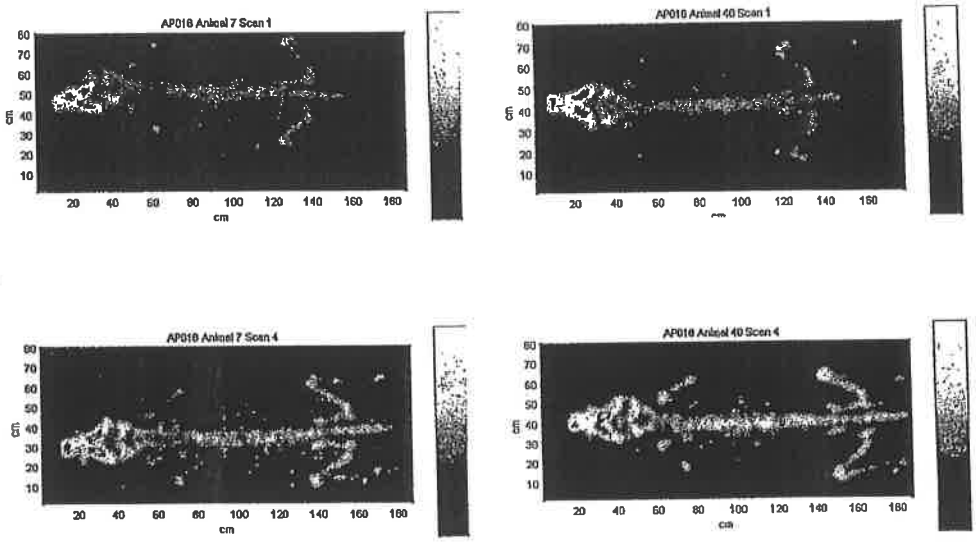

AP018 Animal 7 Scan 1
AP018 Animal 40 Scan 1
AP018 Animal 7 Scan 4
AP018 Animal 40 Scan 4
cm

Figure 6

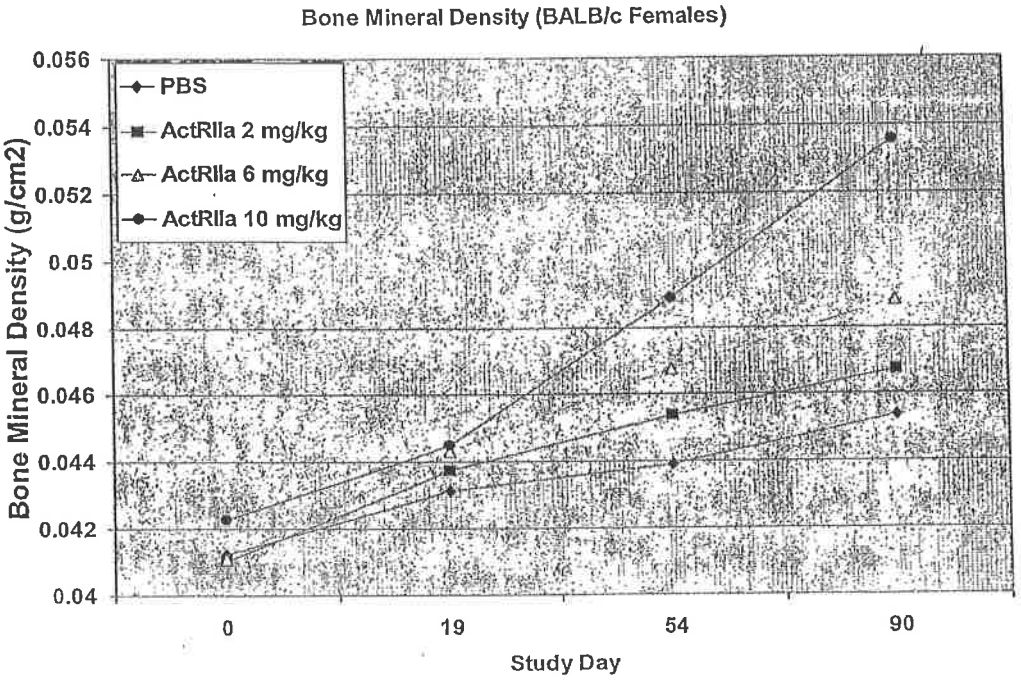

Bone Mineral Density (BALB/c Females)
Bone Mineral Density (g/cm2)
0.056
0.054
0.052
0.05
0.048
0.046
0.044
0.042
0.04
PBS
ActRIIa 2 mg/kg
ActRIIa 6 mg/kg
ActRIIa 10 mg/kg
0
19
54
90
Study Day

