Androgenic AEs by Maximum Free T

Phase II and Phase III

% of patients	Placebo N= 703	TTS Upper Decile N=58
Acne	7	10.3
Alopecia	2.7	3.5
Facial Hair	5	5.2
Voice Deepening	1.7	0

Effects of Testosterone in Rhesus Monkey Breast Tissue--Results

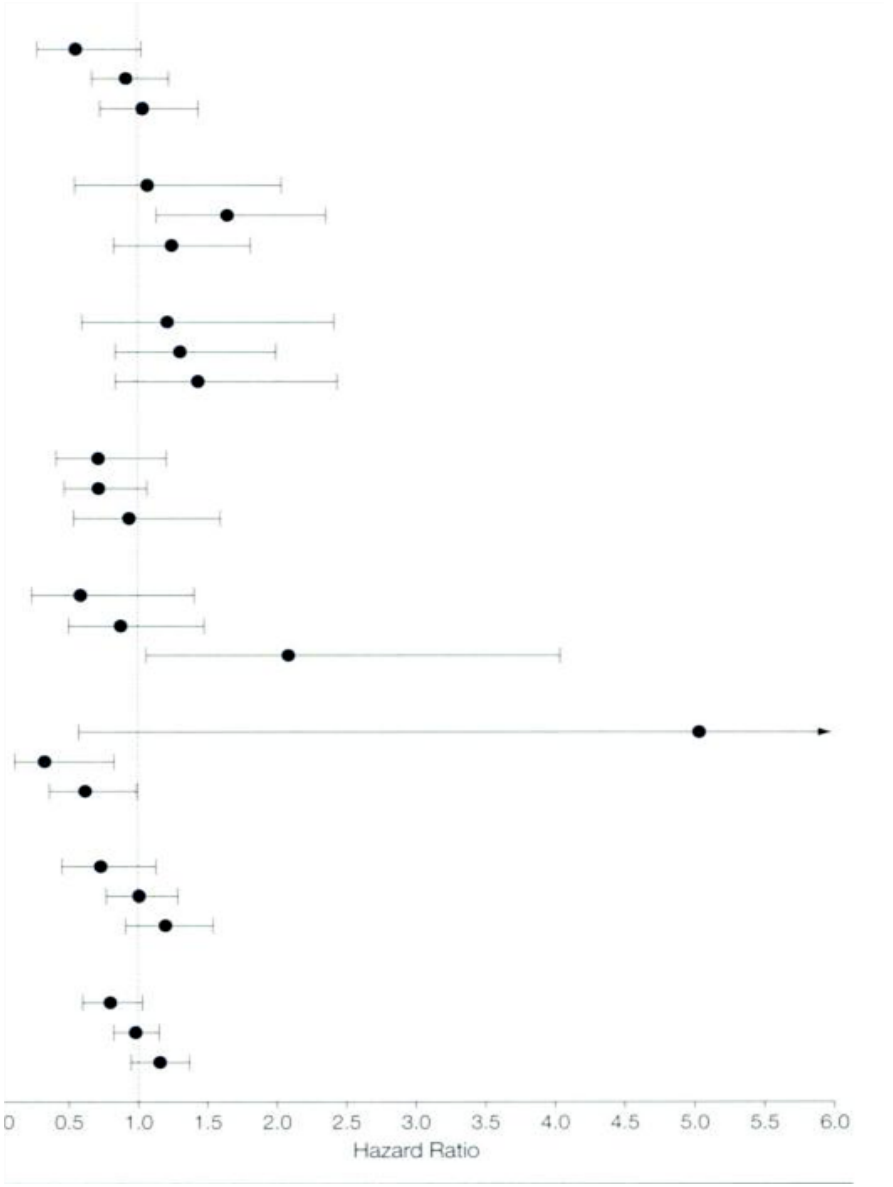
Treatment (n)	E (pg/mL)	P (ng/mL)	T (ng/mL)	Ki67 (%)
Control (5)	≤ 2	0.89 ± 0.13	≤ 10	7.89 ± 1.9
E (4)	256 ± 62	0.61 ± 0.3	≤ 10	30.32 ± 3.7
E/P (4)	330 ± 98	2.83 ± 0.8	≤ 10	32.19 ± 4.9
E/T (5)	250 ± 75	0.53 ± 0.1	40 ± 11	16.76 ± 1.6

- E/T was not different from control (p=0.07)
- E/T was different from E (p =0.01) and E/P (p =0.005)
- At roughly physiological levels, addition of testosterone reduced mammary tissue proliferation in OVX monkeys compared with estradiol alone; level is no different from control.
- Flutamide administered to intact female monkeys for three months to suppress testosterone production doubled the proliferation rate.

