

## Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Davis SR, Moreau M, Kroll R, et al. Testosterone for low libido in postmenopausal women not taking estrogen. *N Engl J Med* 2008;359:2005-17.

<b>Web Table 1. Mean blood laboratory parameters at baseline and mean change from baseline at week 52</b>			
<b>Blood laboratory parameter (units)</b>	<b>Placebo N=277</b>	<b>TTS 150mcg N=267</b>	<b>TTS 300mcg N=267</b>
<b>Total Cholesterol (mg/dL)</b>			
Baseline	227.5	229.5	227.5
Change from Baseline	-7.6	-8.8	-13.4
% Markedly Abnormal High	1.2%	0.9%	0.0%
<b>HDL-Cholesterol (mg/dL)</b>			
Baseline	71.0	72.0	69.5
Change from Baseline	0.9	-1.9	-2.2
% Markedly Abnormal Low	0.0%	0.0%	0.8%
<b>LDL-Cholesterol (mg/dL)</b>			
Baseline	134.5	135.1	134.9
Change from Baseline	-8.1	-7.9	-9.9
% Markedly Abnormal High	3.2%	3.0%	1.3%
<b>Triglycerides (mg/dL)</b>			
Baseline	110.2	111.2	115.6
Change from Baseline	-0.9	7.0	-2.1
% Markedly Abnormal High	1.6%	5.6%	2.5%
<b>Glucose (mg/dL)</b>			
Baseline	90.9	90.8	90.5
Change from Baseline	-0.7	-1.0	-1.0
% Markedly Abnormal Low	0.0%	0.0%	0.0%
% Markedly Abnormal High	0.0%	0.9%	0.4%
<b>Insulin (μIU/mL)</b>			
Baseline	9.6	9.7	9.8
Change from Baseline	-0.1	1.0	0.4
% Markedly Abnormal High	4.0%	6.6%	5.1%
<b>Alkaline Phosphatase (U/L)</b>			
Baseline	88.4	88.6	89.4
Change from Baseline	-3.5	-3.7	-4.9
% Markedly Abnormal High	0.4%	0.0%	0.0%
<b>Alanine Aminotransferase (SGPT) (U/L)</b>			
Baseline	23.2	22.7	24.0
Change from Baseline	0.0	-0.1	-1.1
% Markedly Abnormal High	1.2%	0.4%	0.0%
<b>Aspartate Aminotransferase (SGOT) (U/L)</b>			
Baseline	22.9	22.7	23.2
Change from Baseline	0.2	0.5	0.3
% Markedly Abnormal High	0.0%	0.0%	0.0%
<b>Bilirubin (mg/dL)</b>			
Baseline	0.53	0.52	0.57
Change from Baseline	-0.02	-0.01	-0.03
% Markedly Abnormal High	0.0%	0.0%	0.0%
<b>Hematocrit (%)</b>			
Baseline	41.09	41.26	41.20
Change from Baseline	-0.56	-0.31	-0.34
% Markedly Abnormal Low	0.0%	0.0%	0.0%
<b>Activated Partial Thromboplastin Time (sec)</b>			
Baseline	30.78	30.50	30.93
Change from Baseline	1.35	0.69	1.08
% Markedly Abnormal Low	0.0%	0.4%	1.3%
% Markedly Abnormal High	4.5%	1.8%	3.4%
<b>Fibrinogen (mg/dL)</b>			
Baseline	407.9	395.1	405.2
Change from Baseline	9.7	17.9	15.2
% Markedly Abnormal Low	0.0%	0.0%	0.0%
% Markedly Abnormal High	3.7%	1.8%	3.0%
<b>Prothrombin Time (sec)</b>			
Baseline	11.55	11.60	11.57
Change from Baseline	0.16	0.14	0.15
% Markedly Abnormal Low	0.0%	0.0%	0.0%
% Markedly Abnormal High	2.9%	0.0%	1.3%

See Web Table 2 for reference ranges and markedly abnormal criteria.