Figure 7

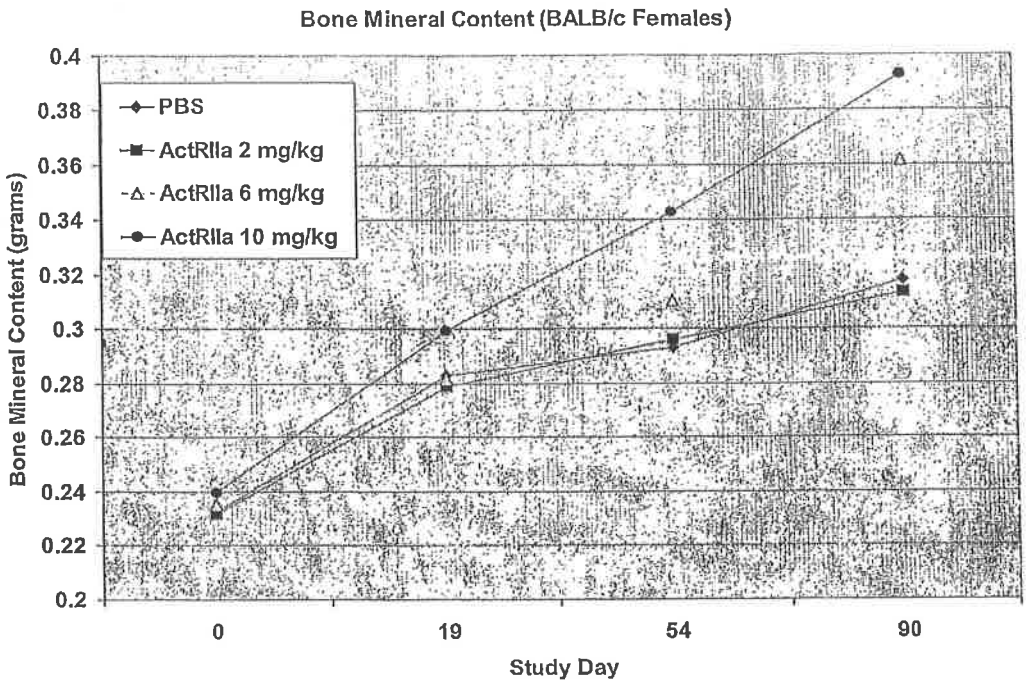

Bone Mineral Content (BALB/c Females)
Bone Mineral Content (grams)
0.4
0.38
0.36
0.34
0.32
0.3
0.28
0.26
0.24
0.22
0.2
PBS
ActRIIa 2 mg/kg
ActRIIa 6 mg/kg
ActRIIa 10 mg/kg
0
19
54
90
Study Day

Figure 8

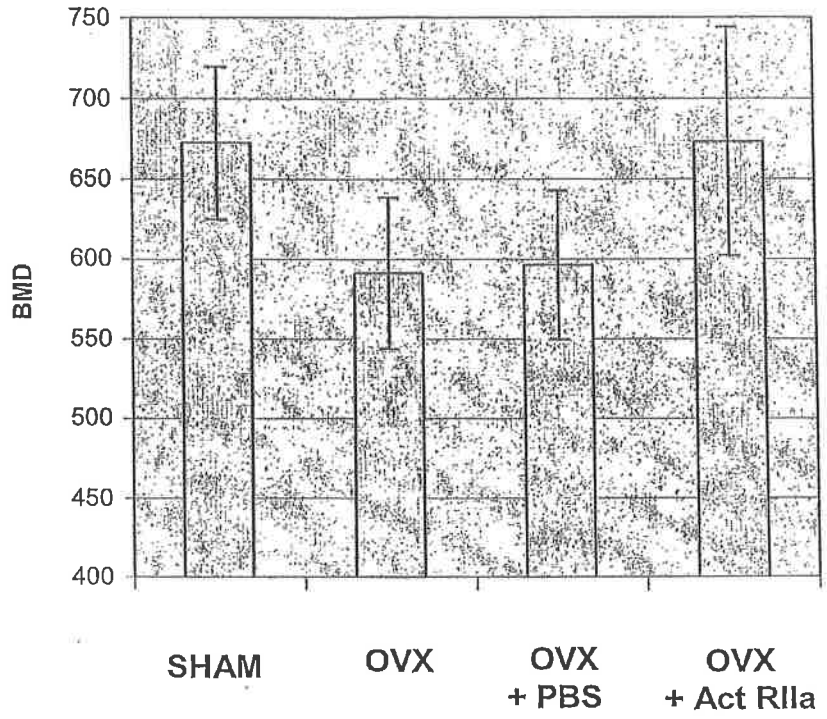

750
700
650
600
550
500
450
400
BMD
SHAM
OVX
OVX
+ PBS
OVX
+ Act RIIa

Figure 9

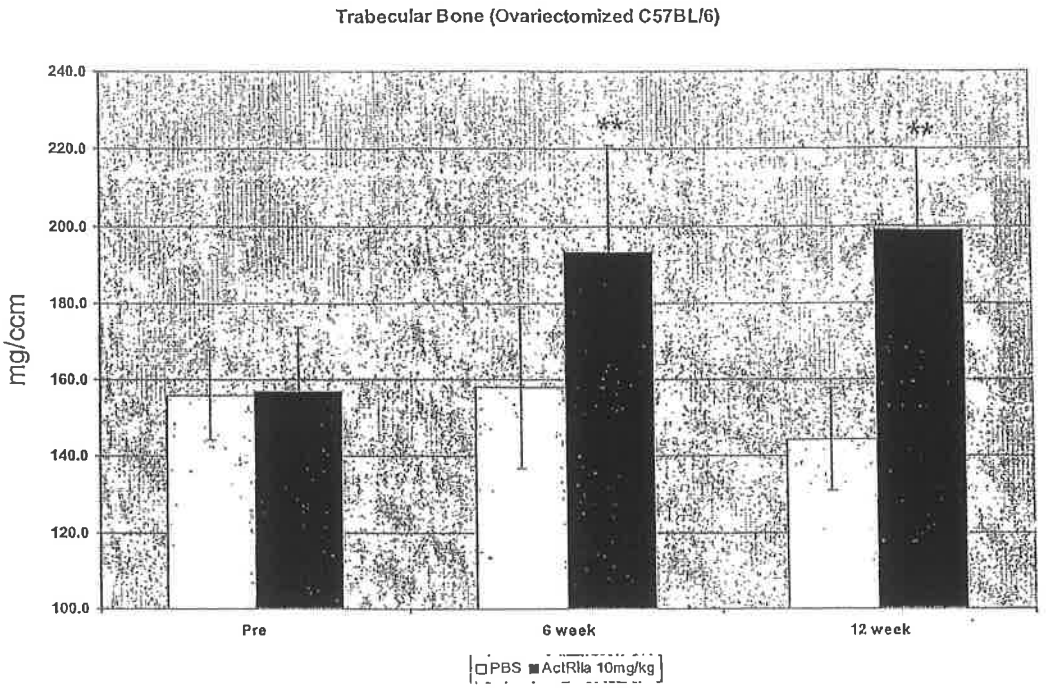

Trabecular Bone (Ovariectomized C57BL/6)
mg/ccm
240.0
220.0
200.0
180.0
160.0
140.0
120.0
100.0
**
**
Pre
6 week
12 week
PBS
ActRIIa 10mg/kg