Dimitrakakis et al, Menopause 10 (4) 292-298 (2003)

Selected Clinical Outcomes by Participant Age and Randomization Assignment

Outcome by Age, y	No. Cases Annualized (%) CEE	Placebo	Hazard Ratio 95% CI)	P-value for Interaction
Coronary Heart Disease				
50-59	16 (0.14)	29 (0.24)	0.56 (0.30-1.03)	
60-69	87 (0.54)	98 (0.59))	0.92 (0.69-1.23))	
70-79	74 (0.88)	72 (0.84)	1.04 (0.75-1.44))	.14
Stroke				
50-59	19 (0.16)	19 (0.16)	1.08 (0.57-2.04)	
60-69	79 (0.49)	50 (0.30)	1.65 (1.16-2.36)	.59
70-79	60 (0.71)	49 (0.57)	1.25 (0.85-1.82)	
Venous Thromboembolism				
50-59	18 (0.15)	15 (0.13)	1.22 (0.62-2.42)	
60-69	49 (0.31)	39 (0.23)	1.31 (0.86-2.00)	
70-79	34 (0.32)	24 (0.28)	1.44 (0.86-2.44)	.39
Invasive Breast Cancer				
50-59	25 (0.21)	35 (0.29)	0.72 (0.43-1.21)	
60-69	42 (0.26)	60 (0.66)	0.72 (0.49-1.07)	.51
70-79	27 (0.32)	29 (0.34)	0.94 (0.56-1.60)	
Colorectal Cancer				
50-59	8 (0.07)	14 (0.12)	0.59 (0.25-1.41)	
60-60	26 (0.16)	31 (0.19)	0.88 (0.52-1.48)	.048
70-79	27 (0.32)	13 (0.15)	2.09 (1.08-4.04)	
Hip Fracture				
50-59	5 (0.04)	1 (0.01)	5.04 (0. 59-43.17)	
60-69	6 (0.04)	19 (0.11)	0.33 (0.13-0.83)	.39
70-79	27 (0.32)	44 (0.52)	0.62 (0.38-1.00)	
Total Death				
50-59	34 (0.29)	47 (0.39)	47 (0.39)	
60-69	127 (0.79)	131 (0.79)	131 (0.79)	.19
70-79	130(1.54)	111(1.30)	111(1.30)	
Global Index				
50-59	104 (0.89)	104 (0.89)	104 (0.89)	
60-69	312 (1.95)	312 (1.95)	312 (1.95)	.08
70-79	276 (3.28)	276 (3.28)	276 (3.28)	



CEE=conjugated equine estrogen, CI=confidence interval

Multi-faceted Approach to Maximize Safe Use of Intrinsa

Educational plans:

- Package insert and patient information leaflet to promote safe use
- Tools to help clinicians and patients diagnose/ recognize HSDD and identify appropriate patients
- Web based education on the appropriate use of the product, prevalence and clinical implications of HSDD
- CME programs supported by unrestricted grants

Mean Change from Baseline in Efficacy Endpoints

	Satisfying Sexual Activity	Desire	Distress
MCID	**>1**	**≥8.9**	**≤ -20**
Phase III TTS Patients	**1.8**	**10.8**	**-22.7**
Responders in Clinical Relevance Study	**4.4**	**21.0**	**-36.5**

Sexuality After Hysterectomy with and without Oophorectomy

	BSO w/ ERT	BSO w/o ERT	No BSO
Semi-structured Interview	N=23	N=25	N=28
Libido same or better	52%	44%	82%*
Libido worse	48%	56%	18%*

