Advisory Committee Briefing Document

Intrinsa® (testosterone transdermal system)
NDA No. 21-769

Procter & Gamble Pharmaceuticals, Inc.

Advisory Committee for Reproductive Health Drugs
2 December 2004

AVAILABLE FOR PUBLIC DISCLOSURE WITHOUT REDACTION.

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Attachments:

1. Proposed product labeling (Package Insert and Patient Information Leaflet)
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1. Executive Summary

Hypoactive sexual desire disorder is defined in the DSM-IV as a condition characterized by low or absent sexual desire that causes personal distress or difficulties (American Psychiatric Association, 2000). Estimates of its prevalence indicate that 17% to 30% of the 10 million surgically menopausal women in the US may have this condition, which is associated with negative effects on the women and on their relationships. At present, there is no approved pharmacologic treatment, and there is a need for safe and effective agents to treat this condition.

Surgically menopausal women typically experience a 50% reduction in serum testosterone compared with their preoperative levels (Judd et al., 1974; Hughes et al., 1991). When P&GP began clinical development of a dose form that would deliver testosterone safely and effectively to women, a transdermal dosage form was selected for its ability to systemically deliver a relatively constant and low dose of testosterone that is not affected by first pass hepatic metabolism.

Intrinsa is a matrix transdermal system that delivers approximately 300 mcg/day of testosterone systemically when worn on the abdomen and changed twice weekly. The proposed indication is:

> "Intrinsa is indicated for the treatment of hypoactive sexual desire disorder in surgically menopausal women receiving concomitant estrogen therapy.
> Hypoactive sexual desire disorder is the persistent or recurrent deficiency (or absence) of sexual thoughts/fantasies and/or desire for or receptivity for sexual activity, which causes personal distress or interpersonal difficulties. Low sexual desire may be associated with low sexual activity, sexual arousal problems or orgasm difficulties."

Because no existing instrument was patient-based and designed specifically to measure aspects of sexuality important to women with HSDD, P&GP undertook an extensive program of instrument development. This program was based on information obtained during one-on-one interviews with patients and took place in the US and Europe, in seven languages. Three instruments were developed: the Sexual Activity Log (SAL) that captures the number of sexual episodes, the Profile of Female Sexual Function (PFSF) that measures desire and other aspects of sexuality, and the Personal Distress Scale that measures distress associated with low sexual desire. These instruments have been shown to be valid and reliable in measuring aspects of sexuality in postmenopausal women with HSDD. The instrument development program was reviewed with the FDA, and the Division of Reproductive and Urologic Drug Products (DRUDP) agreed to the use of these 3 instruments in the Phase III studies. The clinical development program was consistent with the FDA draft guidance for drugs to treat female sexual dysfunction.

Four randomized, placebo-controlled, double-blind, parallel-group trials [Phase IIb studies 1999068 and 1999092; Phase III studies SM 1 (2001133) and SM 2 (2001134)] provide evidence of the safety and efficacy of the 300 mcg/day testosterone transdermal system in the treatment of surgically menopausal women with HSDD (Executive Summary Table 1). Patients in these clinical trials had all undergone hysterectomy and bilateral oophorectomy at least 6 months prior to study entry and had been on stable concomitant estrogen therapy for at least 3 months before study entry. They were in stable monogamous sexual relationships with partners who were

sexually functional. The process for identifying patients with hypoactive sexual desire for inclusion in the clinical trials was developed in accordance with the diagnostic criteria for HSDD described in the DSM-IV (American Psychiatric Association, 2000) and is consistent with the FDA draft guidance on development of drugs for female sexual dysfunction.

Executive Summary Table 1
Selected Design Characteristics of Safety and Efficacy Studies

Study Number	Phase/ Region	Study Design	Concomitant Estrogen Therapy	Testosterone Dose Groups mcg/day (ITT Patients)
Pivotal Phase III Studies (Efficacy and Safety)				
SM 1 (2001133)	III/ US, Canada, Australia	24-week randomized, DB, PC, efficacy and safety period followed by 28-week OL safety period in SM women. (An additional 52-week safety extension is on-going.)	Oral or transdermal	0 (n = 279) 300 (n = 283)
SM 2 (2001134)	III/ US, Canada, Australia	24-week randomized, DB, PC, efficacy and safety period followed by 28-week OL safety period in SM women. (An additional 52-week safety extension of this study is on-going.)	Oral or transdermal	0 (n = 266) 300 (n = 266)
Phase II Studies (Efficacy and Safety)				
1999068	IIb/ US	24-week randomized, DB, PC, efficacy and safety period followed by 28-week DB, PC safety extension period in SM women. Dose ranging study.	Oral	0 (n = 119) 150 (n = 107) 300 (n = 110) 450 (n = 111)
1999092	IIb/ EU, Australia	24-week randomized, DB, PC, efficacy and safety in SM women	Transdermal	0 (n = 39) 300 (n = 37)
T96006	IIa/ US	36-week randomized, DB, PC, 3-period crossover in SM women (n = 65) (Reported in Shifren et al., 2000)	Oral	0 150 300
Phase III Studies in Naturally Menopausal Women (Supporting Safety Data)				
NM 1 (2002006)	III/ US, Canada, Australia	24-week randomized, DB, PC, efficacy and safety period in NM women	Oral estrogen with continuous progestin	0 (n = 273) 300 (n = 276)
NM 2 (2002005)	III/ US, Canada, Australia	52-week randomized, DB, PC, efficacy and safety study (24-week primary efficacy period, 52-week blinded, placebo-controlled safety period) in NM women	Oral estrogen with continuous progestin	0 (n = 117) 300 (n = 241) (another 250 patients are continuing and not included in this summary)

DB = double blind; PC = placebo controlled; OL = open label; SM = surgically menopausal; NM = naturally menopausal; ITT = intent-to-treat.

These Phase II and Phase III studies have demonstrated that the 300 mcg/day testosterone transdermal system is effective in the treatment of HSDD in surgically menopausal women on concomitant estrogen therapy (Executive Summary Tables 2 and 3). The primary endpoint of the Phase III studies was frequency of satisfying sexual activity and the two principal secondary endpoints were sexual desire and distress. All three of these endpoints are important and showed statistically significant improvement in women who received transdermal testosterone compared with women who received placebo in each Phase III study. Improvements were also seen in all other efficacy endpoints (i.e., arousal, pleasure, orgasm, responsiveness, self-image, concerns). Overall, treatment benefits were seen as early as 4 weeks with maximal effects in total satisfying episodes and sexual desire seen by approximately 12 weeks. Beneficial effects were maintained for the remainder of the 24-week efficacy period. A consistent pattern of efficacy was seen across subpopulations, as described in section 3.2.5.

Executive Summary Table 2
Changes in Sexual Desire, Personal Distress, and Frequency of Total Satisfying Episodes
Phase III Studies

Endpoint Study Number	TTS (mcg/day)	n	Baseline Mean[a]	Mean Change from Baseline at Week 24[a,b]	p value[c]
Frequency of Total Satisfying Episodes					
SM 1	0	273	2.94	0.98	
	300	276	2.82	2.13	0.0003
SM 2	0	255	3.19	0.73	
	300	258	3.04	1.56	0.0010
Sexual Desire					
SM 1	0	269	20.82	6.90	
	300	269	19.79	11.85	0.0006
SM 2	0	257	23.37	6.21	
	300	252	21.67	11.38	0.0006
Personal Distress					
SM 1	0	266	62.57	-16.31	
	300	268	64.78	-23.55	0.0006
SM 2	0	258	66.38	-18.27	
	300	254	66.61	-24.34	0.0091

TTS=testosterone transdermal system

[a] For frequency of total satisfying episodes, baseline mean and mean change from baseline at Week 24 refer to the average 4-week frequency.

[b] Mean change from baseline adjusted for age, estrogen therapy route, pooled centers, and baseline value.

[c]For frequency of total satisfying episodes in Study SM 2, the ANCOVA model assumption of normality was severely violated; therefore, unadjusted mean change from baseline (i.e. no covariate adjustment) is shown and Wilcoxon rank sum analysis was conducted. P-value is for pairwise comparison of change in active vs. placebo.

Executive Summary Table 3
Frequency of Total Satisfying Episodes in Phase IIb Studies

Study Number	Testosterone doses (mcg/day)	n	Baseline Mean[a]	Mean Change from Baseline at Week 24[a]	Mean Weekly Rate at Week 24[b]	Ratio of Rates[c]	p-value[d]
1999068	0	112	0.70	0.30	0.97		
	150	99	0.91	0.27	0.99	1.02	0.8493
	300	108	0.73	0.58	1.26	1.30	0.0493
	450	107	0.65	0.54	1.14	1.18	0.1883
1999092	0	36	0.80	0.28	0.94		
	300	33	0.52	0.77	1.35	1.43	0.0641

[a] Baseline mean and mean change from baseline at Week 24 refer to the average weekly frequency of total satisfying sexual activity captured on the Sexual Activity Log.

[b] Mean weekly rate adjusted for baseline rate, age, marital status, and pooled site.

[c] Ratio of rates corresponds to the ratio of the weekly rate of active treatment group to placebo, adjusted for baseline rate, age, marital status, and pooled site.

[d] Pairwise comparisons of active treatment with placebo in Study 1999068 were performed after tests for linear dose response in co-primary endpoints, sexual desire and total satisfying sexual activity (Poisson regression).

In order to provide additional perspective on what magnitude of change was meaningful to patients, a clinical relevance study (Study CMKUS030993) was conducted in a subset of patients from the SM 1 and SM 2 studies. This study used a well-established anchoring technique to determine what minimum differences in study endpoints (desire, distress, and sexual activity) were meaningful to patients. This anchoring approach ties outcome measures to the patients' perceptions of benefit. A significantly greater percentage of patients in the testosterone group reported experiencing an overall meaningful benefit compared with patients in the placebo group (52% vs. 31%). Receiver operating characteristics (ROC) analyses were used to quantify the minimum changes that were meaningful to patients. When these cutoffs were then used as responder definitions and applied to the entire population of the Phase III studies in a blinded analysis, the proportion of patients identified as responders was similar to the proportion of responders based on the patients' own perception of benefit. The results of this study indicate that patients receive clinically relevant improvements in sexual function with the 300 mcg/day testosterone transdermal system.

The persistence of benefit following treatment discontinuation was assessed in a substudy of Studies SM 1 and 2. In this study, a subset of patients who had agreed to participate in a 52-week extension and had responded to treatment (self assessment) during the first 52 weeks of the study were randomly assigned to receive double-blind treatment with the testosterone transdermal system or placebo for 13 weeks. Of the 205 patients who participated in this substudy, 199 (97%) completed interviews with a trained sex therapist between Weeks 63-65. A significantly higher percentage of patients in the placebo group had a noticeable decrease in desire for sexual

activity from Week 52 to Week 65 compared with the testosterone group. These differences indicate that treatment benefits diminished with cessation of treatment.

The 300 mcg/day testosterone transdermal system demonstrated a favorable safety profile for exposure up to 78 weeks in two studies in surgically menopausal women with HSDD, Studies SM 1 and SM 2. The total number of adverse events and the proportion of patients experiencing were similar in the testosterone and placebo groups during the 6-month, double-blind period of these studies. No significant safety concerns were identified during follow-up safety extension periods in which all patients received open-label active treatment for a total testosterorone exposure of up to 78 weeks. The most common adverse event in both treatment groups during the double-blind period was application site reaction; most of these reactions were mild or moderate in severity and did not lead to study discontinuation. Increases in the proportion of patients with acne and hirsutism reported as adverse events were seen in the testosterone group compared with placebo in the 24-week, double blind period of Study SM 2. These events were generally mild and did not result in discontinuation of treatment.

