

**Supplement material**

**Table I. Postmenopausal Hormone Therapy Effect on Change in Biomarker Levels according to Number of Minor Alleles of Estrogen Receptor SNPs<sup>1</sup>**

Biomarker	E+P vs. E+P Placebo (95% CI)			E-alone vs. E-alone Placebo (95% CI)			Marginal p <sup>2</sup>	Corrected p <sup>3</sup>
	Number of minor alleles			Number of minor alleles				
	0	1	2	0	1	2		
<b>LDL-C, mmol/L</b>								
ESR1 IVS-401	-0.51(-0.73,-0.29)	-0.52(-0.71,-0.33)	-0.52(-0.75,-0.29)	-0.73(-0.98,-0.48)	-0.63(-0.83,-0.43)	-0.53(-0.78,-0.28)	.273	1.000
ESR1 Exon 1+30	-0.39(-0.61,-0.18)	-0.46(-0.64,-0.27)	-0.52(-0.74,-0.29)	-0.72(-0.97,-0.47)	-0.56(-0.76,-0.36)	-0.41(-0.66,-0.15)	.115	0.973
ESR1 IVS1-354	-0.41(-0.60,-0.22)	-0.43(-0.60,-0.25)	-0.43(-0.68,-0.19)	-0.62(-0.84,-0.41)	-0.50(-0.69,-0.31)	-0.37(-0.64,-0.11)	.068	0.909
ESR1 IVS1-1415	-0.41(-0.59,-0.23)	-0.43(-0.60,-0.26)	-0.45(-0.71,-0.20)	-0.58(-0.78,-0.37)	-0.50(-0.69,-0.32)	-0.43(-0.71,-0.15)	.016	0.389
ESR1 IVS1-1505	-0.52(-0.73,-0.30)	-0.51(-0.70,-0.33)	-0.50(-0.74,-0.27)	-0.73(-0.98,-0.49)	-0.62(-0.82,-0.42)	-0.50(-0.76,-0.25)	.226	1.000
ESR1 IVS1-1989	-0.48(-0.63,-0.32)	-0.49(-0.68,-0.27)	-0.49(-0.84,-0.14)	-0.66(-0.83,-0.48)	-0.48(-0.71,-0.26)	-0.31(-0.71,0.09)	.285	1.000
ESR2 1730G	-0.62(-0.82,-0.42)	-0.56(-0.73,-0.38)	-0.49(-0.74,-0.25)	-0.67(-0.89,-0.45)	-0.69(-0.88,-0.50)	-0.71(-0.98,-0.44)	.227	0.999
<b>HDL-C, mmol/L</b>								
ESR1 IVS-401	0.13(0.07,0.20)	0.13(0.08,0.19)	0.14(0.06,0.21)	0.23(0.15,0.31)	0.22(0.16,0.29)	0.22(0.14,0.29)	.462	1.000
ESR1 Exon 1+30	0.12(0.06,0.19)	0.11(0.06,0.17)	0.10(0.03,0.17)	0.20(0.13,0.28)	0.20(0.14,0.26)	0.20(0.12,0.28)	.646	1.000
ESR1 IVS1-354	0.12(0.06,0.18)	0.12(0.07,0.18)	0.13(0.05,0.20)	0.23(0.16,0.30)	0.21(0.15,0.26)	0.18(0.10,0.26)	.371	1.000
ESR1 IVS1-1415	0.12(0.06,0.17)	0.11(0.06,0.17)	0.11(0.03,0.19)	0.21(0.15,0.27)	0.20(0.14,0.56)	0.19(0.10,0.28)	.651	1.000
ESR1 IVS1-1505	0.13(0.06,0.20)	0.13(0.07,0.19)	0.13(0.06,0.20)	0.24(0.16,0.31)	0.22(0.16,0.28)	0.20(0.12,0.28)	.415	1.000
ESR1 IVS1-1989	0.10(0.05,0.15)	0.10(0.04,0.16)	0.10(-0.01,0.21)	0.19(0.13,0.24)	0.19(0.12,0.26)	0.19(0.07,0.32)	.990	1.000
ESR2 1730G	0.11(0.05,0.17)	0.10(0.05,0.16)	0.09(0.01,0.16)	0.20(0.13,0.27)	0.19(0.13,0.26)	0.18(0.10,0.27)	.919	1.000
<b>Triglycerides, mmol/L</b>								
ESR1 IVS-401	0.00(-0.22,0.22)	0.00(-0.16,0.23)	0.07(-0.16,0.31)	0.27(0.01,0.52)	0.22(0.02,0.43)	0.19(-0.06,0.44)	.086	0.950