Figure 10

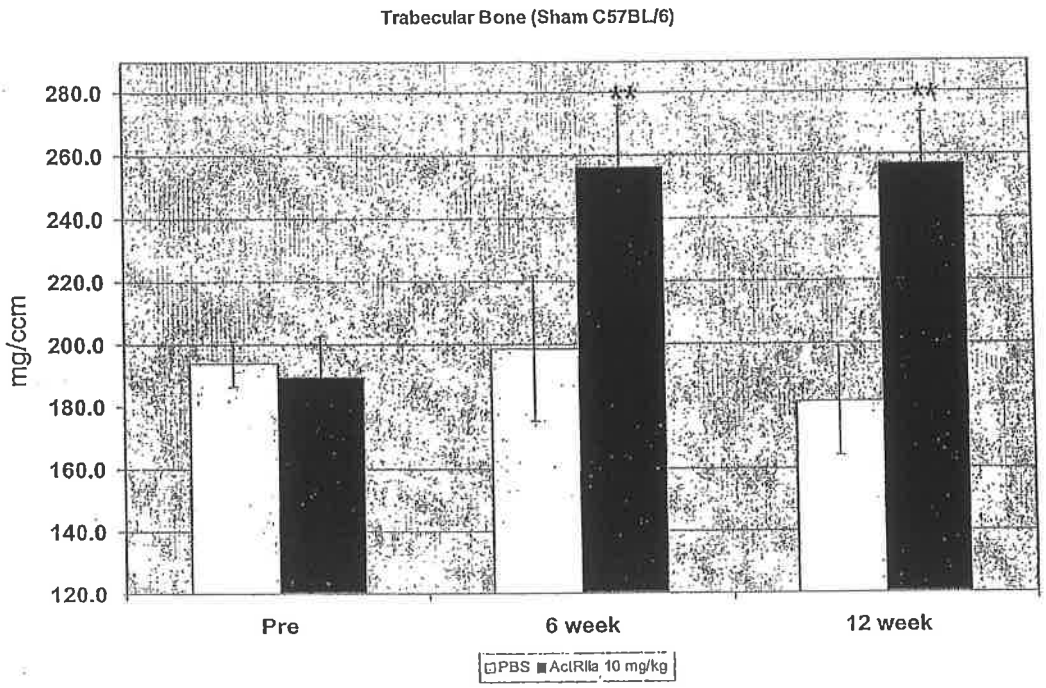

Trabecular Bone (Sham C57BL/6)
mg/ccm
280.0
260.0
240.0
220.0
200.0
180.0
160.0
140.0
120.0
**
**
Pre
6 week
12 week
PBS
ActRIIa 10 mg/kg

Figure 11

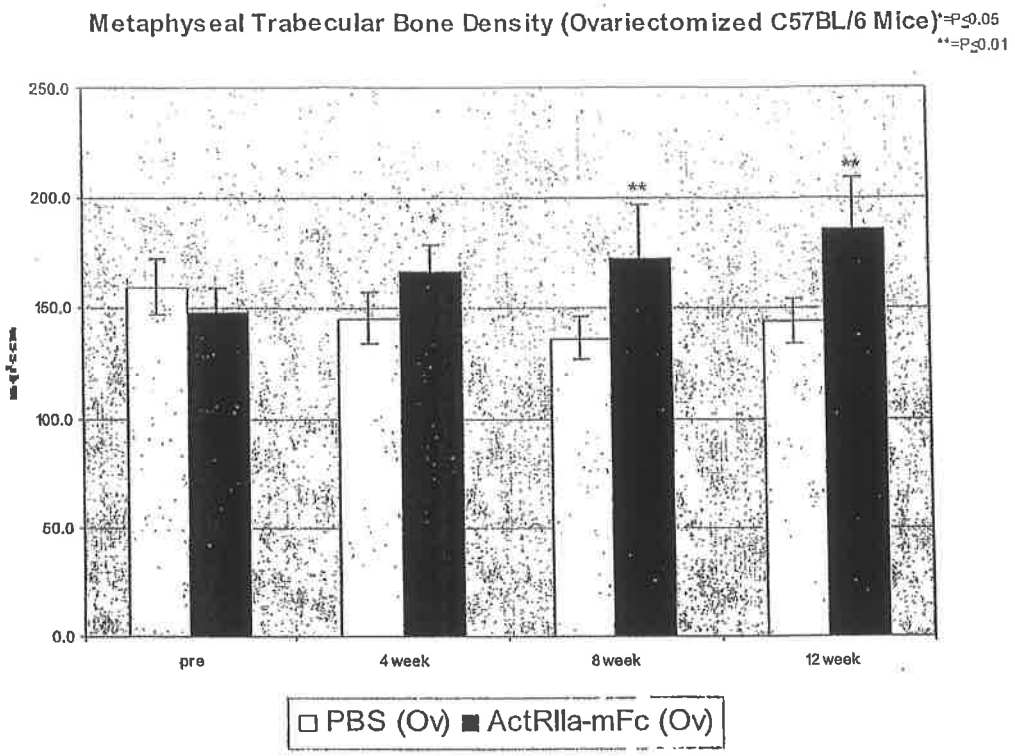

Metaphyseal Trabecular Bone Density (Ovariectomized C57BL/6 Mice)
*=P≤0.05
**=P≤0.01
250.0
200.0
150.0
100.0
50.0
0.0
pre
4 week
8 week
12 week
**
**
PBS (Ov)
ActRIIa-mFc (Ov)