Laboratory parameters were carefully examined to assess potential risks, particularly with respect to cardiovascular and breast safety. No clinically important changes in laboratory parameters were observed with testosterone treatment with exposure of up to 78 weeks in the extension studies.

Safety data from 2 studies in naturally menopausal women with HSDD [a 6-month, double-blind, placebo-controlled study, NM 1 (Study 2002006), and a 12-month, double-blind, placebo-controlled study, NM 2 (Study 2002005); Executive Summary Table 1] were consistent with the findings in the surgically menopausal population and support the favorable safety profile of the transdermal system.

Testosterone is widely distributed in the body. In women, testosterone circulates in blood either bound to sex hormone binding globulin (SHBG, 65-80%), bound to albumin (20-30%), or as the free hormone (0.5-2%), which along with the testosterone component bound to albumin constitutes the bioavailable testosterone. The proposed product contains a total of 8.4 mg of testosterone and systemically delivers a nominal dose of 300 mcg/day over a 3-4 day wear period. The mean serum concentrations of free and total testosterone attains peak concentrations within 24-36 hours after system application and remained in a relatively narrow range (difference between C_{max} and C_{avg} is approximately 30%) over the entire wear period. Once the transdermal system is removed, the serum concentrations of testosterone drop rapidly (within 12 hours) to near baseline values. In efficacy and safety studies, treatment with the 300 mcg/day testosterone transdermal system increased median serum free testosterone concentration to within the premenopausal reference range. Increases in testosterone seen at 24 weeks were maintained through 78 weeks of treatment. There was no evidence of accumulation of testosterone with long-term dosing. Testosterone treatment did not change either serum estradiol or SHBG levels. Among patients receiving testosterone transdermal treatment, patients receiving oral concomitant estrogen had higher SHBG levels and lower free testosterone levels than patients on transdermal concomitant estrogen. Statistically significant correlations were observed between serum free testosterone levels and efficacy measures and between serum free testosterone levels and hirsutism. There were no associations between maximum serum free testosterone concentrations and changes in laboratory parameters.

Overall, the risks associated with administration of the 300 mcg/day testosterone transdermal system for up to 52 to 78 weeks were low and acceptable to patients (based on a low level of withdrawals due to adverse events) and the benefits are clinically meaningful for surgically menopausal patients with HSDD on concomitant estrogen. The 300 mcg/day testosterone transdermal system is effective and has a favorable safety profile when used for the treatment of HSDD in surgically menopausal women on concomitant estrogen therapy.

2. Introduction

2.1 Hypoactive Sexual Desire Disorder: Definition and Impact

Hypoactive sexual desire disorder is defined in the DSM-IV as a condition characterized by low or absent sexual desire that causes personal distress or difficulties. Estimates of its prevalence indicate that from 17% to 30% of the 10 million surgically menopausal women in the US may have this condition, which is associated with negative effects on the women and on their relationships. At present, there is no approved pharmacologic treatment and there is a need for safe and effective agents to treat this condition.

Definition

Hypoactive sexual desire disorder (HSDD) is the persistent or recurrent deficiency or absence of sexual thoughts, fantasies and/or desire for, or receptivity for, sexual activity, which causes marked personal distress or interpersonal difficulties and is not better accounted for by another Axis I disorder (DSM-IV, American Psychiatric Association, 2000). The disorder is described as being frequently associated with problems of sexual arousal or with orgasm difficulties. The DSM-IV also states that " individuals with hypoactive sexual desire disorder may have difficulties developing stable sexual relationships and may have marital dissatisfaction and disruption."

Prevalence

Estimates of the proportion of women who could be classified as having low sexual desire have ranged from 7% to 33%, depending on the population studied and the definition being used (Bancroft et al., 2003; Laumann et al., 1999; Dunn et al., 1998; Osborn et al., 1988; Geiss et al., 2003; Fugl-Meyer and Fugl-Meyer, 1999; Najman et al., 2003; Richters et al., 2003).

A large, multinational study (the Women's International Study of Health and Sexuality, or WISHeS) was conducted by Procter & Gamble Pharmaceuticals, Inc. (P&GP) to obtain estimates of the occurrence of low sexual desire or other sexual complaints and the distress associated with these complaints in pre-, peri-, and postmenopausal women aged 20-70 years. The U.S. portion of this study found that 46% of surgically menopausal women aged 20-49 and 38% of surgically menopausal women aged 50-70 reported decreased interest in sex. Of these surgically menopausal women with low sexual desire, 66% of those aged 20-49 years and 44% of those aged 50-70 years reported being very or extremely bothered by their decreased interest in sex (Leiblum et al., 2003). Based on these estimates, 30% of surgically menopausal women aged 20-49 and 17% of those aged 50-70 report decreased interest in sex and being very or extremely bothered by this decreased interest. The European portion of this study, conducted in France, Germany, Italy, and the U.K., found that 26-39% of surgically menopausal women aged 20-49 and 31-42% of surgically menopausal women aged 50-70 reported decreased interest in sex (Graziottin & Koochaki, 2003). Of these surgically menopausal women with low sexual desire, 43% of those aged 20-49 and 21% of those aged 50-70 years reported being very or extremely bothered by their decreased interest in sex (Graziottin & Koochaki, 2003). Low sexual desire was associated in both studies with significantly less frequent sexual activity, including low frequencies of orgasm and intercourse. Surgically menopausal women with decreased interest in sex were significantly less satisfied with their sexual lives and with their relationships than women with normal sexual desire.

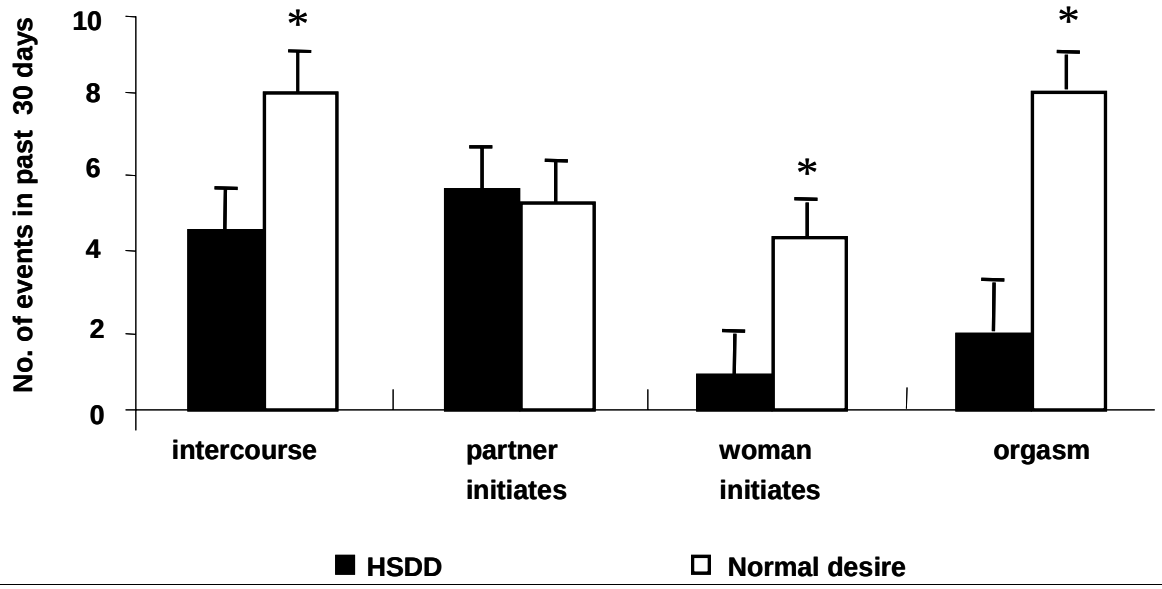
Approximately 10 million women in the US are surgically menopausal (Mattson Jack epidemiologic data, 2004).

Impact of HSDD

Low sexual desire was associated with significantly less frequent sexual activity, including low frequencies of orgasm and intercourse (Leiblum et al., 2003). Surgically menopausal women with decreased interest in sex were significantly less satisfied with their sexual lives and with their relationships than women with higher sexual desire.

The WISHeS also found that menopausal women with HSDD had significantly fewer episodes of sexual activity, fewer orgasms, and fewer episodes of satisfying sexual activity than age-matched menopausal women with normal libido ($p \leq 0.01$) (Figure 1).

Figure 1
Frequency of sexual activities in the past 30 days for women with HSDD and women with normal desire. Data from the WISHeS study.



HSDD=hypoactive sexual desire disorder. HSDD group, n=73; normal desire group, n=346.
*Asterisk indicates significant difference between groups. Data on file, Procter & Gamble Pharmaceutcials.

The impact of HSDD on women was also evaluated by asking women to indicate the frequency with which they experienced a series of emotions or psychological states as a result of their low sexual desire (Table 1). Women with the condition expressed strikingly different emotions compared with women who reported having normal desire.

Table 1.
Emotions and feelings associated with HSDD in menopausal women.
Data from the WISHES survey.

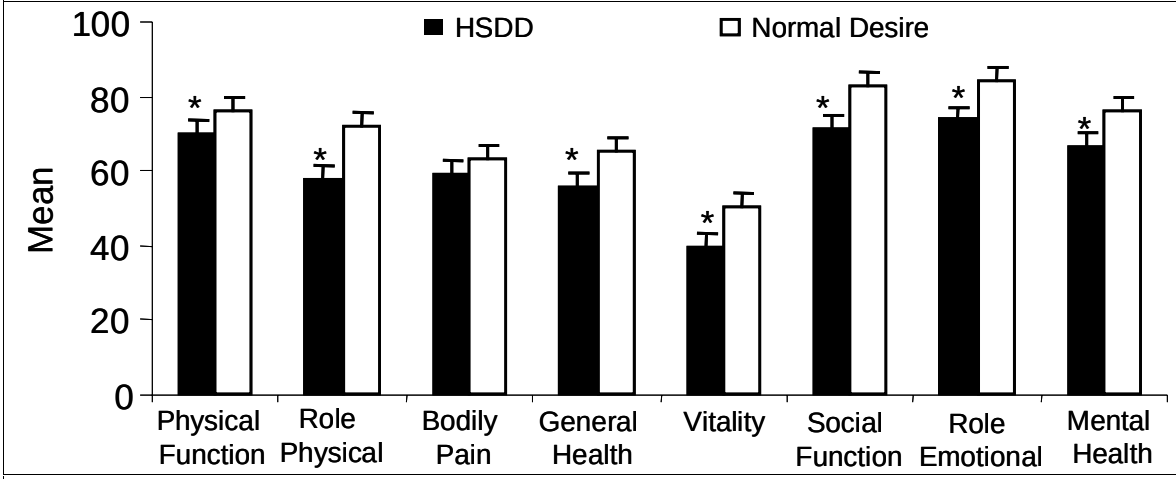
I felt _____ because of my lack of interest in sex.	**Women with HSDD N=73 n (%)**	**Women with Normal Desire N=346 n (%)**
Low self esteem	40 (56)	14 (4)
Ashamed	36 (49)	15 (4)
Like a sexual failure	43 (59)	14 (4)
Less feminine	47 (64)	20 (6)
Hopeless	54 (74)	27 (8)
Troubled	51 (70)	18 (5)
Frustrated	58 (79)	16 (5)
Concerned	62 (85)	24 (7)
Unhappy	64 (88)	35 (10)
Like I was letting my partner down	65 (89)	29 (8)

HSDD=hypoactive sexual desire disorder
Percents are based upon number of women for whom data were available.
Data on file, Procter & Gamble Pharmaceuticals.