ERT=Estrogen replacement therapy

Nathorst-Boos et al. *J Psychosom Obstet Gynaecol* 1993;14:283

*** p<0.05**

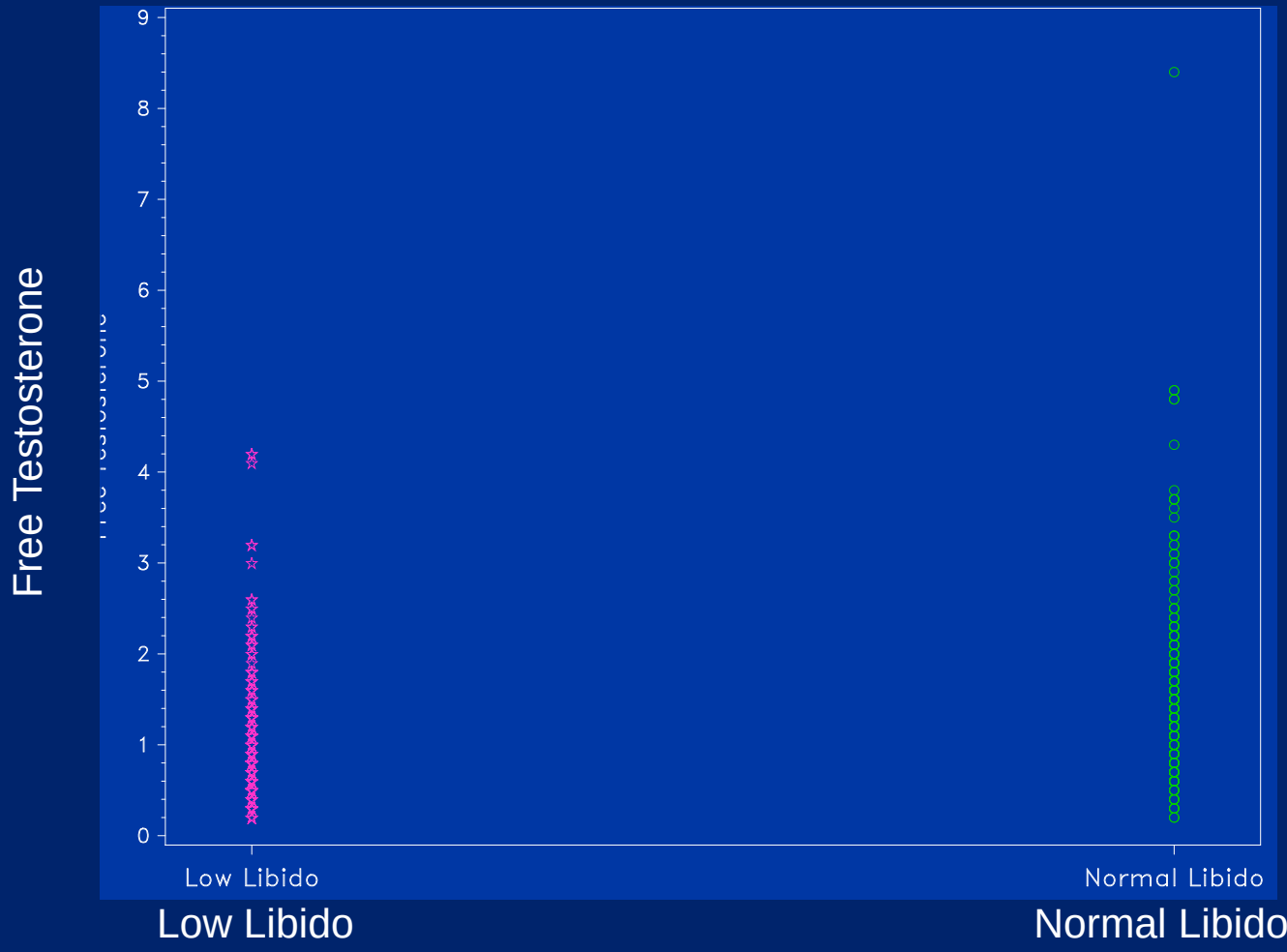
Power Considerations for Breast Cancer

Assuming an event rate of 0.3%/year, alpha=0.05, one-sided test, with 15% disenrollment and 50% discontinuation, and 3 controls per Intrinsa user

Year from launch	RR	Person years for Intrinsa	Power
1	2.0	2837	72%
2	1.7	8148	86%
3	1.5	14510	85%
4	1.4	21320	84%
5	1.4	28319	92%