Figure 12

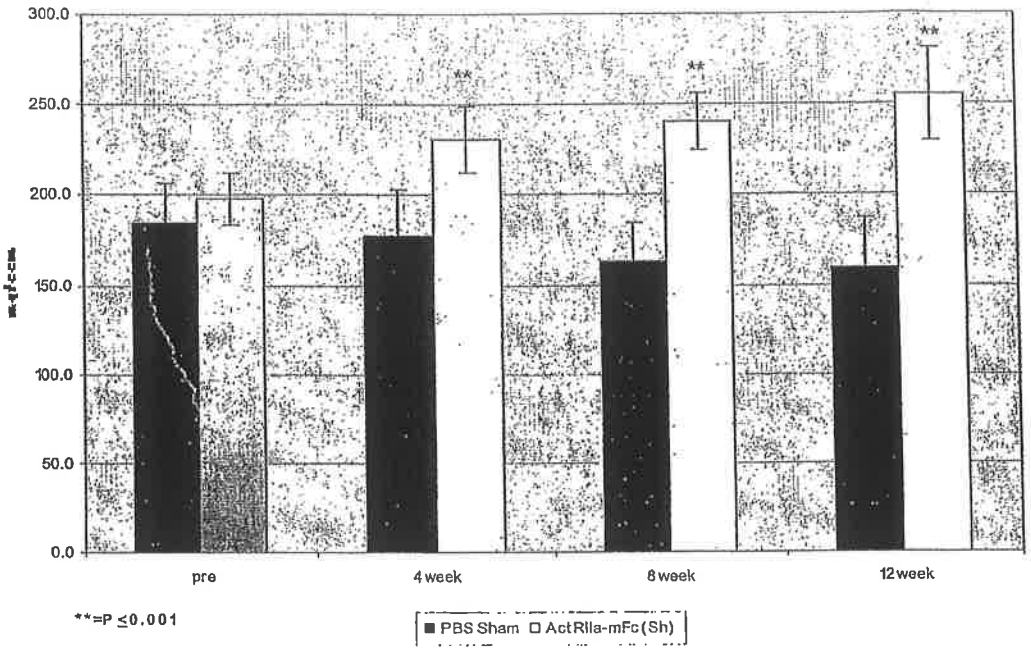

Metaphyseal Trabecular Bone Density (Sham Operated C57BL/6 mice)
300.0
250.0
200.0
150.0
100.0
50.0
0.0
pre
4 week
8 week
12 week
**=P ≤0.001
PBS Sham
ActRIIa-mFc(Sh)

Figure 13

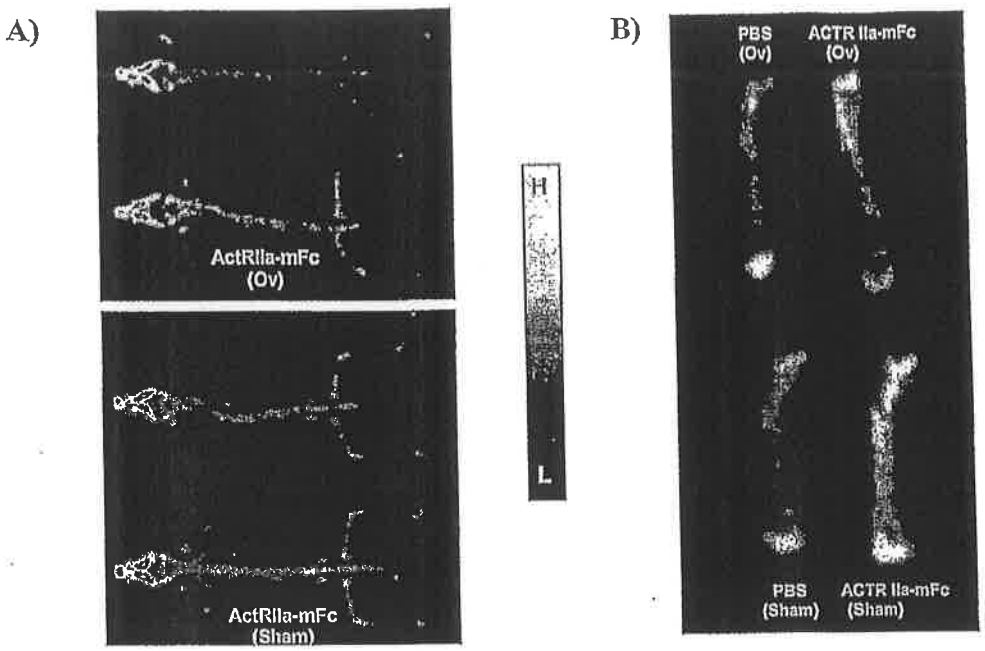

A)
ActRIIa-mFc
(Ov)
ActRIIa-mFc
(Sham)
H
L
B)
PBS
(Ov)
ACTR IIa-mFc
(Ov)
PBS
(Sham)
ACTR IIa-mFc
(Sham)