ESR1 Exon 1+30	0.00(-0.21,0.23)	0.06(-0.12,0.25)	0.11(-0.11,0.34)	0.32(0.07,0.57)	0.25(0.05,0.46)	0.19(-0.06,0.44)	.131	0.999
ESR1 IVS1-354	0.10(-0.08,0.30)	0.10(-0.08,0.27)	0.08(-0.16,0.33)	0.31(0.10,0.53)	0.29(0.10,0.48)	0.27(0.00,0.54)	.146	0.998
ESR1 IVS1-1415	0.11(-0.07,0.29)	0.10(-0.07,0.27)	0.09(-0.16,0.34)	0.32(0.12,0.53)	0.29(0.10,0.48)	0.26(-0.02,0.54)	.123	0.998
ESR1 IVS1-1505	0.02(-0.19,0.24)	0.04(-0.15,0.23)	0.06(-0.18,0.29)	0.27(0.02,0.52)	0.24(0.03,0.44)	0.21(-0.05,0.46)	.105	0.994
ESR1 IVS1-1989	0.15(-0.00,0.00)	0.25(0.05,0.46)	0.36(-0.00,0.72)	0.39(0.21,0.57)	0.38(0.15,0.61)	0.37(-0.04,0.78)	.504	1.000
ESR2 1730G	0.18(-0.02,0.38)	0.23(0.05,0.40)	0.27(0.02,0.52)	0.46(0.23,0.68)	0.40(0.21,0.59)	0.35(0.07,0.62)	.828	1.000
<b>C-reactive protein, mg/L</b>								
ESR1 IVS-401	-0.28(-2.90,2.35)	-0.06(-2.34,2.21)	0.15(-2.64,2.95)	0.03(-2.97,3.04)	1.76(-0.67,4.20)	3.50(0.47,6.52)	.244	1.000
ESR1 Exon 1+30	-0.16(-2.76,2.45)	0.39(-1.82,2.59)	0.93(-1.76,3.62)	0.65(-2.32,3.62)	2.32(-0.05,4.70)	4.00(1.00,6.99)	.459	1.000
ESR1 IVS1-354	0.31(-1.97,2.59)	0.46(-1.63,2.56)	0.61(-2.34,3.56)	0.74(-1.80,3.29)	2.78(0.54,5.03)	4.82(1.67,7.97)	.232	1.000

Biomarker	E+P vs. E+P Placebo (95% CI)			E-alone vs. E-alone Placebo (95% CI)			Marginal p <sup>2</sup>	Corrected p <sup>3</sup>
	Number of minor alleles			Number of minor alleles				
	0	1	2	0	1	2		
ESR1 IVS1-1415	0.46(-1.71,2.63)	0.51(-1.58,2.60)	0.56(-2.51,3.63)	1.86(-0.59,4.32)	2.55(0.33,4.78)	3.24(-0.06,6.55)	.889	1.000
ESR1 IVS1-1505	-0.17(-2.76,2.42)	0.09(-2.16,2.35)	0.35(-2.44,3.15)	0.44(-2.51,3.40)	1.99(-0.42,4.40)	3.54(0.49,6.59)	0.374	1.000
ESR1 IVS1-1989	0.53(-1.38,2.43)	1.02(-1.38,3.43)	1.52(-2.67,5.72)	1.99(-0.17,4.14)	4.10(1.39,6.81)	6.21(1.38,11.05)	0.705	1.000
ESR2 1730G	0.23(-2.17,2.64)	1.83(-0.34,4.01)	3.43(0.43,6.43)	3.75(1.10,6.40)	2.96(0.64,5.28)	2.17(-1.12,5.47)	0.280	1.000
<b>E-selectin, mcg/L</b>								
ESR1 IVS-401	-11.4(-14.9,-7.91)	-11.0(-14.1,-7.97)	-10.7(-14.4,-6.87)	-9.35(-13.5,-5.21)	-10.1(-13.4,-6.79)	-10.9(-15.0,-6.71)	0.233	1.000
ESR1 Exon 1+30	-11.3(-14.8,-7.77)	-11.2(-14.1,-8.16)	-11.0(-14.7,-7.36)	-9.11(-13.2,-5.05)	-10.0(-13.2,-6.78)	-10.9(-15.0,-6.78)	0.234	1.000
ESR1 IVS1-354	-10.6(-13.7,-7.49)	-9.49(-12.3,-6.65)	-8.41(-12.4,-4.39)	-8.89(-12.4,-5.37)	-8.80(-11.9,-5.74)	-8.72(-13.0,-4.39)	0.151	0.999
ESR1 IVS1-1415	-9.94(-12.9,-7.00)	-9.13(-12.0,-6.31)	-8.32(-12.5,-4.14)	-7.86(-11.2,-4.50)	-8.71(-11.7,-5.67)	-9.55(-14.1,-5.03)	0.198	1.000