In addition to negative feelings about themselves, women often express concern about the effect of their low desire on the partner and on the relationship.

The impact of HSDD on overall health status has also been evaluated in the WISHeS using the SF-36 Health Survey, a well-established instrument for such assessments. Statistically significant decreases were observed in all domains of the SF-36 in women with HSDD compared with women reporting normal desire (Figure 2).

Figure 2.
SF-36 domain scores in women with HSDD and women with normal desire.



HSDD=hypoactive sexual desire disorder. HSDD group, n=73; normal desire group, n=346. Asterisk indicates significant difference between groups.

Despite some level of debate among researchers about measurement issues and operational definitions of the sexual dysfunctions, it is clear that a clinically important proportion of surgically menopausal women have HSDD and suffer from its impact on their lives and relationships.

Physiology of HSDD in Surgically Menopausal Women

Surgically menopausal women typically experience a 50% reduction in serum testosterone compared with their preoperative levels (Judd et al., 1974; Hughes et al., 1991). In surgically menopausal women, the physical changes associated with menopause can occur quickly because of the sudden drop in hormone levels. Many of these women present with a symptom complex that includes sexual dysfunction secondary to a decline in androgen levels (Lobo, 2001).

Abnormalities in testosterone levels are recognized in the DSM-IV as one cause of HSDD. The usefulness of testosterone in treating HSDD among menopausal women has been suggested by a number of small research studies since the 1950s (Cameron and Braunstein, 2004). However, the meaningfulness of these studies has been limited by study design factors, small sample sizes, and the lack of valid and reliable instruments for measuring sexual function in menopausal women.

The effects of testosterone implants or injections on sexual function in postmenopausal women also receiving estrogen have been evaluated in previous studies (Davis et al., 1995; Sherwin & Gelfand, 1987). These studies showed an additive effect of testosterone with estrogen over estrogen alone. A later randomized, placebo-controlled study evaluated the 150 mcg/day and 300 mcg/day doses of TTS in surgically menopausal women on stable doses of estrogen and found improvements in frequency of sexual activity and in pleasure/orgasm, as measured by the Brief Index of Sexual Functioning in Women, and in well-being and mood, as measured by the Psychological General Well-Being index (Shifren et al., 2000).

Need for Safe and Effective Treatments

None of the current androgen products available by prescription in the U.S. are formulated for the safe and effective treatment of HSDD in women. Marketed testosterone products indicated for the treatment of hypogonadism in men deliver about 10 to 20 times the concentrations of testosterone than are necessary for treatment of HSDD in women. In the absence of approved products that deliver testosterone levels appropriate for women, these high-dose male products are being used off-label by women, despite the fact that the product labels list use by women as a contraindication. During 2003, 21% of the total prescriptions of branded testosterone products for men (i.e., Depo®-Testosterone, Androgel®, Testoderm®, Testoderm® TTS, Androderm®) were written for women (National Disease and Therapeutic Index, IMS Health, 2003), and female sexual dysfunction is one of the most common diagnoses associated with these prescriptions. This figure represents 145,000 prescriptions and may be an underestimate because some prescriptions may be written in a spouse's name to avoid problems with insurance reimbursement. The levels of testosterone these products deliver are 10-20 times higher than the levels needed for women with HSDD.

In addition to the brand name products, use of generic and compounded testosterone products by women is also substantial. Over the years 2000-2003, 1,315,000 prescriptions for generic or compounded testosterone products were written for women, with 114,000 of these written for women with the diagnosis of female sexual dysfunction (National Disease and Therapeutic Index, IMS Health, 2003). Although some compounded products may be prepared at lower testosterone concentrations that are more appropriate for women, compounded products in general are subject to fewer quality controls than drug products produced by pharmaceutical manufacturers, and may not be accurately prepared or fully characterized (FDA/Center for Drug Evaluation and Research. Report: Limited FDA survey of compounded drug products).

Evidence of off-label use of male testosterone products and compounded or generic testosterone by women with a diagnosis of female sexual dysfunction demonstrates that there is a substantial and unmet medical need for a testosterone product whose safety and efficacy in women has been established.

2.2 Product Description and Intended Use

Intrinsa is a 28 cm^2 matrix transdermal system containing 8.4 mg testosterone that delivers approximately 300 mcg/day of testosterone systemically when worn on the abdomen and changed twice weekly. The proposed indication is:

> "Intrinsa is indicated for the treatment of hypoactive sexual desire disorder in surgically menopausal women receiving concomitant estrogen therapy.
> Hypoactive sexual desire disorder is the persistent or recurrent deficiency (or absence) of sexual thoughts/fantasies and/or desire for or receptivity for sexual activity, which causes personal distress or interpersonal difficulties. Low sexual desire may be associated with low sexual activity, sexual arousal problems or orgasm difficulties."

When P&GP began clinical development of a dose form that would deliver testosterone safely and effectively to women, a transdermal dosage form was selected for its ability to systemically deliver a relatively constant and low dose of testosterone that is not affected by first pass hepatic metabolism.

3. Clinical Program

3.1 Instrument development

Because no existing instrument was patient-based and designed specifically to measure aspects of sexuality important to women with HSDD, P&GP undertook an extensive program of instrument development. This program was based on information obtained during one-on-one interviews with patients and took place in the US and Europe, in seven languages. Three instruments were developed: the Sexual Activity Log (SAL)© that captures the number of sexual episodes, the Profile of Female Sexual Function (PFSF)© that measures desire and other aspects of sexuality, and the Personal Distress Scale (PDS)© that measures distress associated with low sexual desire. These instruments have been shown to be valid and reliable in women with HSDD. This development program was reviewed with FDA, and the Division of Reproductive and Urologic Drug Products agreed to the use of these 3 instruments in the Phase III studies.

At the start of the Intrinsa clinical development program, a number of instruments for the assessment of sexual function had been published in the scientific literature. None of them, however, were developed using a patient-based approach designed to capture the aspects of sexual function that were reported as most important by women with HSDD. In addition, none of the published instruments were available in translated versions that had been validated in a wide range of languages and cultural groups. Therefore, psychometric instruments that would be valid and reliable for measuring clinical outcomes in menopausal women receiving treatment for HSDD had to be developed.

The desired approach to psychometric instrument development, using a population of menopausal women with HSDD, was outlined by the FDA's Division of Reproductive and Urologic Drug Products (DRUDP). This approach was then followed by P&GP to develop 3 psychometric instruments to capture self-reports of sexual activities, thoughts, and feelings as efficacy endpoints in the testosterone transdermal system safety and efficacy studies. These instruments were the Sexual Activity Log© (SAL) that enables patients to accurately count and record episodes of sexual activity, the Profile of Female Sexual Function© (PFSF) that measures sexual desire and other aspects of sexual function, and the Personal Distress Scale© (PDS), that measures personal distress associated with patients' lack of interest in sex

The development of the SAL, PFSF, and PDS included 3 major stages, depicted graphically in Figure 3.

Figure 3
Development of Instruments Used to Measure Sexual Activity and Function in Clinical Studies

These 3 stages of instrument development are described in the text below. More detail about the development and validation process can be found in publications by Derogatis et al., 2004, and McHorney et al., 2004.

3.1.1 Preliminary Instrument Development

This first phase of instrument development was used to generate potential questions, inventory items, and domains. For the PFSF and PDS, this phase of instrument development began with a series of interviews (some one-on-one and some in focus groups) with menopausal patients meeting diagnostic criteria for HSDD to qualitatively assess the nature and importance of issues related to their loss of sexual desire. These patients were either surgically or naturally menopausal and were taking estrogen or estrogen/progestin therapy. A series of interviews was also conducted with clinicians to understand their clinical experiences with HSDD patients. The interviews at this stage were conducted in the U.S., U.K., Germany, France, and Italy, with 64 surgically menopausal women, 25 naturally menopausal women, and 96 clinicians participating.

The interviews indicated that there were important unmet medical needs for patients with HSDD after menopause. Many aspects of sexual function were reported to be affected, including most notably a dramatic loss of libido, decrease in sexual activity, and decrease in pleasure and satisfaction from sexual activity when it occurred. The observations of physicians and other clinicians closely matched those of the patients. In addition, it was noted that the same constellation of symptoms and concerns was expressed by patients and clinicians in all of the countries in which interviews were conducted.

To complete the qualitative phase of psychometric instrument development, a last set of focus group interviews was conducted with an additional 27 surgically menopausal women with HSDD. The purpose of this last set of interviews was to generate verbatim statements from patients as potential items for inclusion in the PFSF and PDS. These interviews were conducted by an

experienced psychometrician and generated over 450 potential items describing subjective aspects of HSDD and associated distress in the population of oophorectomized women.

The final step in the preliminary instrument development was to produce the initial version of the PFSF and PDS. A group of respected psychometricians undertook this work, assisted by P&GP employees with expertise in focus groups and psychological measurement. This team reviewed the entire catalog of potential items and selected the smallest number required to capture the range of concepts expressed. This process produced a set of 83 items arranged into hypothesized domains constituting preliminary versions of the PFSF and PDS.

At the same time as the PFSF and PDS instrument development was preceding, the preliminary development of the SAL was being undertaken in a separate set of interviews with oophorectomized and non-oophorectomized women. The SAL was developed to provide a way for patients in clinical trials of therapies for HSDD to accurately count sexual activity and to classify activity that did and did not include orgasm, and was or was not satisfying. Because women may experience sexual activity that they consider satisfying even if no orgasm occurs, it was important to identify the optimal format and most appropriate wording for capturing satisfying sexual activity in a way that was consistent with women's experiences.

The initial development of the SAL began with interviews conducted in several cities in the U.S. and U.K. to learn how women quantify their sexual activity. This was followed by a process of constructing alternative versions of a diary and testing them in 42 one-on-one cognitive interviews with women ages 35-70. A cognitive interview is a structured interview in which a subject fills out one or more versions of a psychometric instrument and then is asked about what she thought was meant by each question and what her thought process was as she answered. Results of these interviews were used to further refine successive versions of the SAL.

Major findings from the interviews were that women tended to count sexual activity by thinking about an episode of sexual activity as one event, rather than by counting particular types of sexual contact that occurred during the episode, and that women tended to think about their episodes of sexual activity in 2 categories: those that included intercourse and those that did not include intercourse. Women with low sexual activity strongly preferred a weekly diary to a daily diary, and were able to recall sexual activity over this period without difficulty.

In the development of the SAL, 8 different versions of the instrument were tested, evolving through a number of different formats. By the end of the process, a version of the SAL had been developed that was understandable and easy to use, and provided data on outcomes needed to examine clinical efficacy of HSDD treatments. This version was taken forward into the next stage of instrument development, along with the preliminary versions of the PFSF and PDS.