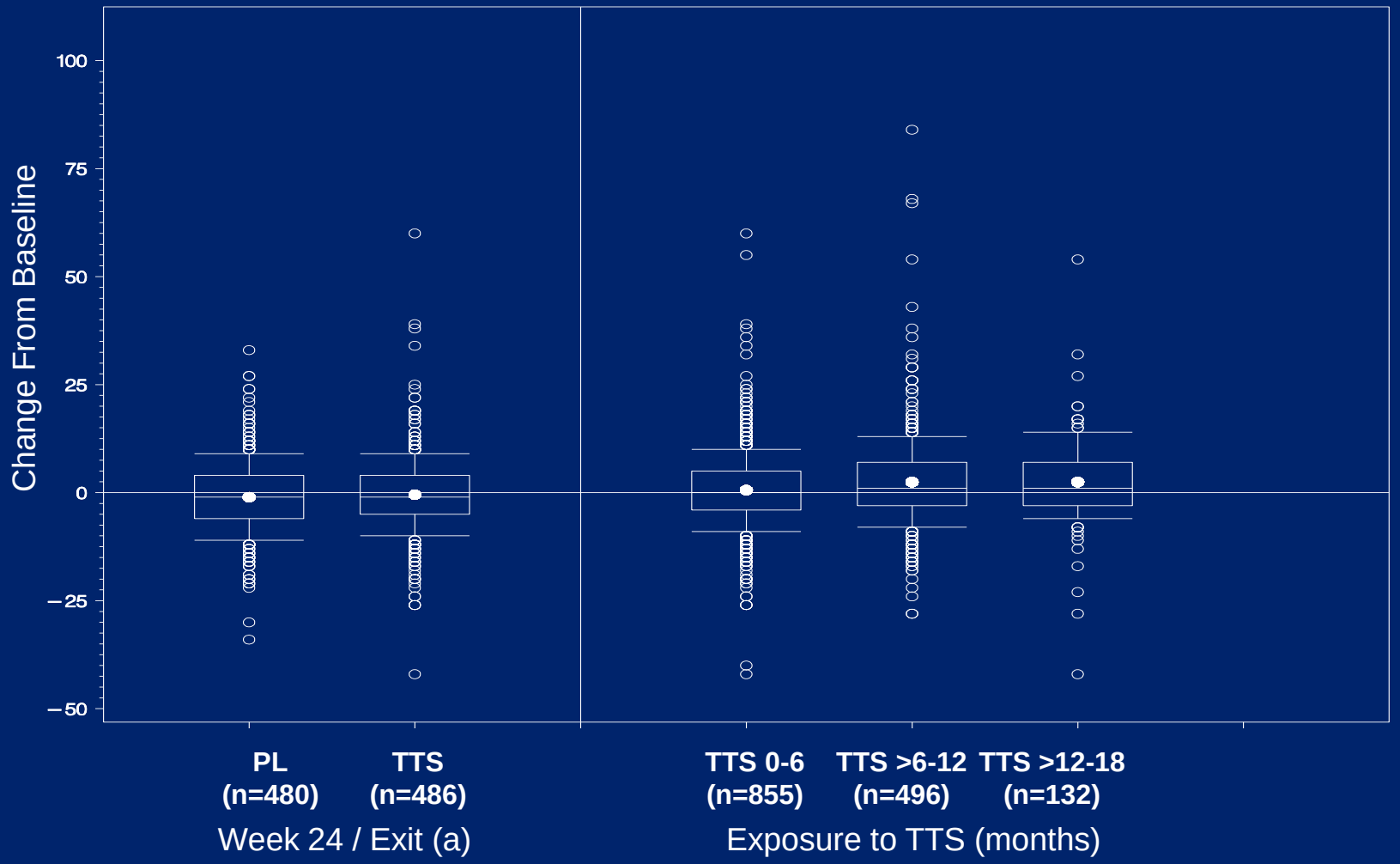
JAMA. 2004;291:1701-1712

Overlap of Free-T Between Low Libido and Normal Libido Women (SM Population Validation Studies)