Figure 14

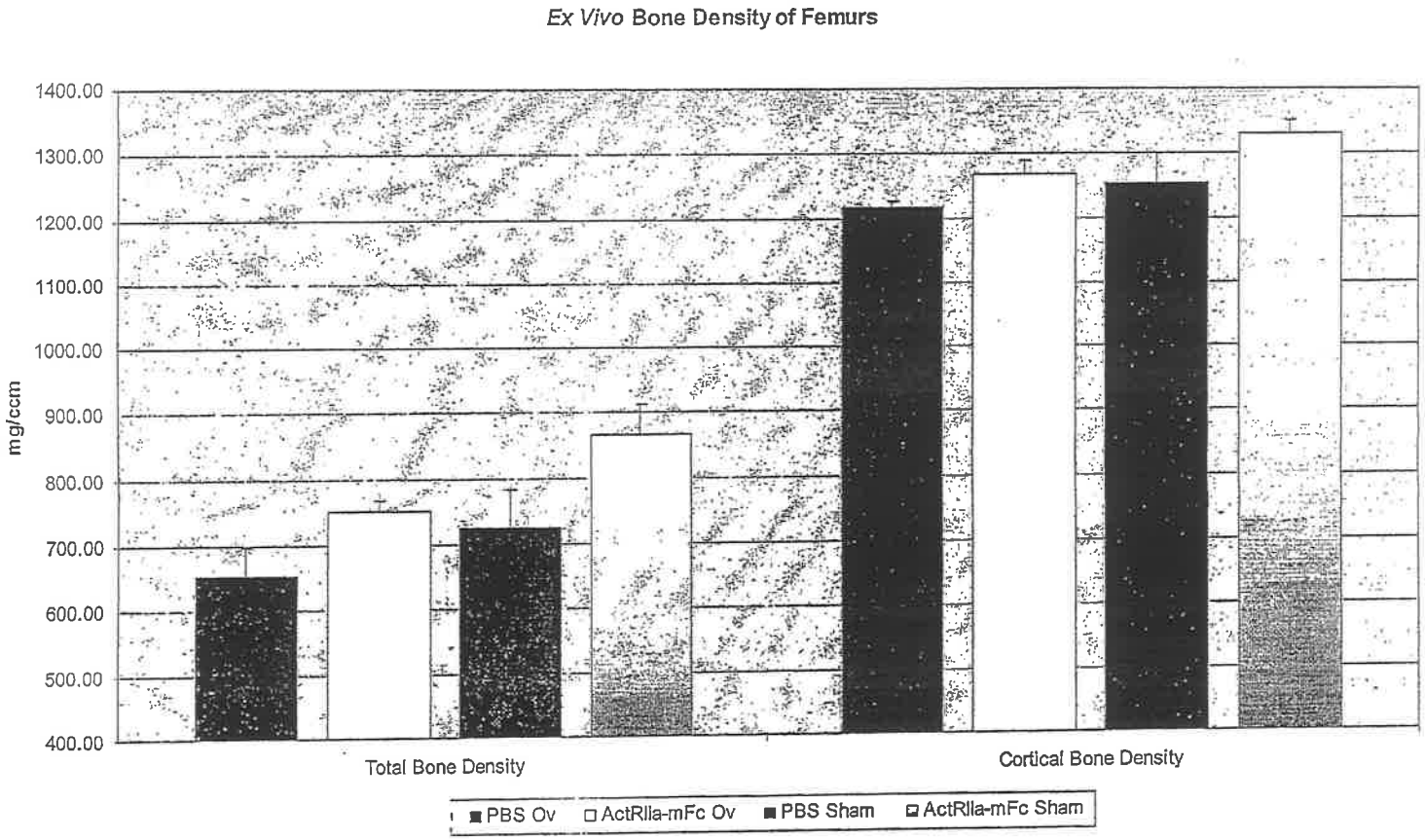

Ex Vivo Bone Density of Femurs
1400.00
1300.00
1200.00
1100.00
1000.00
900.00
800.00
700.00
600.00
500.00
400.00
mg/ccm
Total Bone Density
Cortical Bone Density
PBS Ov
ActRIIa-mFc Ov
PBS Sham
ActRIIa-mFc Sham