Baseline contains all patients with baseline values

Change from Baseline contains all patients with baseline and Week 52 values

Markedly Abnormal includes all post-baseline visits except for follow-up visits.

**Web Table 2. Reference Ranges and Markedly Abnormal Criteria for blood laboratory parameters**

Laboratory Test (Units)	Reference Range	Markedly Abnormal Criteria <sup>a</sup>	
		Limits	Percent Change
Total Cholesterol (mg/dL)	130-200	> 280 mg/dL	> 30% ↑
HDL-Cholesterol (mg/dL)	40-80	< 34 mg/dL	> 30% ↓
LDL-Cholesterol (mg/dL)	0-130	> 160 mg/dL	> 30% ↑
Triglycerides (mg/dL)	45-250	> 250 mg/dL	> 30% ↑
Glucose <sup>b</sup> (mg/dL)	Fasting (Age ≤ 65): 68-118 Fasting (Age ≥ 66): 82-115	> 140 mg/dL < 50 mg/dL	> 15% ↑/↓
Insulin (μIU/mL)	6-27	> 25 μIU/mL	> 30% ↑
Alkaline Phosphatase (U/L)	40-100	≥ 3X ULN	> 20% ↑
Alanine Aminotransferase (U/L)	6-37	≥ 3X ULN	> 30% ↑
Aspartate Aminotransferase (U/L)	10-36	≥ 3X ULN	> 30% ↑
Bilirubin (mg/dL)	0.2-1.2	≥ 2.0 mg/dL	> 50% ↑
Hematocrit (%)	Age ≤ 65: 35.0-47.0 Age ≥ 66: 33.0-46.0	≤ 32%	> 30% ↓
Activated Partial Thromboplastin Time (sec)	20.6-39.9	> ULN < LLN	> 30% ↑/↓
Fibrinogen (mg/dL)	184-514	< 100 mg/dL > 600 mg/dL	> 0% ↑/↓
Prothrombin Time (sec)	10.0-13.0	> ULN < LLN	> 30% ↑/↓

ULN = upper limit of normal; LLN = lower limit of normal

<sup>a</sup> A value was defined as markedly abnormal if it was outside the limits *and* in excess of the allowed percent change from baseline.

<sup>b</sup> Application of the markedly abnormal criteria was based on the fasting criteria for all samples. The criteria for non-fasting are presented only to show what was initially planned.

**Web Table 3. Serum Hormone Concentrations at Baseline and after 24 and 52 Weeks.\***

<b>Hormone</b> [reference range]†	<b>Treatment</b>		<b>Baseline</b>			<b>Week 24</b>			<b>Week 52</b>			<b>P-Value‡</b>
	<b>Group</b>	<b>N</b>	<b>Baseline</b>	<b>N</b>	<b>Week 24</b>	<b>N</b>	<b>Week 24</b>	<b>N</b>	<b>Week 52</b>	<b>N</b>	<b>Week 52</b>	
Free testosterone [0.9 – 7.3 pg/mL]	Placebo	275	1.30 [0.6, 2.3]	136	1.35 [0.7, 3.0]	135	1.50 [0.7, 2.9]				<0.001	
	150 mcg/day	260	1.30 [0.6, 2.5]	136	4.20 [1.9, 7.8]	127	3.70 [1.9, 6.7]				0.44	
	300 mcg/day	265	1.20 [0.6, 2.5]	153	6.60 [3.0, 13.3]	137	6.10 [2.6, 10.4]				0.20	
Bioavailable testosterone [0.8 – 8.6 ng/dL]	Placebo	250	2.06 [1.02, 3.76]	108	1.84 [0.83, 3.71]	NA	NA				0.05	
	150 mcg/day	238	1.99 [0.95, 4.07]	107	5.12 [2.19, 10.16]	NA	NA				NA	
	300 mcg/day	241	1.99 [0.88, 4.25]	118	8.24 [2.98, 16.96]	NA	NA				NA	
Total testosterone [12 – 50 ng/dL]	Placebo	276	15.0 [8.0, 27.0]	138	16.0 [8.0, 26.0]	135	18.0 [10.0, 30.0]				<0.001	
	150 mcg/day	264	16.5 [9.0, 27.0]	136	42.0 [23.0, 72.0]	127	45.0 [22.0, 78.0]				0.53	
	300 mcg/day	265	15.0 [8.0, 26.0]	155	67.0 [30.0, 111.0]	137	66.0 [28.0, 117.0]				0.34	
Total dihydro- testosterone [7 – 31 ng/dL]	Placebo	181	8.0 [3.0, 13.0]	124	7.0 [4.0, 14.0]	101	8.0 [5.0, 13.0]				0.01	
	150 mcg/day	180	8.0 [4.0, 13.0]	132	12.5 [7.0, 21.0]	91	14.0 [7.0, 22.0]				0.92	
	300 mcg/day	170	7.0 [0.0, 12.0]	143	18.0 [9.0, 28.0]	104	17.0 [9.0, 28.0]				0.32	