3.1.2 Qualitative Linguistic Development and Validation

This next stage of instrument development was undertaken to translate the instruments into target languages and to ensure content validity of the instruments in all translated versions. MAPI Research Institute in Lyon, France was contracted to translate the PFSF, PDS, and SAL into the target languages: English as spoken in the U.S., U.K., and Australia; Spanish as spoken in the

U.S.; native and Canadian French; Dutch; German; and Italian. Cognitive interviews with the translated instruments were conducted with 111 surgically menopausal women in 8 countries to explore the women's understanding of each item and to identify items with ambiguous or multiple meanings. Finally, a separate group of translators was assembled by MAPI to perform an international harmonization of the instruments. This process consisted of a word-by-word and item-by-item review of the instruments with all translators simultaneously present to ensure cross-language uniformity of meaning. At the conclusion of this process, translated versions of all 3 instruments were ready for quantitative development and validation studies.

3.1.3 Quantitative Development and Validation

Following the qualitative development and international harmonization, versions of the PFSF, PDS, and SAL were developed and evaluated in 3 non-randomized, parallel-group, multicenter clinical studies conducted in the U.S., Canada, and Europe/Australia (Studies 1999069, 1999070, and 1999071). These studies enrolled surgically menopausal women who met criteria for HSDD (n = 224 in U.S., 33 in Canada, 90 in Europe and Australia) and age-matched control women who had intact ovaries and normal libido (n = 146 in U.S., 32 in Canada, 82 in Europe and Australia). Surgically menopausal women in these studies were receiving estrogen therapy. Subjects completed the SAL at home weekly during the 4-week studies and the PFSF and PDS at the clinical sites after 2 weeks and after 4 weeks.

Item reduction with the PFSF and PDS was performed using data from the U.S. study to determine the most effective subset of items for inclusion in the final versions of the instruments and the domains that best captured the dimensions of sexual function and distress that were being characterized. Data from the Canadian and European/Australian studies were then analyzed to determine whether the U.S. results also applied to these countries and to identify any modifications that needed to be made.

A number of well-accepted analysis techniques were used to determine the best items and domains for the PFSF and PDS (Nunnally and Bernstein, 1994; McHorney et al., 2004). Final versions of the PFSF and PDS were created on the basis of these analyses. The SAL was found to have acceptable reliability and validity as tested; therefore, no further changes were made to the SAL.

The final versions of the PFSF, PDS, and SAL performed in similar ways in the U.S., Canadian, and European/Australian studies and demonstrated construct validity, reliability, internal consistency, and the ability to discriminate between surgically menopausal women with HSDD and age-matched normal women. Sexuality profiles of women with HSDD, as well as the degree of distress caused by HSDD in menopausal women, are similar in the U.S., Canada, and Europe/Australia, as can be seen in Figures 4-6 below.

Figure 4
Total Satisfying Sexual Episodes per 4 Weeks in Women with HSDD and Normal Women in Europe, the U.S., and Canada as Measured by the SAL.

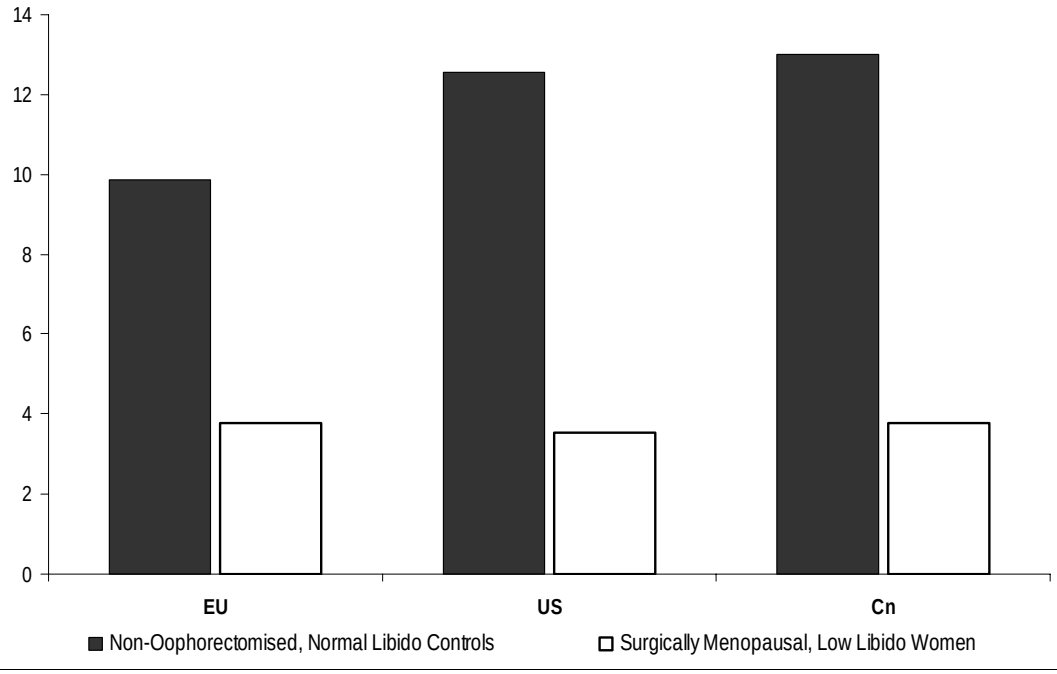
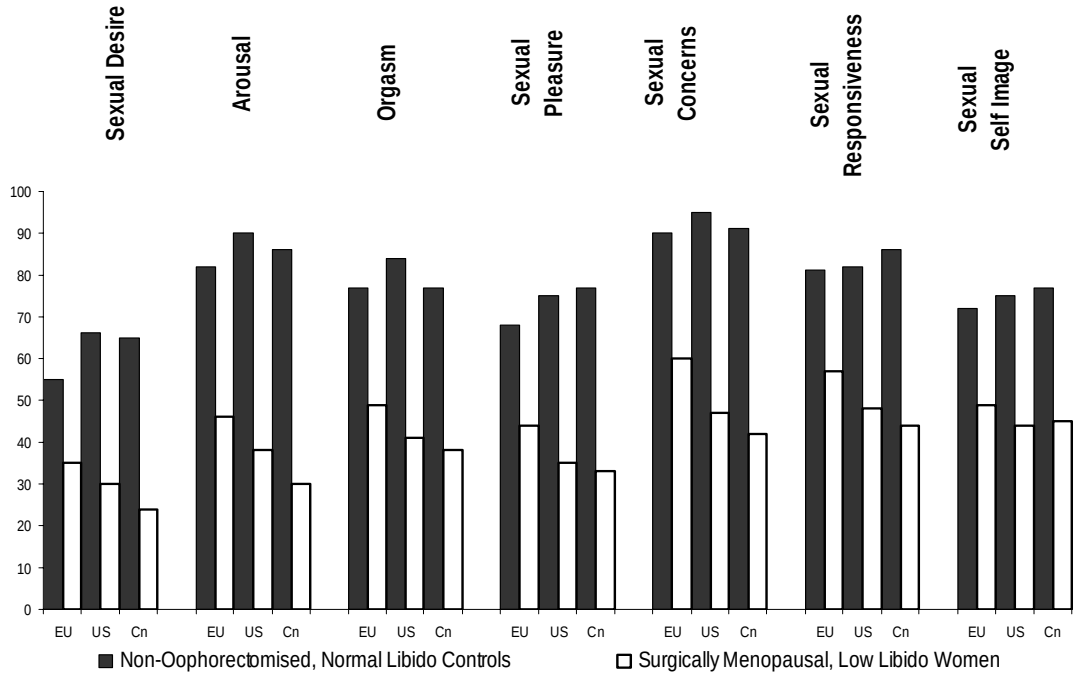
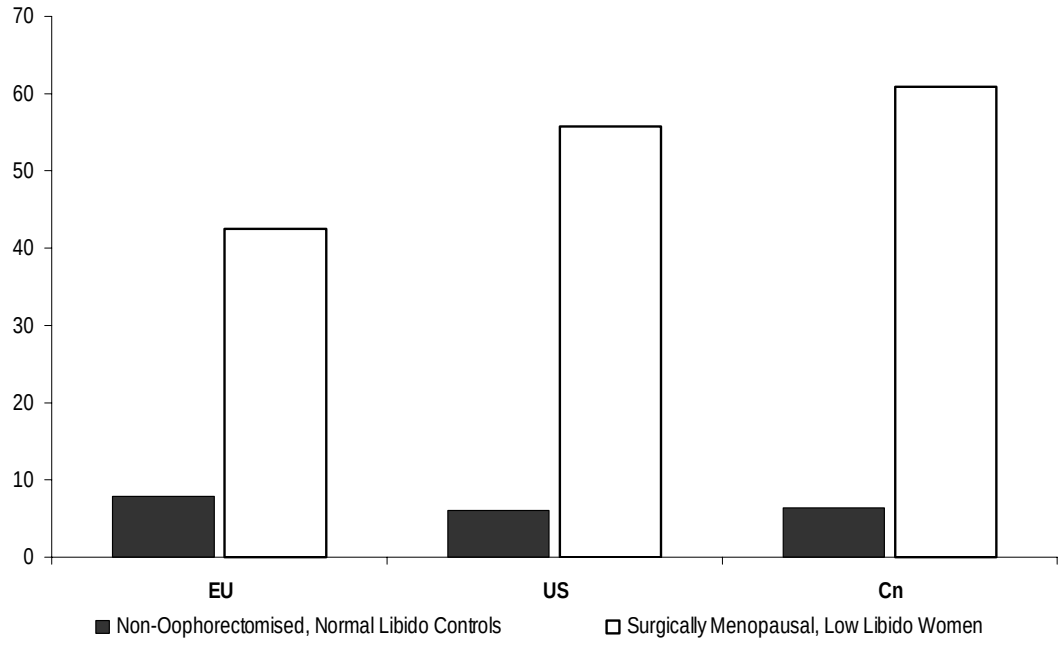


Figure 5
Sexuality Profiles for Women with HSDD and Normal Women in Europe, the U.S., and Canada as Measured by the PFSF.



HSDD=hypoactive sexual desire disorder; PFSF=Profile of Female Sexual Function; EU=Europe; US=United States; Cn=Canada.

Figure 6
Personal Distress in Women with HSDD and Normal Women in Europe, the U.S., and Canada as Measured by the PDS.



HSDD=hypoactive sexual desire disorder; PDS=Personal Distress Scale; EU=Europe; US=United States; Cn=Canada.

To assure the reliability and validity of the final instruments, as well as to extend the validation to naturally menopausal women with HSDD, a confirmatory validation study was undertaken. In this nonrandomized, parallel group, multicenter study in the U.S. (Study 2000124), surgically menopausal women who met criteria for HSDD (n = 59), naturally menopausal women who met criteria for HSDD (n = 88), and age-matched control women who had intact ovaries and normal libido (n = 104), completed the SAL at home weekly for 4 weeks and the PFSF, PDS, and Derogatis Index of Sexual Function (DISF) at baseline and at 4 weeks. The DISF, a previously developed instrument, was included in order to compare the results using that instrument with those obtained using the new instruments. Analysis of study results confirmed that the final instruments were valid and reliable in surgically menopausal women with HSDD and extended this conclusion to naturally menopausal women with HSDD. All tests of discriminant ability, test-retest reliability, internal consistency, and convergent validity performed acceptably. Further details of the PFSF confirmatory validation study can be found in the publication by Derogatis et al., 2004.

3.1.4 Final Forms of the Psychometric Instruments

Taken together, the PFSF, PDS, and SAL measure a wide range of sexual parameters in women with HSDD, including activity (SAL), desire, and associated features of sexuality, such as arousal and pleasure (PFSF), and personal distress experienced by women with the disorder (PDS). All efficacy endpoints in the Phase III studies were evaluated using these 3 instruments. The use of

the SAL, PFSF, and PDS in Phase III clinical trials of TTS was discussed with and agreed to by the Division of Reproductive and Urologic Drug Products (DRUDP) at FDA.