Figure 15

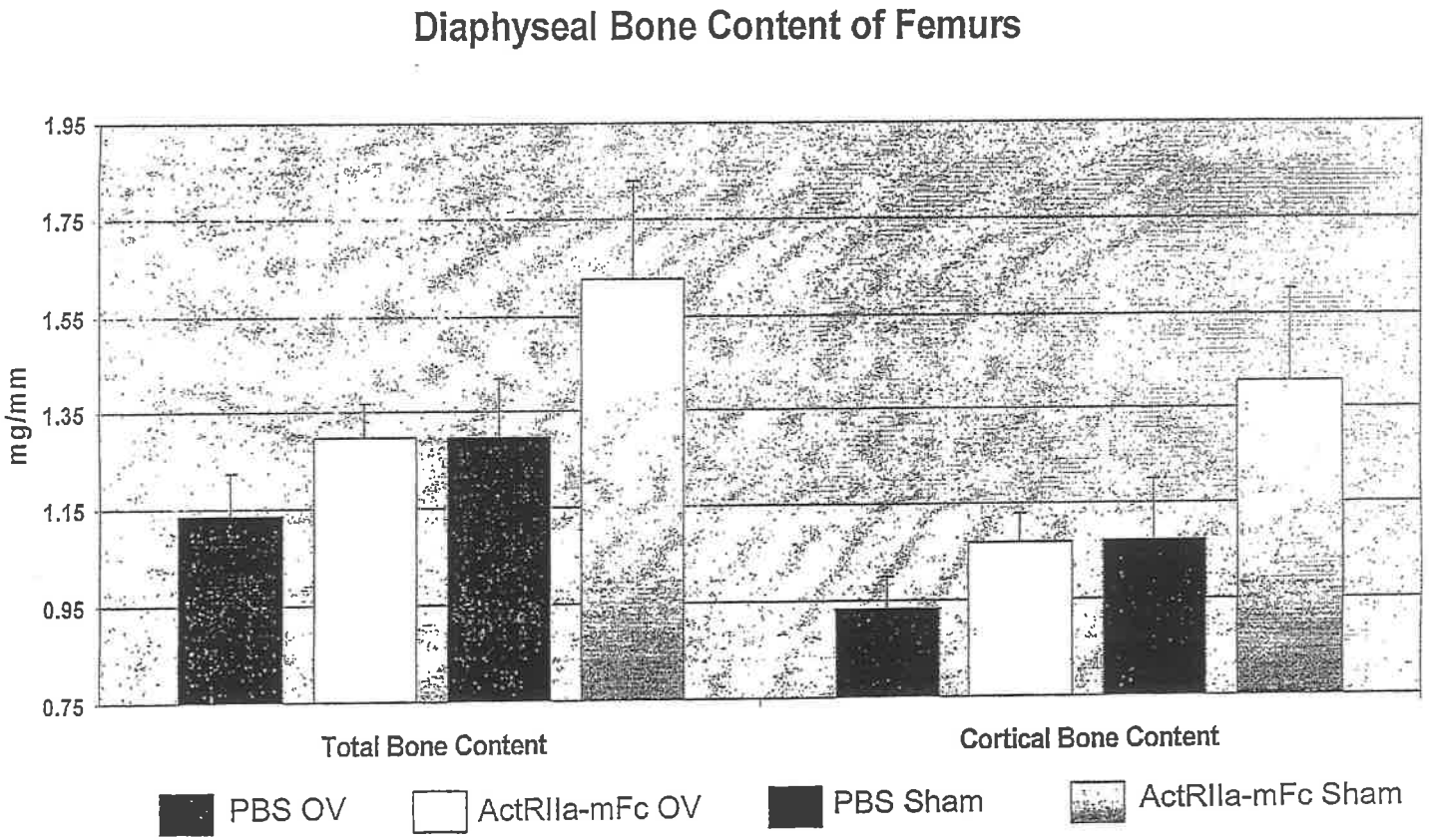

Diaphyseal Bone Content of Femurs
1.95
1.75
1.55
1.35
1.15
0.95
0.75
mg/mm
Total Bone Content
Cortical Bone Content
PBS OV
ActRIIa-mFc OV
PBS Sham
ActRIIa-mFc Sham

Figure 16

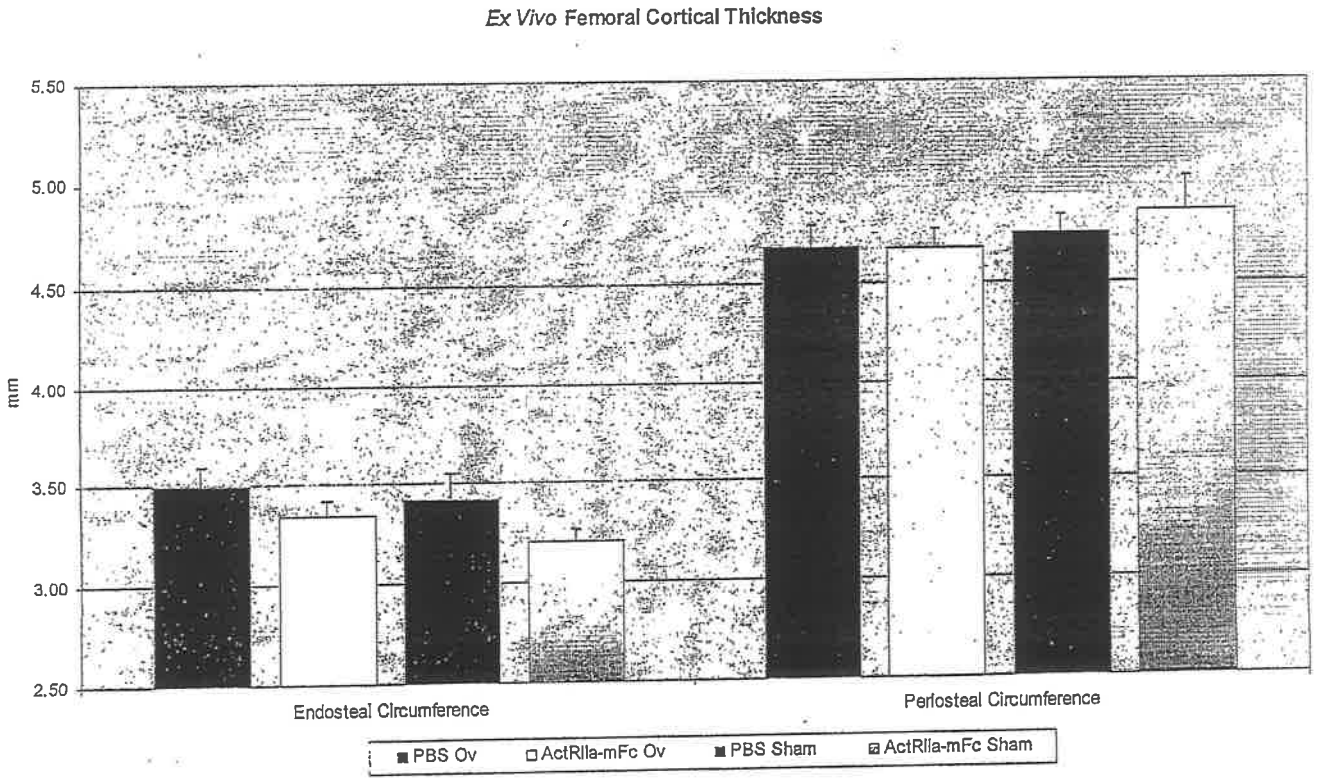

Ex Vivo Femoral Cortical Thickness
5.50
5.00
4.50
4.00
3.50
3.00
2.50
mm
Endosteal Circumference
Periosteal Circumference
PBS Ov
ActRIIa-mFc Ov
PBS Sham
ActRIIa-mFc Sham