**Web Table 3. (Continued.)**

<b>Hormone</b>	<b>Treatment</b>							
<b>[reference range]†</b>	<b>Group</b>	<b>N</b>	<b>Baseline</b>	<b>N</b>	<b>Week 24</b>	<b>N</b>	<b>Week 52</b>	<b>P-Value‡</b>
Sex hormone binding globulin	Placebo	277	42.0 [23.0, 74.0]	142	44.0 [24.0, 79.0]	133	43.0 [23.0,78.0]	0.42
[13 - 98 nmol/L]	150 mcg/day	266	46.0 [25.0, 81.0]	140	47.0 [27.5, 87.5]	128	43.0 [24.0, 80.0]	0.02
	300 mcg/day	267	41.0 [21.0, 75.0]	147	41.0 [21.0, 73.0]	138	41.0 [21.0, 75.0]	0.004
Free Estradiol	Placebo	215	0.07 [0.03, 0.18]	99	0.10 [0.04, 0.51]	125	0.07 [0.03, 0.18]	0.82
[0.2 – 1.1 pg/mL; follicular phase]	150 mcg/day	202	0.06 [0.03, 0.15]	100	0.13 [0.05, 0.39]	113	0.08 [0.03, 0.19]	<0.001
	300 mcg/day	202	0.07 [0.03, 0.17]	119	0.13 [0.05, 0.41]	128	0.07 [0.03, 0.21]	0.79
Total Estradiol	Placebo	240	6.0 [3.0, 13.0]	99	8.0 [4.0, 33.0]	126	6.0 [3.0, 15.0]	0.78
[12 – 101 pg/mL; follicular phase]	150 mcg/day	229	5.0 [3.0, 12.0]	101	9.0 [5.0, 23.0]	115	6.0 [3.0, 17.0]	<0.001
	300 mcg/day	229	6.0 [3.0, 14.0]	120	10.0 [5.0, 24.5]	131	6.0 [3.0, 14.0]	0.69
Estrone	Placebo	235	20.0 [11.0, 38.0]	80	20.0 [13.0, 47.0]	129	23.0 [14.0, 45.0]	0.007
[15 - 150 pg/mL; early follicular phase]	150 mcg/day	236	19.5 [12.0, 35.0]	77	21.0 [12.0, 40.0]	125	23.0 [14.0, 40.0]	<0.001
	300 mcg/day	232	20.0 [10.0, 34.0]	85	21.0 [11.0, 34.0]	132	20.0 [12.0, 38.0]	<0.001

\* Values are medians [10<sup>th</sup>, 90<sup>th</sup> percentile ranges]. Hormone values are summarized for patients who had blood samples collected within 5 days of the last patch application date before the scheduled study visit.

† Reference ranges generated at Quest Diagnostics using data from premenopausal women (18-49 years of age).

‡ P-values based on repeated measures ANOVA with a linear time trend using log-transformed data. Only post baseline visits are included for free, total, and bioavailable testosterone and total dihydrotestosterone for the two active treatment groups. Note that serum free and total testosterone and SHBG concentrations after 12 weeks are not shown in the table but are included in the analyses.