The final forms of these instruments are outlined in Table 2.

Table 2
Instruments Used to Measure Sexual Activity and Function in TTS Clinical Studies

Sexual Activity Log (SAL)

Counts sexual activity, with and without intercourse and orgasm, over the previous 7 days.

Profile of Female Sexual Function (PFSF)

Measures sexual function in 7 Domains over the previous 30 days.

Endpoints:

- Desire
- Arousal
- Pleasure
- Orgasm
- Responsiveness
- Self Image
- Concerns

Scoring: Scores on each domain are normalized so that they range from 0 - 100. Scores of 0, 20, 40, 60, 80, and 100 correspond, on average, to the following categories of response: "Never," "Seldom," "Sometimes," "Often," "Very Often," and "Always," respectively. Note that an increase in the Sexual Concerns score indicates a decrease in patients' concerns related to sexuality.

Personal Distress Scale (PDS)

Measures how a woman has felt about her lack of interest in sex over the previous 30 days.

Endpoint:

- Distress

Scoring: Scores on the PDS are normalized so that they range from 0 - 100. Scores of 0, 20, 40, 60, 80, and 100 correspond, on average, to the following categories of response: "Never," "Seldom," "Sometimes," "Often," "Very Often," and "Always," respectively.

3.2 Efficacy in Surgically Menopausal Women with HSDD

The 300 mcg testosterone transdermal system is effective in the treatment of HSDD in surgically menopausal women on concomitant estrogen therapy, as shown in 2 Phase III studies and in 2 Phase IIb studies. The women who received testosterone experienced increased frequency of satisfying sexual activity, increased sexual desire, and decreased distress compared with women who received placebo. Improvements were also seen in all other efficacy endpoints (i.e., arousal, pleasure, orgasm, responsiveness, self-image, concerns). Overall, treatment benefits were seen as early as 4 weeks with maximal effects in total satisfying episodes and sexual desire seen by approximately 12 weeks. Beneficial effects were maintained for the remainder of the 24-week efficacy period. A consistent pattern of efficacy was seen across subpopulations.

The two Phase III trials and one of two Phase IIb safety and efficacy trials were conducted in the US, Canada and Australia; the other supporting efficacy trial was conducted in western Europe and Australia. These trials were of nearly identical design (Table 3). US residents comprised ninety percent or greater of the population in the pivotal trials.

Table 3
Selected Design Characteristics of Studies in Surgically Menopausal Women with HSDD

Study Number	Phase/ Region	Study Design	Concomitant Estrogen Therapy	Testosterone Dose Groups mcg/day (ITT Patients)
Pivotal Phase III Studies				
SM 1 (2001133)	III/ US, Canada, Australia	24-week randomized, DB, PC, efficacy and safety period followed by 28-week OL safety period in SM women. (An additional 52-week safety extension is on-going.)	Oral or transdermal	0 (n = 279) 300 (n = 283)
SM 2 (2001134)	III/ US, Canada, Australia	24-week randomized, DB, PC, efficacy and safety period followed by 28-week OL safety period in SM women. (An additional 52-week safety extension is on-going.)	Oral or transdermal	0 (n = 266) 300 (n = 266)
Supporting Studies				
SM 1 + SM2 Persistence of Treatment Benefit	III/ US, Canada, Australia	13-week randomized, DB, PC follow-up period (Weeks 53-65) to evaluate persistence of treatment benefit in women who had participated in studies SM 1 and SM 2.	Oral or transdermal	0 (n = 103) 300 (n = 102)
CMK US030993 Clinical Relevance	III/ US	One-on-one patient interviews conducted immediately after the 24-week DB period of Studies SM 1 and SM 2.	Oral or transdermal	0 (n = 68) 300 (n = 64)
Phase II Studies				
1999068	IIb/ US	24-week randomized, DB, PC, efficacy and safety period followed by 28-week DB, PC safety extension period in SM women. Dose ranging study.	Oral	0 (n = 119) 150 (n = 107) 300 (n = 110) 450 (n = 111)
1999092	IIb/ EU, Australia	24-week randomized, DB, PC, efficacy and safety in SM women	Transdermal	0 (n = 39) 300 (n = 37)
T96006	IIa/ US	36-week randomized, DB, PC, 3-period crossover in SM women (n = 65) (Reported in Shifren et al., 2000)	Oral	0 150 300

DB = double blind; PC = placebo controlled; OL = open label; SM = surgically menopausal; NM = naturally menopausal; ITT = intent-to-treat.

3.2.1 Patient Population

Patients in these clinical trials had all undergone hysterectomy and bilateral oophorectomy at least 6 months before study entry. They were generally healthy, with no serious medical disorders, and had been on stable concomitant estrogen therapy for at least 3 months before study entry. They were in stable monogamous sexual relationships that they perceived to be secure and communicative, with partners who were sexually functional. In the Phase III studies, the average age was approximately 49 years and the length of the relationship was approximately 19 years (see Table 9). Although women from 20 to 70 years of age were allowed to enroll, only 26

women (<2%) in the combined Phase IIb and Phase III study population were ≥ 65 years of age, and only 90 women (6%) were aged 60 to 64 years.

The process for identifying patients with hypoactive sexual desire disorder for inclusion in the clinical trials was developed in accordance with the diagnostic criteria for HSDD described in the DSM-IV (American Psychiatric Association, 2000) and with the FDA's draft guidance on development of drugs for female sexual dysfunction.

The 5 screening questions to identify patients with low libido beginning after menopause and causing distress were:

- Before your ovaries were removed, would you say that, in general, your sex life was good and satisfying?
- Since your ovaries were removed, do you feel you have experienced a meaningful loss in your level of desire for sex?
- Since your ovaries were removed, do you feel you have experienced a significant decrease in your sexual activity?
- Are you concerned about or bothered by your current level of desire for or interest in sex?
- Would you like to see an increase in your level of interest in or desire for sex and sexual activity?

Exclusion criteria were used, along with the 5 questions, to ensure that patients had HSDD and that this condition was acquired following oophorectomy. The study exclusion criteria were designed to prevent enrollment of patients whose low libido could likely be accounted for by other factors, such as depression, medication use, substance abuse, or by some other psychological or medical condition. The study inclusion/exclusion criteria were in alignment with the Princeton Consensus Statement's decision-making algorithm for identifying women with HSDD who are appropriate candidates for androgen therapy (Bachman et al., 2002). This decision-making algorithm included the requirement that menopausal HSDD patients be receiving estrogen therapy so that androgen effects could be assessed in a context of adequate estrogen to suppress vasomotor symptoms and vulvovaginal atrophy. DRUDP accepted the 5 screening questions and inclusion/exclusion criteria as valid for selection of the study population.

3.2.2 Efficacy Endpoints

The endpoints in the Phase IIb and Phase III clinical trials were consistent with the FDA's draft guidance, "Female Sexual Dysfunction: Clinical Development of Drug Products for Treatment" and the diagnostic criteria for HSDD from the DSM-IV-TR (American Psychiatric Association, 2000) and were prospectively defined in the study protocols and statistical analysis plans.

In accordance with guidance from FDA, total satisfying sexual activity was designated the primary efficacy endpoint in the Phase III trials and was also an important endpoint in the Phase IIb trials. Total satisfying sexual activity was calculated by summing episodes of satisfying sexual activity that included intercourse and episodes of satisfying sexual activity that did not include intercourse, as recorded by the SAL.

Two other efficacy endpoints, the increase in sexual desire as measured by the sexual desire domain of the PFSF and the decrease in distress as measured by the PDS, are defining features of HSDD and were given priority over other efficacy endpoints.

3.2.3 Phase II Studies

3.2.3.1 Design of Phase II Studies

Three Phase II efficacy studies were conducted in surgically menopausal women with HSDD on concomitant estrogen therapy. Of these, 2 Phase IIb trials (Studies 1999068 and 1999092) were randomized, placebo-controlled, double-blind, parallel-group studies (Table 4). The third study (Study T96006), a Phase IIa cross-over study using different measurement tools, has been described by Shifren et al., 2000.

Table 4. Phase IIb Studies
Design Characteristics

	Study 1999068 (N=447)	**Study 1999092 (N=77)**
Countries	US	UK, France, Germany, Holland, Italy, Australia
Doses (µg/day)	0, 150, 300, 450	0, 300
Estrogen use	Oral	Transdermal
Stratification	Premarin 0.625mg/day vs. other oral doses	0.05mg/day estradiol vs. other transdermal doses
Duration	24 weeks + 28 week safety extension	24 weeks
	Common Inclusion Criteria Answer 'yes' to ALL the following: • Before oophorectomy, was your sex life satisfying? • Since oophorectomy have you lost desire for sex? • Since oophorectomy has sexual activity decreased? • Are you concerned about you level of sexual desire? • Would you like to increase in sexual desire and activity?	• 20-70 years old and generally healthy • BMI in the range 18-30 • Surgically menopausal >1 year prior to study • Stable relationship, partner present >50% of the time • Serum free-T < 3.5pg/ml at baseline • Stable estrogen dose for > 3 months prior to study.

Study 1999068 (Phase IIb)

Study 1999068 was a multicenter, randomized, double-blind, placebo-controlled, parallel-group, dose-ranging study conducted in surgically menopausal women with HSDD on concomitant oral estrogen therapy that included a 24-week efficacy period and a 28-week safety extension period. Exclusion and inclusion criteria were similar to those used in the Phase III studies.

Patients were randomized to receive placebo or 150, 300, or 450 mcg/day testosterone. Two transdermal systems were worn simultaneously (14 cm^2 and 28 cm^2 systems) in combinations of active and placebo that, when combined, delivered 0, 150, 300, or 450 mcg/day testosterone. Patients applied the investigational transdermal systems to their abdomen twice weekly (each system was worn for approximately 3-4 days). All women were to maintain their concomitant oral estrogen therapy during the study.

The primary efficacy endpoints of this study were changes in sexual desire (as measured by the sexual desire domain of the PFSF) and frequency of satisfying sexual activity (as measured by the SAL). An analysis of covariance adjusting for pooled centers, baseline value, age and marital

status was used to assess the effect of treatment on changes in sexual desire. A GEE Poisson regression analysis was used to assess the effect of treatment on frequency of satisfying activity between 21 to 24 weeks adjusting for those covariates previously mentioned.

A gatekeeper approach was used to control type I error with testing over multiple primary endpoints and dose groups. For each endpoint, a linear dose response was tested using the linear contract corresponding to the treatment groups. Individual pairwise comparisons were made between each active treatment group and placebo but no adjustments for multiple statistical comparisons were made.

Secondary efficacy endpoints were analyzed using the methods described above for the primary efficacy endpoints.

A total of 447 patients were enrolled in the U.S. (39 clinical sites); 319 (71%) patients completed through Week 24. A total of 155 patients enrolled in the double-blind, placebo-controlled, 28-week safety extension period; 133 (86%) patients completed through Week 52. Patients in this study had to have a serum free testosterone level less than the median value of the reference range for premenopausal women and a body mass index (BMI) between 18 and 30 kg/m^2, in addition to the major inclusion criteria used in the Phase III studies (Table 7).

Treatment effects of 0, 150, 300, or 450 mcg/day transdermal testosterone on sexual functioning were measured by the SAL, PFSF, and PDS during the 24-week, double-blind efficacy period. Serum samples were analyzed for determination of free, total, and bioavailable testosterone; SHBG; free and total DHT; free and total estradiol; and estrone.