ESR1 IVS1-1505	-11.1(-14.6,-7.69)	-10.7(-13.7,-7.64)	-10.2(-14.0,-6.39)	-8.33(-12.4,-4.30)	-9.72(-13.0,-6.46)	-11.1(-15.3,-6.95)	0.255	1.000
ESR1 IVS1-1989	-9.36(-11.9,-6.79)	-11.6(-15.1,-8.14)	-13.9(-20.1,-7.66)	-8.23(-11.2,-5.29)	-10.0(-13.7,-6.31)	-11.8(-18.4,-5.20)	0.832	1.000
ESR2 1730G	-9.82(-13.1,-6.53)	-8.24(-11.2,-5.29)	-6.66(-10.8,-2.54)	-7.43(-11.1,-3.76)	-7.77(-11.0,-4.57)	-8.11(-12.7,-3.53)	0.738	1.000
<b>Matrix metalloproteinase-9, mcg/L</b>								
ESR1 IVS-401	75.35(20.45,130.3)	60.84(13.26,108.4)	46.34(-12.8,105.5)	33.62(-30.6,97.79)	37.94(-13.4,89.24)	42.26(-22.4,107.0)	0.505	1.000
ESR1 Exon 1+30	41.06(-13.1,95.18)	37.53(-8.23,83.30)	34.01(-22.4,90.45)	17.15(-44.9,79.20)	19.77(-29.6,69.13)	22.39(-41.2,85.97)	0.856	1.000
ESR1 IVS1-354	70.91(22.78,119.0)	56.27(12.14,100.4)	41.63(-21.2,104.5)	31.66(-23.0,86.31)	39.00(-8.50,86.50)	46.35(-21.3,114.0)	0.594	1.000
ESR1 IVS1-1415	72.09(26.26,117.9)	50.12(6.34,93.91)	28.15(-37.1,93.39)	31.67(-20.4,83.73)	37.67(-9.42,84.77)	43.67(-27.0,114.3)	0.436	1.000
ESR1 IVS1-1505	75.49(21.24,129.7)	58.13(11.07,105.2)	40.78(-18.4,99.97)	36.28(-26.3,98.90)	36.46(-14.2,87.11)	36.64(-28.6,101.8)	0.625	1.000
ESR1 IVS1-1989	51.85(12.40,91.31)	47.57(-4.97,100.1)	43.28(-50.5,137.1)	42.51(-2.07,87.10)	24.59(-30.9,80.05)	6.67(-91.5,104.8)	0.891	1.000
ESR2 1730G	112.6(61.72,163.5)	83.03(37.87,128.2)	53.43(-9.64,116.5)	63.41(7.34,119.5)	68.33(19.29,117.4)	73.25(2.62,143.9)	0.035	0.697
<b>Fibrinogen, g/L</b>								
ESR1 IVS-401	-0.26(-0.498,-0.41)	-0.35(-0.54,-0.15)	-0.43(-0.67,-0.19)	-0.37(-0.63,-0.11)	-0.27(-0.47,-0.56)	-0.16(-0.42,0.10)	0.223	1.000
ESR1 Exon 1+30	-0.30(-0.52,-0.74)	-0.32(-0.51,-0.13)	-0.35(-0.58,-0.11)	-0.41(-0.67,-0.16)	-0.24(-0.45,-0.38)	-0.07(-0.33,0.19)	0.072	0.757
ESR1 IVS1-354	-0.25(-0.44,-0.52)	-0.37(-0.54,-0.19)	-0.48(-0.74,-0.23)	-0.31(-0.53,-0.91)	-0.23(-0.42,-0.34)	-0.14(-0.42,0.13)	0.054	0.782
ESR1 IVS1-1415	-0.29(-0.47,-0.10)	-0.39(-0.57,-0.22)	-0.50(-0.76,-0.24)	-0.29(-0.50,-0.84)	-0.26(-0.45,-0.68)	-0.23(-0.51,0.61)	0.199	0.978
ESR1 IVS1-1505	-0.30(-0.52,-0.75)	-0.36(-0.55,-0.17)	-0.42(-0.66,-0.18)	-0.38(-0.63,-0.13)	-0.27(-0.48,-0.65)	-0.16(-0.43,0.10)	0.235	1.000
ESR1 IVS1-1989	-0.31(-0.47,-0.15)	-0.31(-0.52,-0.11)	-0.32(-0.67,0.41)	-0.28(-0.47,-0.10)	-0.88(-0.32,0.14)	0.11(-0.31,0.52)	0.491	1.000
ESR2 1730G	-0.31(-0.52,-0.11)	-0.22(-0.41,-0.36)	-0.13(-0.39,0.13)	-0.18(-0.41,0.54)	-0.18(-0.37,0.25)	-0.17(-0.46,0.11)	0.445	1.000