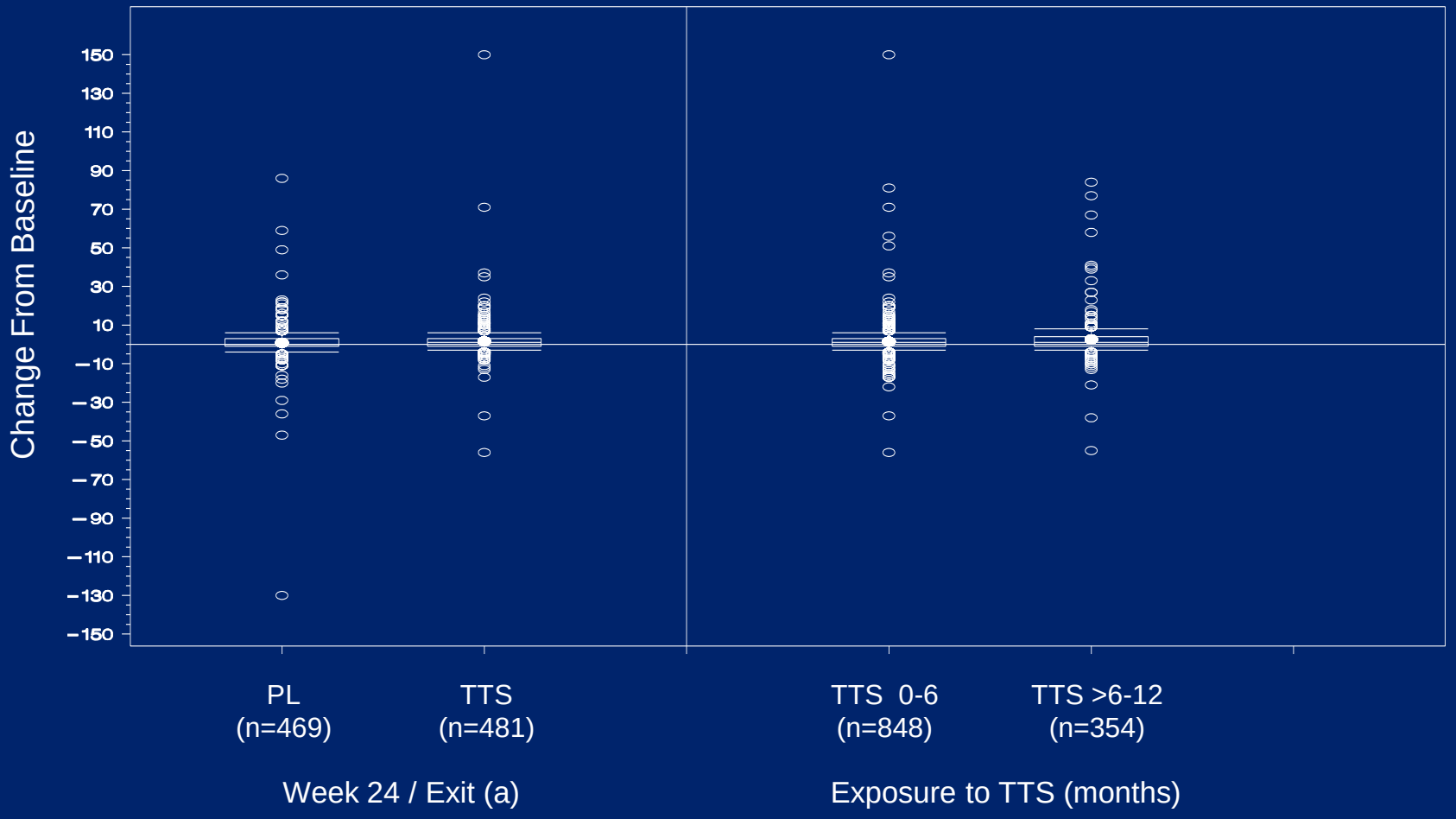


Glucose (mg/dL)

Change from Baseline SM 1 & SM 2



Insulin (μIU/mL)
Change from Baseline SM 1 & SM 2



Lipid Profile in NM 2 at 52 Weeks

Excluding Patients Starting Antihyperlipidemics Post-Baseline*

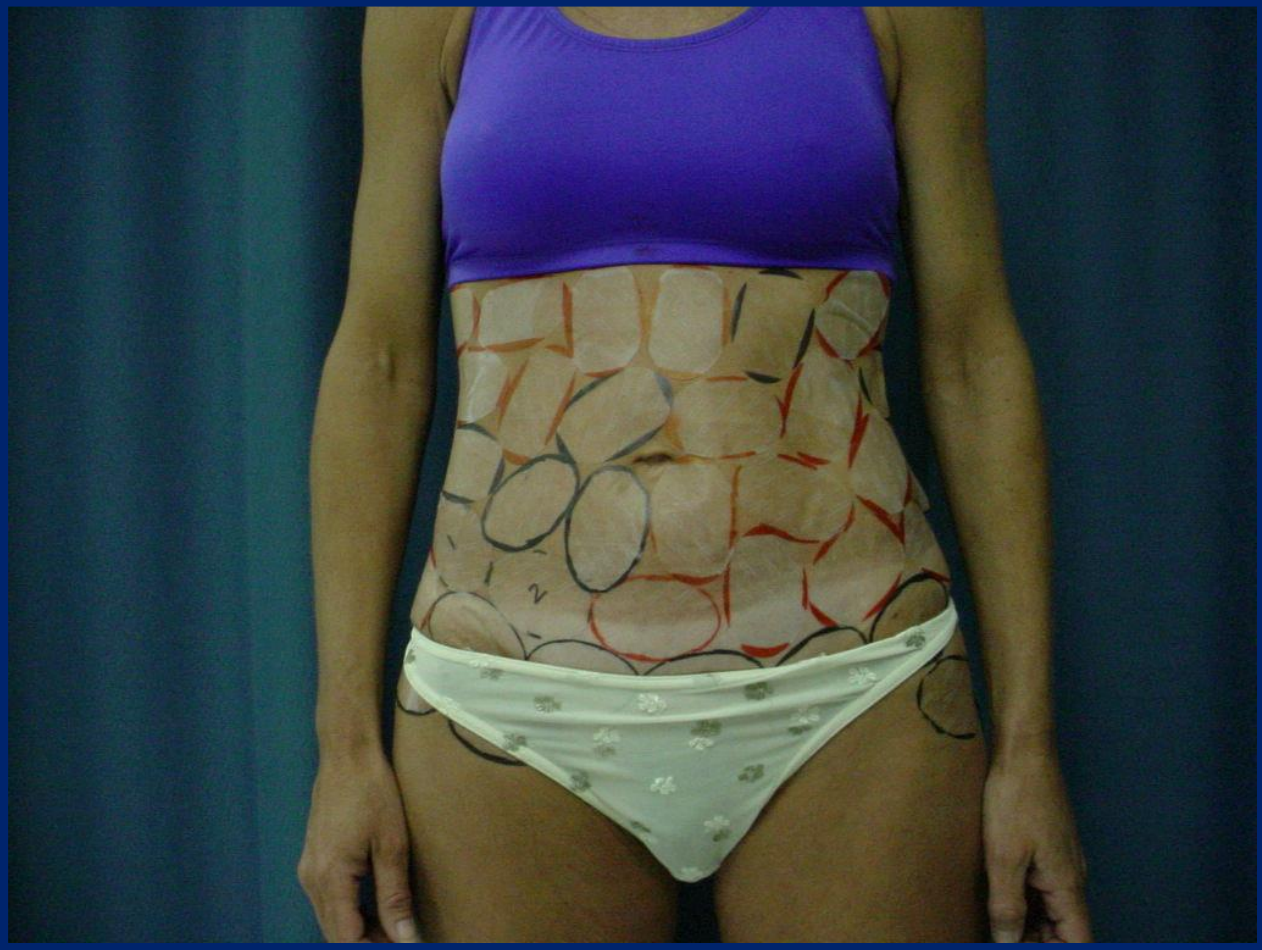
	Interim Data 1:2 Randomization	
Baseline/ Change from BL	PL N=108	TTS N=234
Total Cholesterol (mg/dL)	210.8 **2.0**	208.9 **6.5**
HDL (mg/dL)	63.2 **3.1**	63.6 **2.3**
LDL (mg/dL)	122.7 **-0.5**	120.5 **3.5**
Triglycerides (mg/dL)	124.8 **-3.6**	124.6 **3.6**