Figure 17

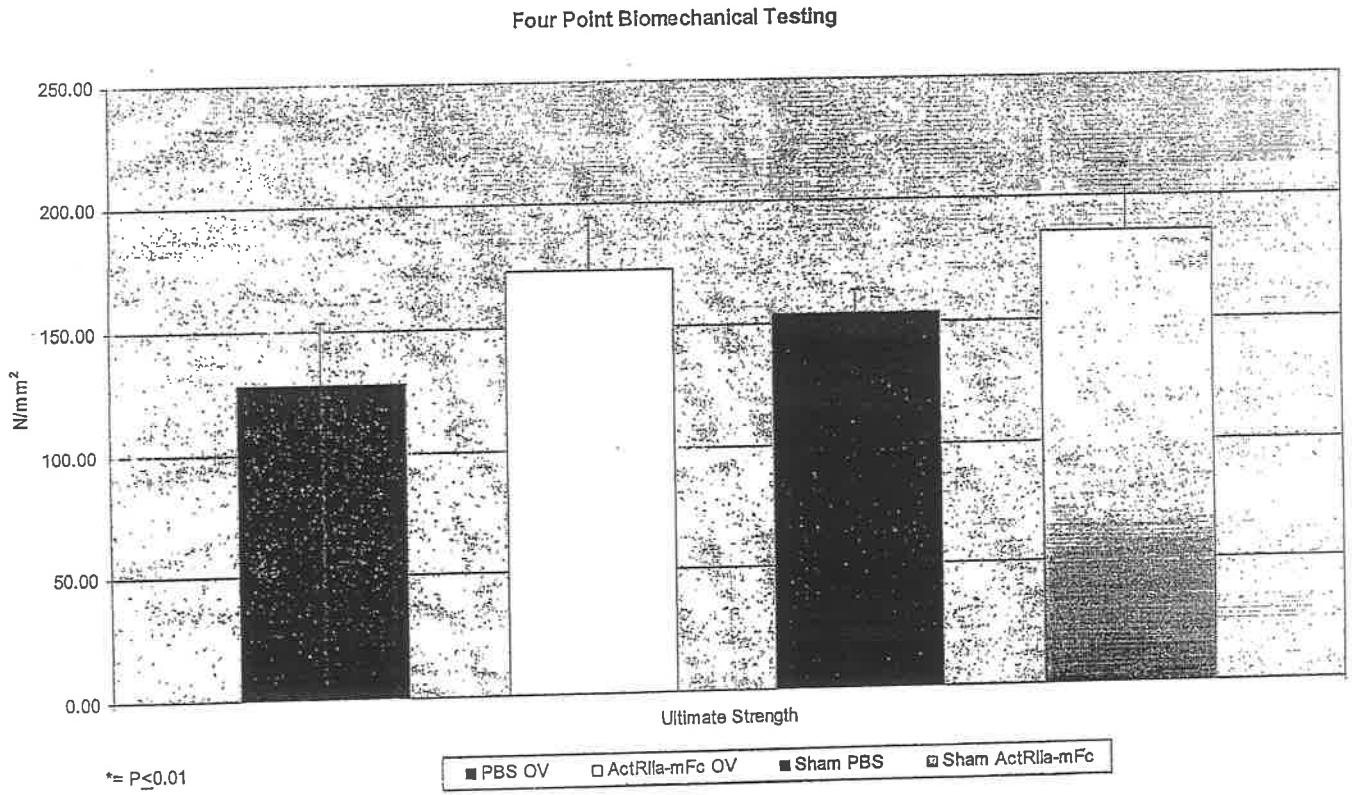
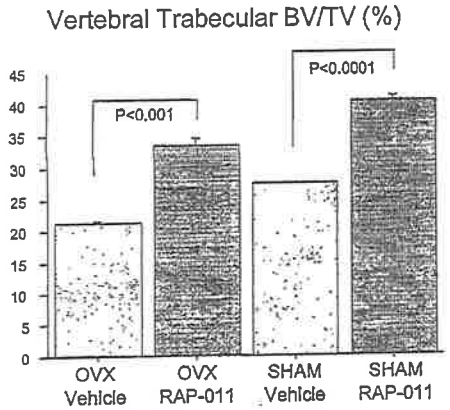
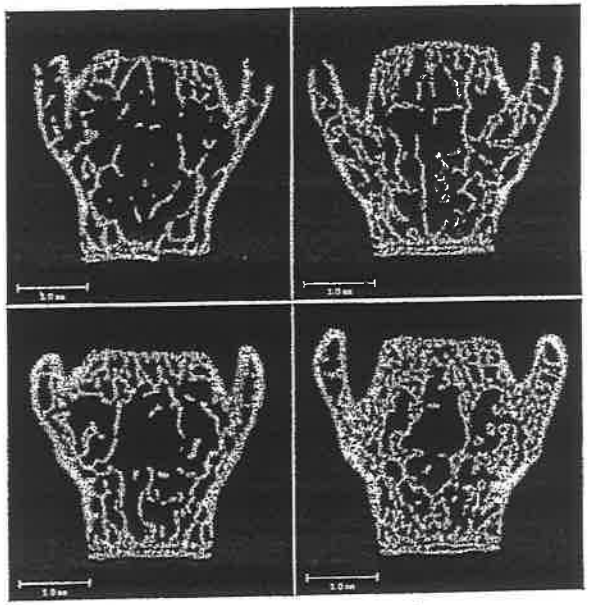

Four Point Biomechanical Testing
250.00
200.00
150.00
100.00
50.00
0.00
N/mm²
Ultimate Strength
*= P≤0.01
PBS OV
ActRIIa-mFc OV
Sham PBS
Sham ActRIIa-mFc

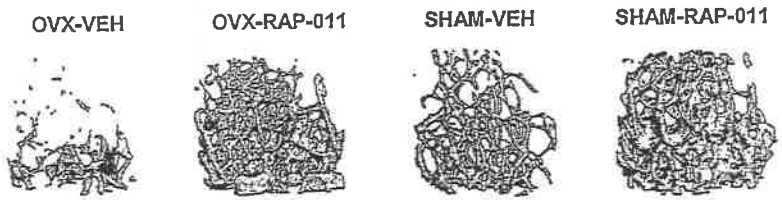
Figure 18





microCT data shown at end of study (age 24 wks)

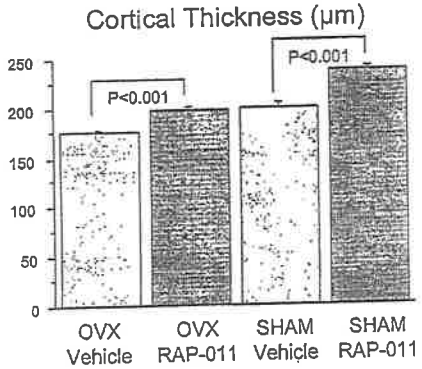
Figure 19



@ 12 weeks	OVX-VEH	OVX-RAP-011	SHAM-VEH	SHAM-RAP-011
Tb N (mm^{-1})	2.1 ± 0.3	3.5 ± 0.2 **	3.0 ± 0.2	4.1 ± 0.2 **
Tb Sp (µm)	486.2 ± 79	283.9 ± 21 **	332.4 ± 25	230.2 ± 12 **
Conn D (mm^{-3})	8.4 ± 6	85.1 ± 13.7 **	41.4 ± 14.8	131.2 ± 16.5 **