<b>PAI-1 Ag, mcg/L</b>								
ESR1 IVS-401	-13.9(-27.3,-0.45)	-13.5(-25.1,-1.91)	-13.1(-27.4,1.12)	-22.9(-38.4,-7.42)	-14.5(-27.0,-2.00)	-6.04(-21.7,9.57)	0.203	1.000
ESR1 Exon 1+30	-10.1(-23.6,3.34)	-11.1(-22.5,0.24)	-12.2(-26.0,1.62)	-14.6(-30.1,0.91)	-11.6(-23.9,0.75)	-8.58(-24.4,7.19)	0.789	1.000
ESR1 IVS1-354	-16.6(-28.2,-4.90)	-10.6(-21.3,0.06)	-4.66(-19.7,10.42)	-18.5(-31.8,-5.23)	-12.1(-23.6,-0.56)	-5.66(-22.0,10.70)	0.178	0.999
ESR1 IVS1-1415	-15.5(-26.6,-4.42)	-9.75(-20.4,0.89)	-4.00(-19.7,11.70)	-14.9(-27.7,-2.14)	-12.4(-23.8,-0.90)	-9.77(-27.0,7.46)	0.231	1.000

Biomarker	E+P vs. E+P Placebo (95% CI)			E-alone vs. E-alone Placebo (95% CI)			Marginal p <sup>2</sup>	Corrected p <sup>3</sup>
	Number of minor alleles			Number of minor alleles				
	0	1	2	0	1	2		
ESR1 IVS1-1505	-10.7(-23.9,2.52)	-10.9(-22.3,0.60)	-11.0(-25.3,3.24)	-18.8(-34.1,-3.64)	-11.2(-23.6,1.10)	-3.62(-19.4,12.14)	0.462	1.000
ESR1 IVS1-1989	-3.58(-13.3,6.13)	-13.1(-25.3,-0.93)	-22.6(-43.8,-1.54)	-7.65(-18.7,3.42)	-4.07(-18.2,10.08)	-0.50(-25.8,24.75)	0.073	0.975
ESR2 1730G	1.87(-10.5,14.19)	-6.10(-17.2,4.97)	-14.1(-29.7,1.52)	-3.27(-17.1,10.51)	-5.18(-17.1,6.73)	-7.09(-24.1,9.91)	0.034	0.886
<b>Plasmin-antiplasmin, nmol/L</b>								
ESR1 IVS-401	1.71(1.12,2.30)	1.06(0.55,1.57)	0.41(-0.22,1.04)	1.36(0.68,2.04)	1.08(0.53,1.62)	0.79(0.11,1.48)	0.001	0.296
ESR1 Exon 1+30	1.31(0.71,1.90)	0.93(0.42,1.43)	0.55(-0.06,1.16)	0.90(0.22,1.59)	0.90(0.36,1.45)	0.90(0.21,1.60)	0.118	1.000
ESR1 IVS1-354	1.72(1.21,2.23)	0.85(0.39,1.32)	-0.02(-0.68,0.64)	1.24(0.66,1.82)	1.06(0.55,1.56)	0.87(0.16,1.58)	0.000	0.014
ESR1 IVS1-1415	1.64(1.15,2.12)	0.71(0.25,1.17)	-0.21(-0.90,0.47)	1.16(0.60,1.71)	1.01(0.51,1.50)	0.85(0.10,1.60)	0.000	0.014
ESR1 IVS1-1505	1.73(1.15,2.31)	1.04(0.53,1.54)	0.35(-0.28,0.97)	1.33(0.66,1.99)	1.06(0.52,1.60)	0.80(0.11,1.49)	0.001	0.214
ESR1 IVS1-1989	0.75(0.34,1.16)	1.03(0.51,1.55)	1.31(0.41,2.21)	0.73(0.26,1.20)	0.83(0.23,1.42)	0.92(-0.14,1.99)	0.423	1.000
ESR2 1730G	1.06(0.50,1.61)	0.84(0.34,1.33)	0.62(-0.08,1.33)	0.77(0.15,1.38)	0.90(0.37,1.43)	1.03(0.27,1.79)	0.630	1.000
<b>Homocysteine, mg/L</b>								
ESR1 IVS-401	-0.46(-1.22,0.31)	-0.67(-1.34,0.00)	-0.89(-1.71,-0.07)	-0.60(-1.48,0.29)	-0.66(-1.38,0.06)	-0.72(-1.61,0.18)	0.038	0.754
ESR1 Exon 1+30	-0.66(-1.43,0.10)	-0.88(-1.54,-0.23)	-1.11(-1.90,-0.31)	-1.27(-2.15,-0.38)	-0.88(-1.59,-0.18)	-0.50(-1.39,0.40)	0.059	0.948