*** 7.7% Placebo vs 2.9% TTS**

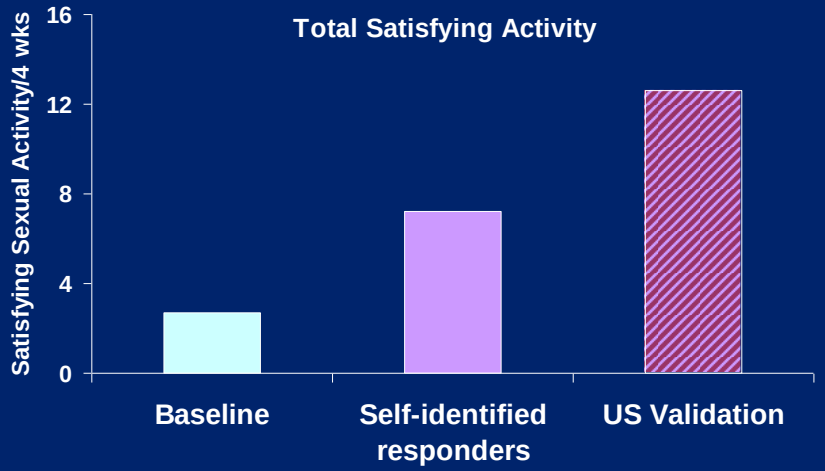
Carbohydrate Metabolism
NM 1 & 2

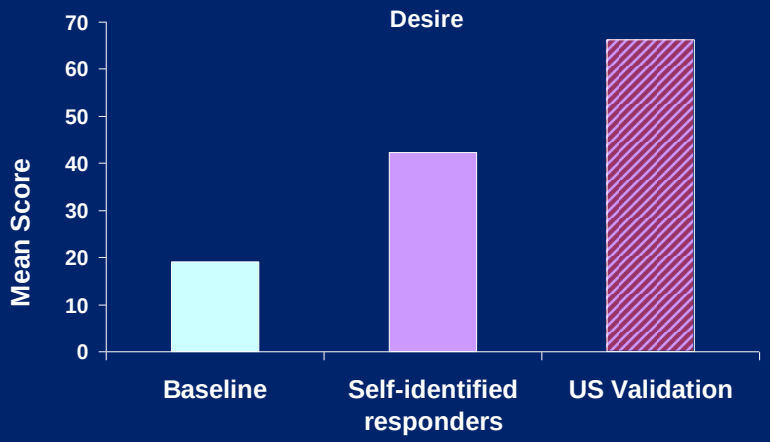
Mean Baseline/ Δ From Baseline	NM 1 Placebo n=273	NM 1 TTS n=276	NM 2 interim Placebo n=117	NM 2 interim TTS n=241
Glucose (mg/dL)	87.1	86.6	85.6	86.3
	1.1	**0.8**	**1.1**	**1.1**
HbA_{1C} (%)	5.3	5.3	5.3	5.3
	0.05	**0.08**	**-0.05**	**-0.02**
Insulin (μIU/mL)	7.5	7.5	7.4	8.2
	1.6	**0.6**	**1.7**	**0.6**