Study 1999092 (Phase IIb)

Study 1999092 was a multicenter, randomized, 24-week, DB, PC, parallel-group design study conducted in surgically menopausal women with HSDD on concomitant transdermal estrogen therapy. A total of 77 patients were enrolled in Europe and Australia (15 clinical sites); 61 (79%) patients completed through Week 24. Major inclusion criteria were similar to those in the other Phase IIb study, except that women had to be receiving a stable dose of transdermal (rather than oral) estrogen therapy prior to study entry. Patients were randomized to receive placebo or 300 mcg/day TTS for 24 weeks. The sexual desire domain of the PFSF and the frequency of total satisfying episodes from the SAL at the end of Week 24 were the co-primary efficacy endpoints. These efficacy endpoints were analyzed using the methods described above.

Serum samples were analyzed for determination of free, total, and bioavailable testosterone; SHBG; free and total DHT; free and total estradiol; and estrone.

Study T96006 (Phase IIa)

Study T96006 was a multicenter, randomized, double-blind, placebo-controlled, 3-period crossover study of 2 different doses of transdermally delivered testosterone (150 and 300 mcg/day) conducted in surgically menopausal women with HSDD who were receiving concomitant oral estrogen therapy. Each treatment period was 3 months long, and there was no

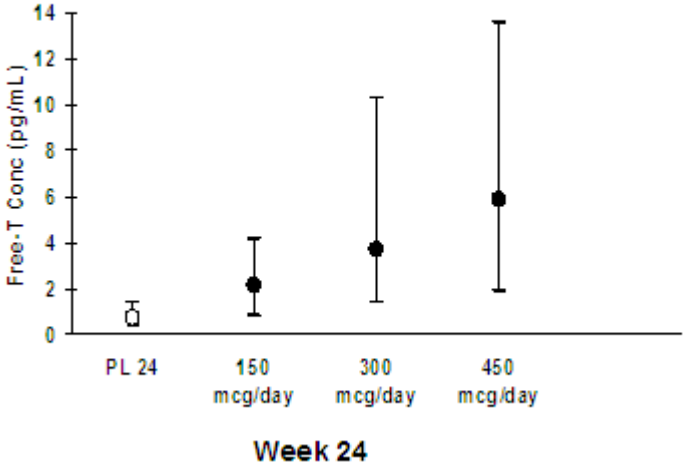
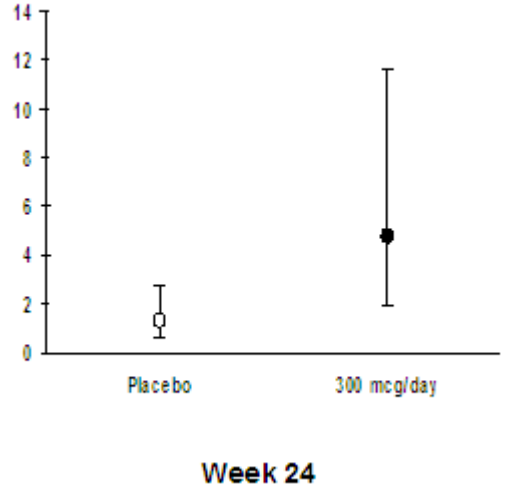
washout period between successive treatment periods. Sexual function, the primary efficacy variable, was evaluated using the Brief Index of Sexual Function in Women (BISF-W) (a 22-item, multiple-choice questionnaire). The 300 mcg/day testosterone dose resulted in a significantly higher BISF-W composite score ($p = 0.05$ for the comparison with placebo) and increases in BISF-W scores for frequency of sexual activity and pleasure-orgasm ($p = 0.03$ for both comparisons with placebo). No statistically significant improvements in the primary efficacy endpoints were observed for the 150 mcg/day dose. The results of Study T96006 were reported in the *New England Journal of Medicine* (Shifren et al., 2000).
Because this study had a cross-over design and used different instruments to measure efficacy, these study data were not combined with those of the other Phase II and the Phase III studies in the NDA. However, this study is supportive of the application, because it provides evidence of efficacy for the 300 mcg/dose testosterone transdermal system and no serious safety concerns were identified during the treatment periods.

3.2.3.2 Serum Testosterone Levels in Phase IIb Studies

The median serum free testosterone concentrations for the doses tested in the Phase IIb study 1999068, in which all patients were receiving oral concomitant estrogen, are shown in Figure 7. A linear relationship between dose and concentration was observed. In study 1999092, in which all patients were receiving transdermal concomitant estrogen, the median serum free testosterone level was approximately midway between the levels observed with the 300 mcg/day and 450 mcg/day dose in women on oral estrogen in Study 199068.

The free testosterone concentration with the 300 mcg/day dose in both studies was within the reference range established in 161 premenopausal women aged 18 to 49 years. Additional information about hormone concentrations following administration can be found in section 4.3 of this briefing document.

Figure 7
Serum Free Testosterone at 24 Weeks in Phase IIb Studies

Study 1999068	Study 1999092
	

Solid circles are median values; bars indicate 10th and 90th percentile ranges.

3.2.3.3 Efficacy in Phase IIb Studies

Study 1999068

Linear dose effects approached statistical significance for sexual desire at Week 24 ($p = 0.059$) and for the frequency of total satisfying episodes at Week 24 ($p = 0.062$).

Pairwise comparisons of active treatment with placebo demonstrated a statistically significant increase in the frequency of total satisfying episodes at Week 24 for the 300 mcg/day group compared with placebo, whereas no statistically significant differences were observed for the 150 mcg/day group or the 450 mcg/day group (Table 5 and Figure 8).

There was a statistically significant increase from baseline in the sexual desire score for the 300 mcg/day group at Week 24; the increase from baseline approached statistical significance for the 450 mcg/day group and was not statistically significant for the 150 mcg/day group (Table 6). The positive treatment effect observed in reducing personal distress was not statistically significant for any of the treatment groups at Week 24.

A positive treatment effect was observed with 300 mcg/day testosterone compared with placebo for a majority of the other PFSF domains (Figure 9) and SAL endpoints (data not shown). An increasing dose-response relationship was seen for some endpoints, while for others the greatest effect was seen with the 300 mcg/day dose.

This study demonstrated that the 300 mcg/day testosterone transdermal system improved sexual functioning in surgically menopausal women with HSDD on concomitant oral estrogen therapy.

Study 1999092

The increase from baseline in the frequency of total satisfying episodes approached statistical significance at Week 24 for the 300 mcg/day testosterone group compared with placebo (Table 5 and Figure 8). Statistically significant improvements in sexual desire and personal distress at Week 24 were observed with 300 mcg/day testosterone compared with placebo (Table 6). A positive treatment effect was observed for a majority of the other PFSF domains (Figure 10) and SAL endpoints (data not shown).

This study demonstrated that the 300 mcg/day testosterone transdermal system improved sexual functioning in surgically menopausal women with HSDD on concomitant transdermal estrogen therapy. These improvements were manifested by increases in sexual desire and in counts of sexual activity, satisfying sexual activity, and orgasm, and by decreases in personal distress.

Table 5
Frequency of Total Satisfying Episodes in Phase IIb Studies

Study Number	Testosterone doses (mcg/day)	n	Baseline Mean[a]	Mean Change from Baseline at Week 24[a]	Mean Weekly Rate at Week 24[b]	Ratio of Rates[c]	p-value[d]
1999068	0	112	0.70	0.30	0.97		
	150	99	0.91	0.27	0.99	1.02	0.8493
	300	108	0.73	0.58	1.26	1.30	0.0493
	450	107	0.65	0.54	1.14	1.18	0.1883
1999092	0	36	0.80	0.28	0.94		
	300	33	0.52	0.77	1.35	1.43	0.0641

[a] Baseline mean and mean change from baseline at Week 24 refer to the average weekly frequency of total satisfying sexual activity captured on the Sexual Activity Log.

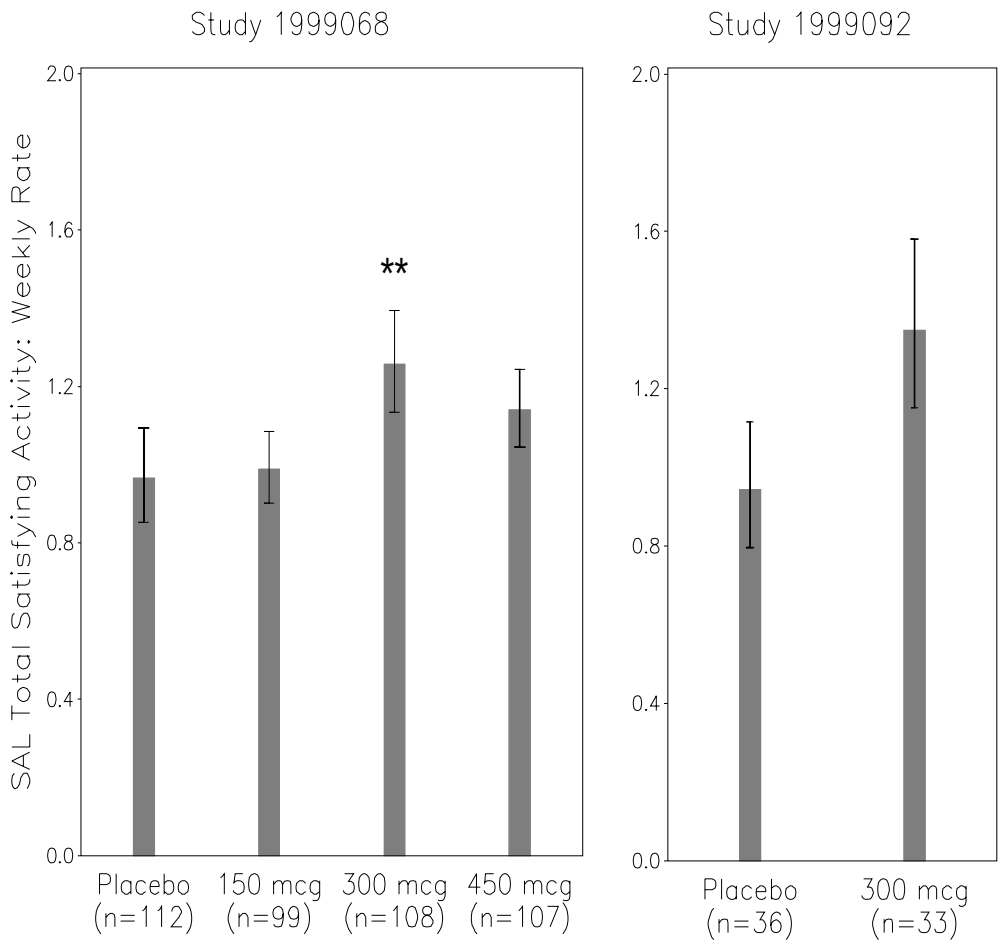
[b] Mean weekly rate adjusted for baseline rate, age, marital status, and pooled site.

[c] Ratio of rates corresponds to the ratio of the weekly rate of active treatment group to placebo, adjusted for baseline rate, age, marital status, and pooled site.

[d] Pairwise comparisons of active treatment with placebo in Study 1999068 were performed after tests for linear dose response in co-primary endpoints, sexual desire and total satisfying sexual activity (Poisson regression).

These results are shown graphically in Figure 8.

Figure 8
Changes in Frequency of Total Satisfying Sexual Activity in Phase II Studies.