** p< 0.01 vs VEH

Figure 20


Cortical Thickness (µm)
250
200
150
100
50
0
P<0.001
P<0.001
OVX Vehicle
OVX RAP-011
SHAM Vehicle
SHAM RAP-011

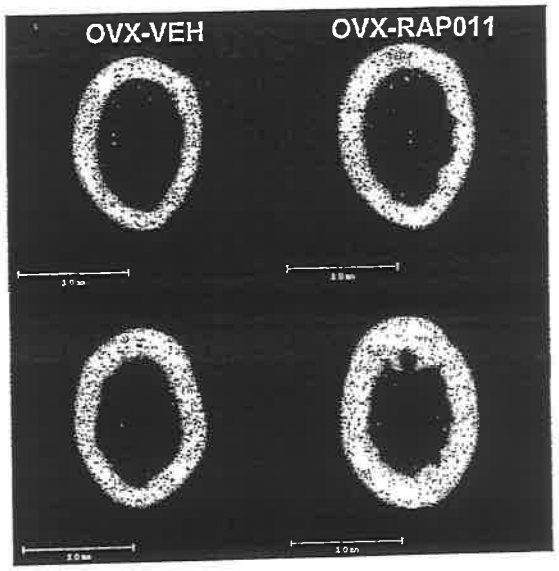
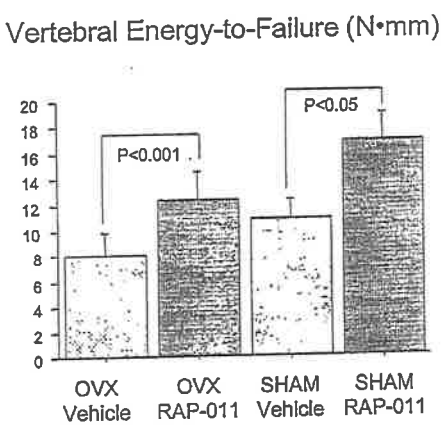

OVX-VEH
OVX-RAP011

Figure 21


Vertebral Energy-to-Failure (N•mm)
20
18
16
14
12
10
8
6
4
2
0
P<0.001
P<0.05
OVX Vehicle
OVX RAP-011
SHAM Vehicle
SHAM RAP-011

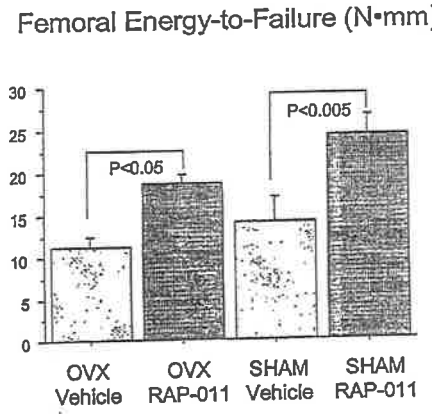
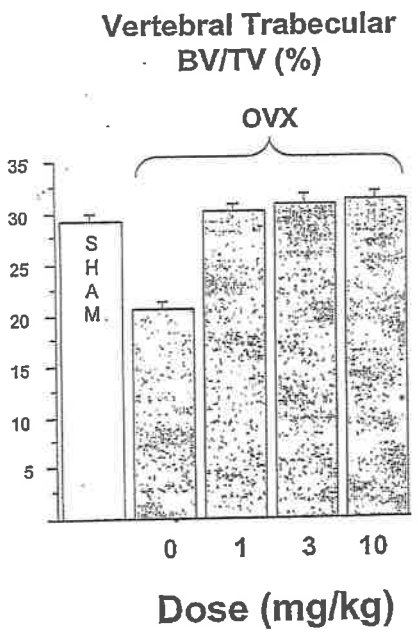

Femoral Energy-to-Failure (N•mm)
30
25
20
15
10
5
0
P<0.05
P<0.005
OVX Vehicle
OVX RAP-011
SHAM Vehicle
SHAM RAP-011

Figure 22


Vertebral Trabecular
BV/TV (%)
OVX
35
30
25
20
15
10
5
S
H
A
M
0
1
3
10
Dose (mg/kg)

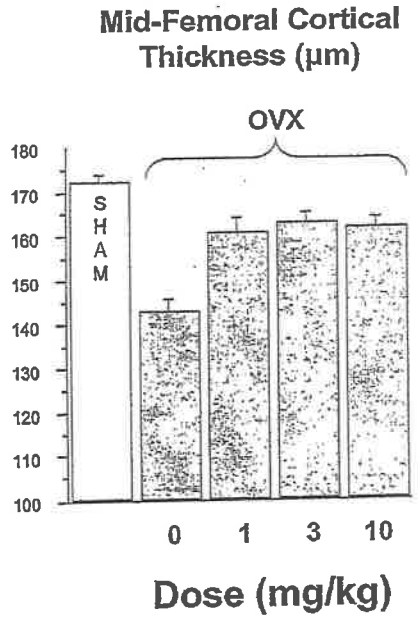

Mid-Femoral Cortical
Thickness (µm)
OVX
180
170
160
150
140
130
120
110
100
S
H
A
M
0
1
3
10
Dose (mg/kg)

Figure 23

	BV/TV (%)	ES/BS (%)	Nob/BPm (/mm)	Noc/BPm (/mm)	Ms/Bs (%)	MAR (um/day)	BFR/BSd (um^3/um^2/day)
PBS mean	7.53	17.36	49.33	7.55	4.206	0.704	0.029
RAP-011 mean	10.88	13.93	40.89	5.34	7.546	0.852	0.065
P value	*0.002*	*0.03*	*0.02*	*0.01*	*0.008*	*0.03*	*0.002*

Figure 24