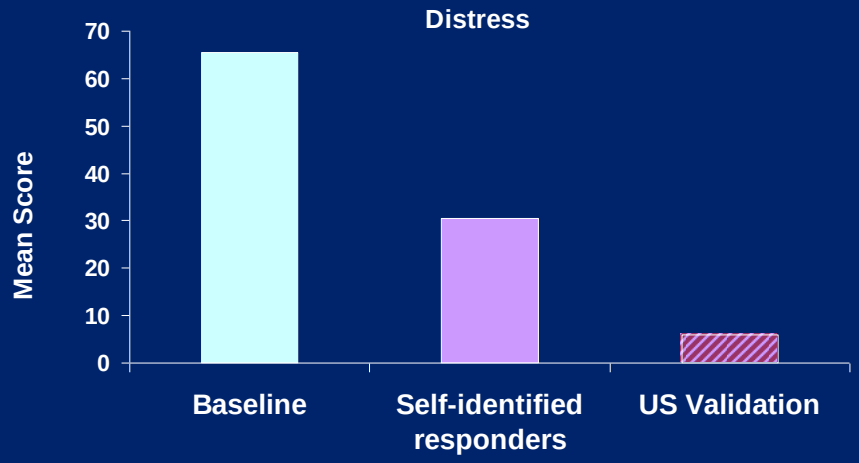
Abuse is Impractical



Phase III Responders Compared to Women without HSDD

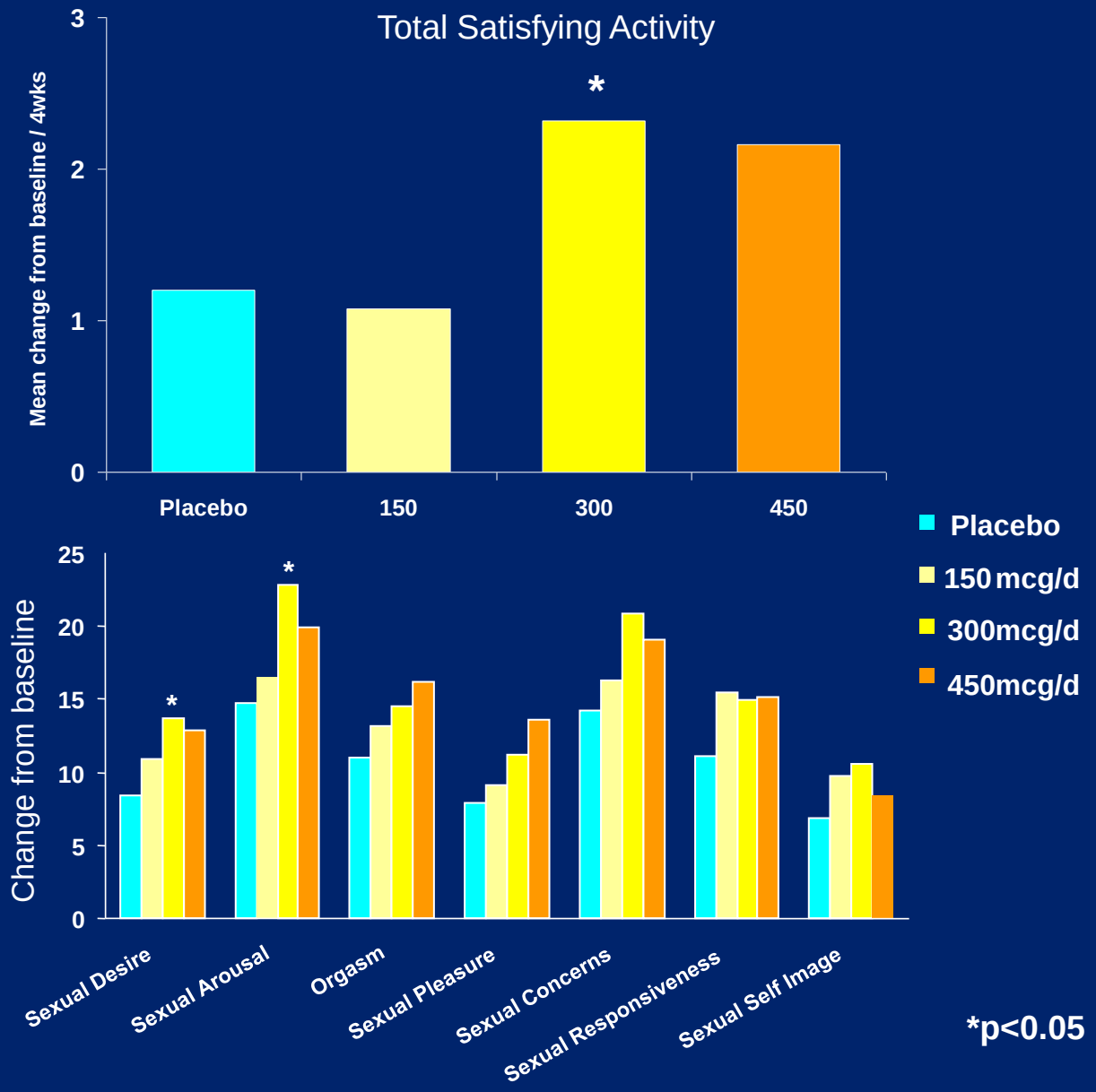






Phase II Trial with Oral Estrogen

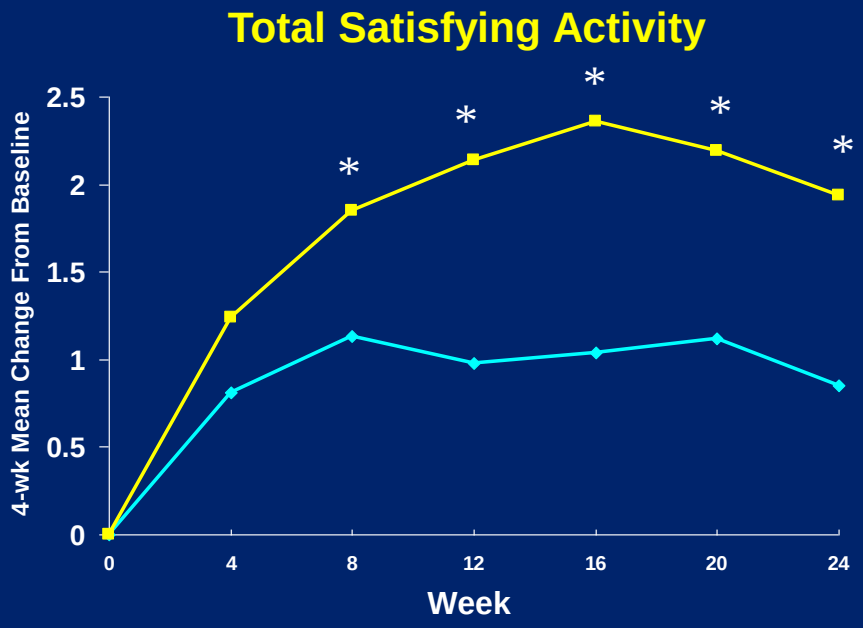
- 150 mcg/day testosterone not different from placebo