The double asterisk indicates a statistically significant difference from placebo.

Table 6
Sexual Desire and Personal Distress in Phase IIb Studies

Study Number	Testosterone doses (mcg/day)	n	Baseline Mean	Mean Change from Baseline at Week 24[a]	p-value[b]
Sexual Desire					
1999068	0	101	20.14	8.38	
	150	93	20.80	10.94	0.3540
	300	102	20.94	13.67	0.0498
	450	101	19.91	12.86	0.0970
1999092	0	35	19.89	5.98	
	300	34	23.12	16.43	0.0214
Personal Distress[c]					
1999068	0	102	34.60	18.70	
	150	95	35.04	22.19	0.3839
	300	98	34.79	24.76	0.1258
	450	101	31.64	21.51	0.4721
1999092	0	31	44.47	3.49	
	300	29	44.25	22.81	0.0025

[a] Mean change from baseline at Week 24 adjusted for age, marital status, pooled centers, and baseline score. ANCOVA model/

[b] Pairwise comparison of mean change, active vs. placebo.

[c] An increase in the scores indicated a decrease in patients' distress. (For Studies SM 1 and SM 2, the Personal Distress scores were transformed so that a decrease in the scores indicated a decrease in patients' distress.)

Figure 9
Changes in PFSF Domains Over 24-Weeks Double-Blind Period in Study 1999068

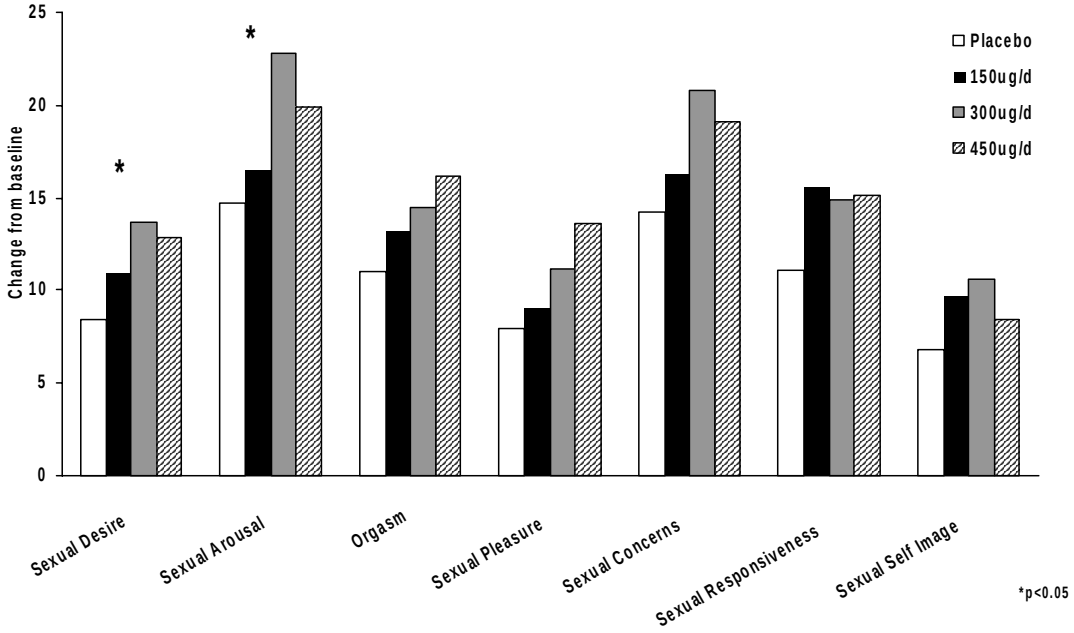
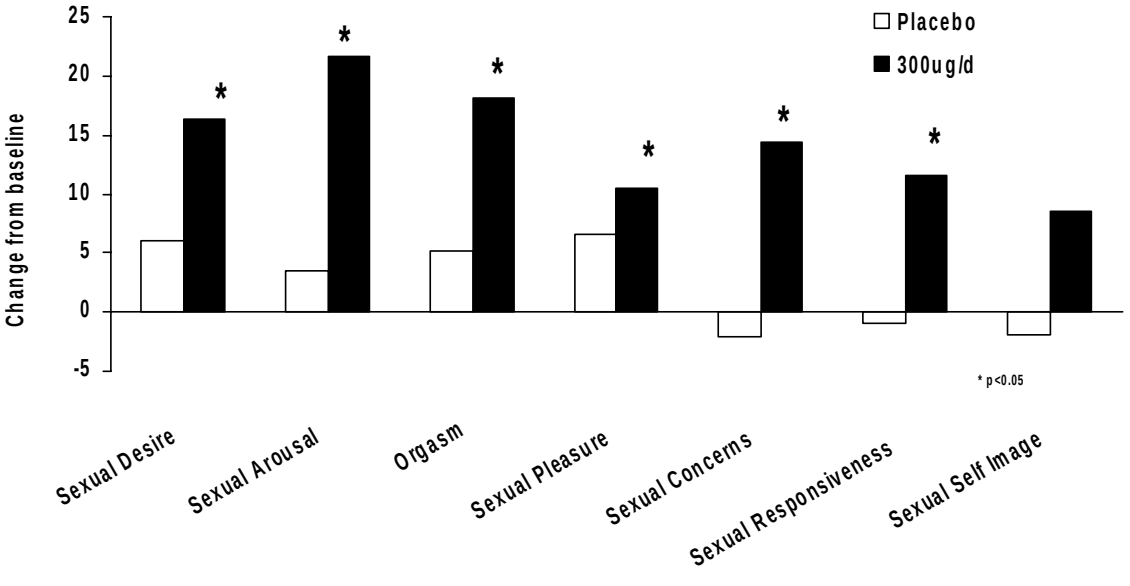


Figure 10
Changes in PFSF Domains Over 24-Weeks Double-Blind Period in Study 1999092



3.2.4 Phase III Studies

3.2.4.1 Design of Phase III Studies

The Phase III program for 300 mcg/day testosterone transdermal system treatment of surgically menopausal women with HSDD consisted of 2 adequate and well-controlled studies (SM 1 and SM 2) (Table 7 and Figure 11). The 300 mcg/day dose was chosen based on the Phase II studies discussed in the previous section.

These 2 studies were nearly identical in design (clinical laboratory tests differed slightly between the studies). Unlike the Phase IIb studies, the Phase III studies did not require patients to have low serum testosterone levels for study entry. Each study was a 52-week, multicenter, multinational study that included a 24-week, randomized, double-blind, placebo-controlled, parallel-group efficacy and safety period, followed by a 28-week open-label safety period.

The objective of the Phase III studies was to assess the efficacy and safety of the 300 mcg/day transdermal system in treating HSDD in surgically menopausal women on concomitant estrogen therapy. The primary efficacy endpoint was the change from baseline in the 4-week frequency of total satisfying sexual activity (Weeks 21-24), as captured by the SAL. Key secondary objectives were to assess sexual desire as measured by the sexual desire domain of the PFSF, personal distress as measured by the PDS score, the other 6 domains of the PFSF, and the SAL total activity and total orgasm endpoints.

Treatment groups were compared using an analysis of covariance (ANCOVA) model, adjusting for concomitant estrogen therapy, baseline rate of activity, age, and pooled center. Model assumptions were assessed qualitatively by visual inspection of the residuals. If model assumptions were severely violated, a Wilcoxon rank-sum test was to be used to test for treatment effects. A last observation carried forward approach was used to account for missing data for patients who did not complete the study. Correlations between changes from baseline in hormone levels and efficacy assessments were evaluated using Spearman correlation coefficients.

Table 7. Phase III Studies
Key Inclusion/Exclusion Criteria for Phase III Studies (SM 1 and SM 2)

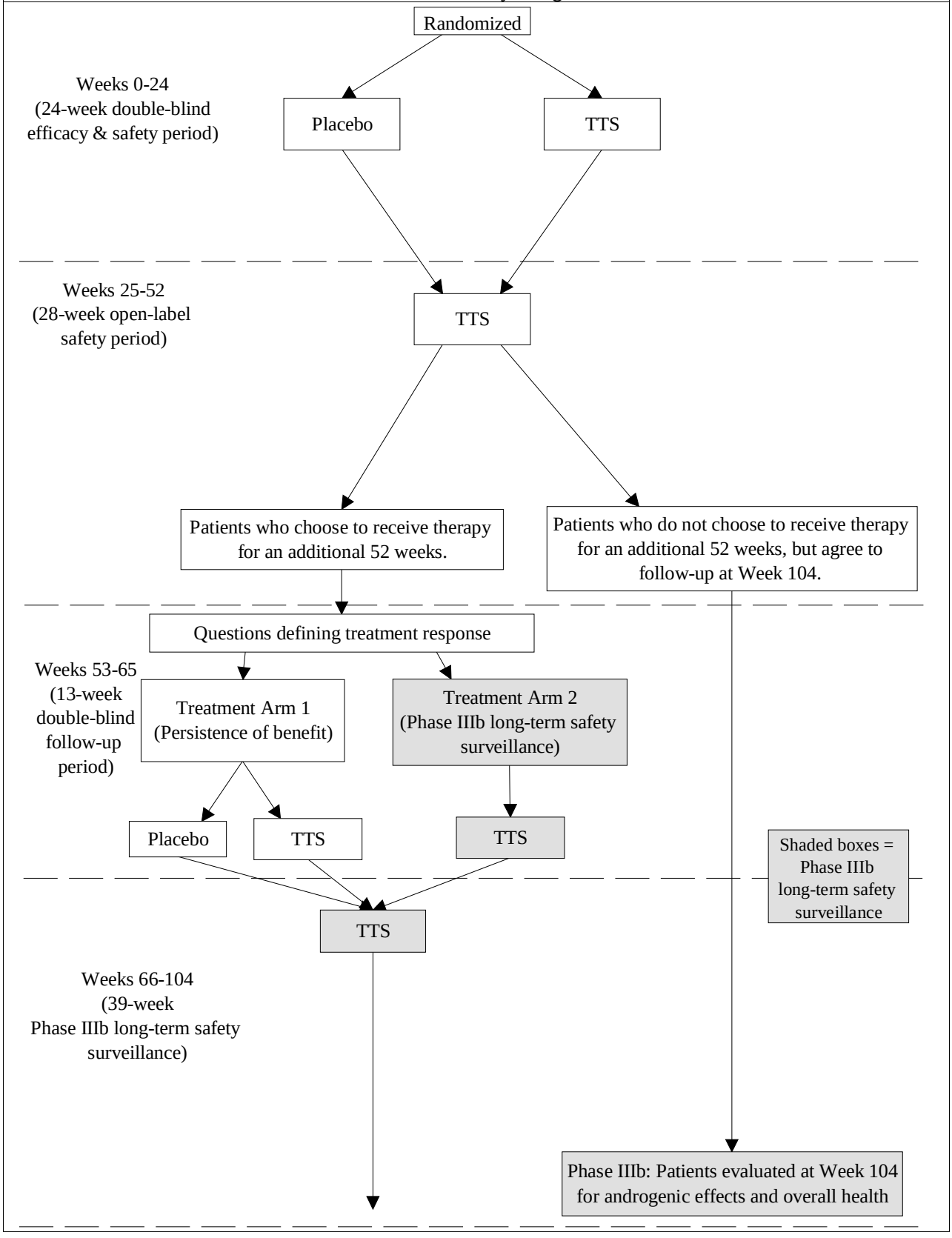
Inclusion Criteria	
• 20-70 years old and generally healthy • Surgically menopausal >6 months prior to study • Stable relationship, partner present >50% of the time • Stable oral or transdermal estrogen dose for > 3 months prior to study.	Answer 'yes' to ALL the following: • Before oophorectomy, was your sex life satisfying? • Since oophorectomy have you lost desire for sex? • Since oophorectomy has sexual activity decreased? • Are you concerned about you level of sexual desire? • Would you like to increase in sexual desire and activity?
Exclusion Criteria	
• Dyspareunia or other limitations to sexual functioning • Recently received androgen therapy • Medications that may interfere with sexual functioning • Currently experiencing significant life stresses	• Significant psychiatric disorder (≥14 on Beck Depression Index) • Severe dermatological problems • History of breast or gynaecological cancer • Baseline TSH above the upper limit of normal

A study to assess clinical relevance of the treatment results (Study CMKUS030993) was performed in a subset of patients completing the 24-week double-blind portion of the Phase III trials. This study is described in Section 3.2.7 of this briefing document.