ESR1 IVS1-354	-0.23(-0.90,0.44)	-0.39(-1.01,0.22)	-0.56(-1.43,0.32)	-0.19(-0.95,0.56)	-0.42(-1.08,0.25)	-0.64(-1.58,0.30)	0.080	0.995
ESR1 IVS1-1415	-0.18(-0.81,0.46)	-0.37(-0.98,0.25)	-0.55(-1.46,0.35)	-0.18(-0.90,0.55)	-0.37(-1.03,0.29)	-0.56(-1.55,0.42)	0.130	0.979
ESR1 IVS1-1505	-0.43(-1.19,0.33)	-0.64(-1.30,0.02)	-0.85(-1.67,-0.03)	-0.55(-1.41,0.32)	-0.63(-1.34,0.08)	-0.71(-1.62,0.20)	0.043	0.777
ESR1 IVS1-1989	-0.64(-1.20,-0.09)	-0.58(-1.29,0.13)	-0.52(-1.75,0.72)	-0.93(-1.56,-0.30)	-0.23(-1.04,0.57)	0.46(-0.98,1.89)	0.018	0.553
ESR2 1730G	-0.42(-1.13,0.29)	-0.59(-1.22,0.05)	-0.75(-1.63,0.13)	-0.99(-1.78,-0.20)	-0.40(-1.08,0.29)	0.20(-0.78,1.18)	0.091	0.976
<b>D-dimer, mg/L</b>								
ESR1 IVS-401	0.21(0.00,0.42)	0.18(-0.01,0.36)	0.14(-0.09,0.37)	0.01(-0.24,0.26)	0.05(-0.15,0.25)	0.09(-0.16,0.34)	0.867	1.000
ESR1 Exon 1+30	0.20(-0.01,0.42)	0.18(-0.01,0.36)	0.15(-0.07,0.37)	0.05(-0.20,0.29)	0.05(-0.15,0.24)	0.05(-0.20,0.30)	0.876	1.000
ESR1 IVS1-354	0.22(0.04,0.41)	0.24(0.07,0.41)	0.25(0.01,0.49)	0.10(-0.11,0.31)	0.10(-0.08,0.29)	0.10(-0.16,0.36)	0.834	1.000
ESR1 IVS1-1415	0.28(0.11,0.46)	0.22(0.05,0.39)	0.16(-0.09,0.41)	0.14(-0.06,0.34)	0.10(-0.08,0.29)	0.06(-0.21,0.33)	0.252	1.000
ESR1 IVS1-1505	0.24(0.03,0.45)	0.21(0.02,0.39)	0.17(-0.06,0.40)	0.04(-0.20,0.28)	0.09(-0.11,0.28)	0.13(-0.12,0.38)	0.768	1.000
ESR1 IVS1-1989	0.13(-0.02,0.29)	0.20(0.00,0.40)	0.26(-0.09,0.61)	-0.03(-0.20,0.15)	0.11(-0.11,0.33)	0.24(-0.15,0.64)	0.446	1.000
ESR2 1730G	0.24(0.05,0.44)	0.14(-0.03,0.32)	0.04(-0.21,0.28)	0.05(-0.16,0.27)	0.04(-0.15,0.23)	0.02(-0.25,0.29)	0.760	1.000

<sup>1</sup> Change from baseline to year one in active treatment arm - change from baseline to year one in placebo arm, estimated from regression models that are linear in the number of minor SNP alleles, adjusted for potential confounders as in Table 1 and Table 2, except that baseline hysterectomy status interacted with treatments and SNPs, thus allowing the treatment\*SNP effect to be different in E-alone and E+P trial.

<sup>2</sup> Three degree of freedom test of no interactions between treatment assignment (active vs. placebo), hysterectomy status and polymorphism that is linear in the number of minor alleles, adjusted for covariates as above.

<sup>3</sup>Multiple comparison permutation adjusted p-values, based on 1,000 permutations. The SNP by treatment interaction was permuted at each iteration.