- 300 mcg/day testosterone safe and efficacious
- 450 mcg/day testosterone similar safety and no additional efficacy

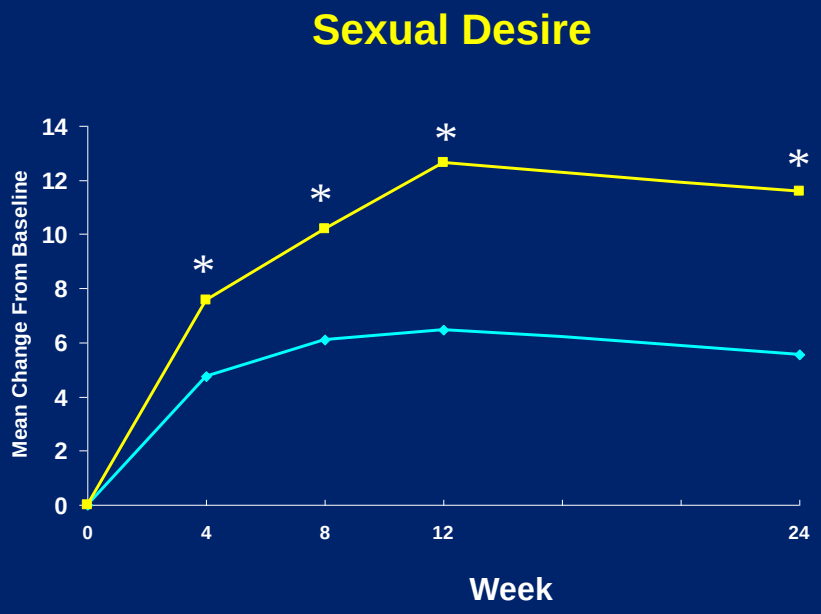


*p<0.05

Time Course of Effect

SM 1 & SM 2





TTS

Placebo

* p< 0.05

Insulin (μIU/mL)
Change from Baseline SM 1 & SM 2