A subset of patients who completed the initial 52 weeks of each study and had agreed to participate in an additional 52-week safety follow-up study (described below) were invited to participate in a 13-week (Weeks 53-65), double-blind, follow-up period to assess the persistence of treatment benefit (based on randomized withdrawal of active treatment). All women who participated in this study were responders during the open-label active treatment phase (self-assessment). Results of this study are discussed in Section 3.2.8 of this briefing document.

Following Studies SM 1 and SM 2, patients could enroll in a long-term safety surveillance period (Phase IIIb) for an additional 52 weeks. Patients who agreed to participate received 300 mcg/day testosterone during the entire 52-week safety surveillance period or from Week 65 on for those enrolled in the persistence of benefit trial described above. The interim data from this period were provided to the FDA in a safety update to the NDA.

Figure 11
Phase III Study Design



Disposition of Patients in the 24-Week, Double-Blind Period of the Phase III Studies

Similar proportions of patients in both treatment groups completed the 24-week, double-blind efficacy portion of the Phase III studies. There were no apparent differences between treatment groups in the reasons for early discontinuation (Table 8).

Table 8
Disposition of Patients in Weeks 0-24 of the Phase III Studies

	SM 1		SM 2	
	Placebo N=279 n (%)	**TTS N=283 n (%)**	**Placebo N=266 n (%)**	**TTS N=266 n (%)**
Completed	230 (82)	221 (78)	206 (77)	212 (79)
Discontinued	49 (18)	62 (22)	60 (23)	55 (21)
Reasons for withdrawal				
Adverse event	19 (7)	24 (8)	22 (8)	22 (8)
Voluntary/other	30 (11)	38 (13)	38 (14)	33 (12)

TTS=testosterone transdermal system

Baseline Characteristics of Patients

The patients enrolled in each of the Phase III trials were similar, and characteristics of the patients were balanced between treatment groups within each trial (Table 9).

Table 9
Baseline Characteristics of the Phase III Study Populations

	SM 1		SM 2	
Characteristic	**Placebo N=279**	**TTS N=283**	**Placebo N=266**	**TTS N=266**
Age, years	49	49	50	48
Race, % Caucasian	87	91	92	89
Length of relationship, years	19	20	19	18
Time since oophorectomy, years	8	9	9	9
Route of concomitant estrogen—oral/transdermal, % of patients.	75/25	74/26	82/18	80/20
Sexual desire score	20.7	19.9	23.2	21.4
Personal distress score	62.4	64.7	66.0	67.1
Total satisfying episodes/4 weeks	2.9	2.8	3.2	3.0

TTS=testosterone transdermal system. Values are means, unless otherwise indicated.

3.2.4.2 Efficacy in Phase III Studies

Effects on Desire, Distress, and Frequency of Satisfying Sexual Activity

The primary endpoint of the Phase III studies was frequency of satisfying sexual activity and the two principal secondary endpoints were sexual desire and distress. All three of these endpoints are important and showed statistically significant improvement in women who received transdermal testosterone compared with women who received placebo in each Phase III study.

The results for the 3 most important efficacy endpoints (frequency of total satisfying episodes of sexual activity, sexual desire, and distress) during the double-blind period of Studies SM 1 and SM 2 are provided in Table 10 and illustrated in Figures 12, 13, and 14.

Patients receiving the 300 mcg/day testosterone transdermal system also experienced an increase in the frequency of total satisfying episodes per 4 weeks (the primary endpoint) that was significantly greater than the increase for patients on placebo. The ANCOVA model assumption of normality was severely violated for the SAL data in Study SM 2, therefore, the Wilcoxon rank-sum analysis was used to compare treatment groups in this study (Table 10).

In both studies, patients receiving the 300 mcg/day testosterone system experienced an increase in sexual desire that was significantly greater than the increase observed in placebo patients. Distress associated with low desire was significantly decreased with 300 mcg/day testosterone treatment compared with placebo in both studies.

Table 10
Changes in Sexual Desire, Personal Distress, and Frequency of Total Satisfying Episodes
Phase III Studies

Endpoint Study Number	TTS (mcg/day)	n	Baseline Mean[a]	Mean Change from Baseline at Week 24[a,b]	p value[c]
Frequency of Total Satisfying Episodes					
SM 1	0	273	2.94	0.98	
	300	276	2.82	2.13	0.0003
SM 2	0	255	3.19	0.73	
	300	258	3.04	1.56	0.0010
Sexual Desire					
SM 1	0	269	20.82	6.90	
	300	269	19.79	11.85	0.0006
SM 2	0	257	23.37	6.21	
	300	252	21.67	11.38	0.0006
Personal Distress					
SM 1	0	266	62.57	-16.31	
	300	268	64.78	-23.55	0.0006
SM 2	0	258	66.38	-18.27	
	300	254	66.61	-24.34	0.0091

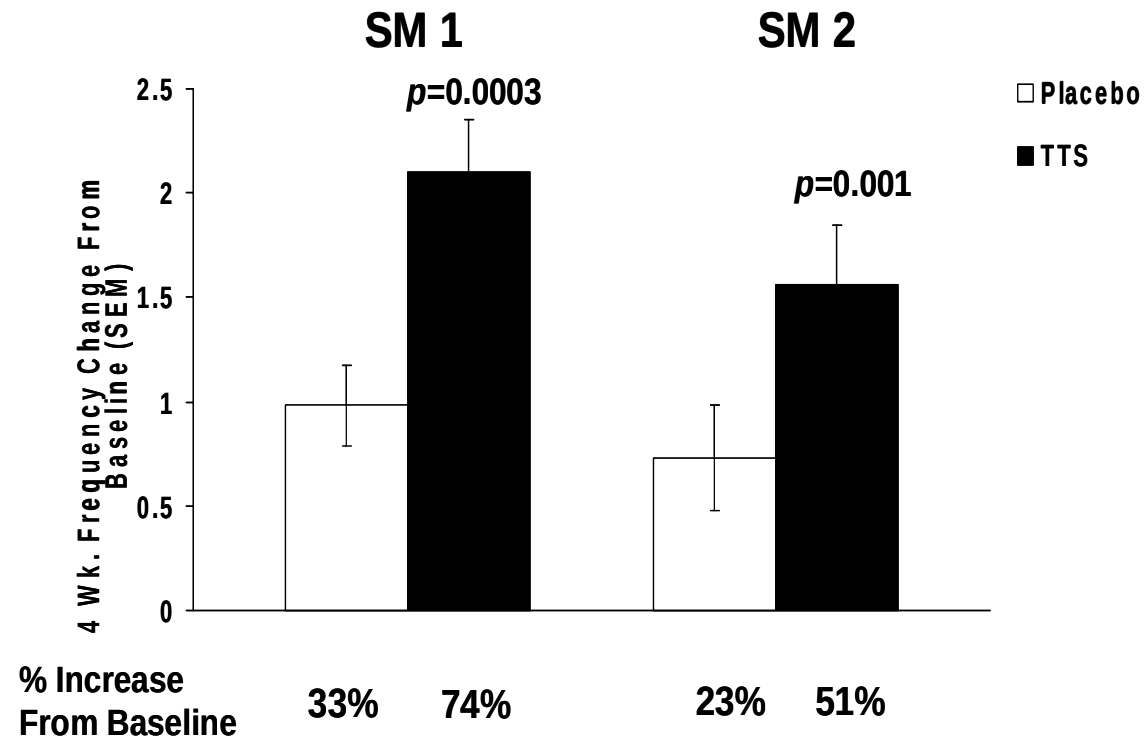
TTS=testosterone transdermal system

[a] For frequency of total satisfying episodes, baseline mean and mean change from baseline at Week 24 refer to the average 4-week frequency.

[b] Mean change from baseline adjusted for age, estrogen therapy route, pooled centers, and baseline value.

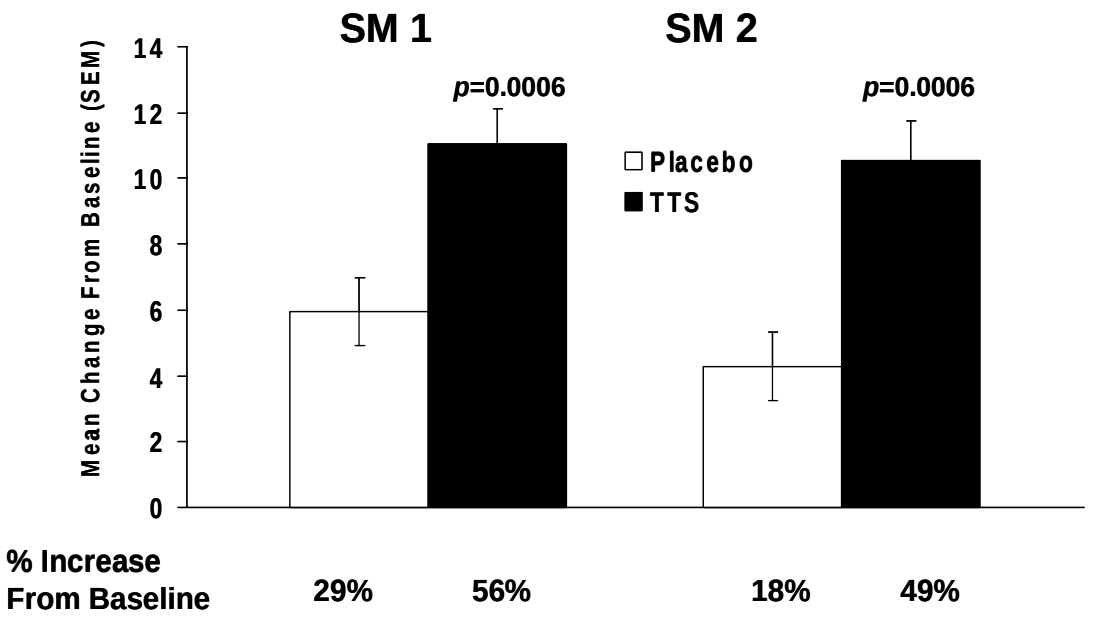
[c]For frequency of total satisfying episodes in Study SM 2, the ANCOVA model assumption of normality was severely violated; therefore, unadjusted mean change from baseline (i.e. no covariate adjustment) is shown and Wilcoxon rank sum analysis was conducted. P-value is for pairwise comparison of change in active vs. placebo.

Figure 12
Change from Baseline in Frequency of Satisfying Sexual Activity
Phase III Studies



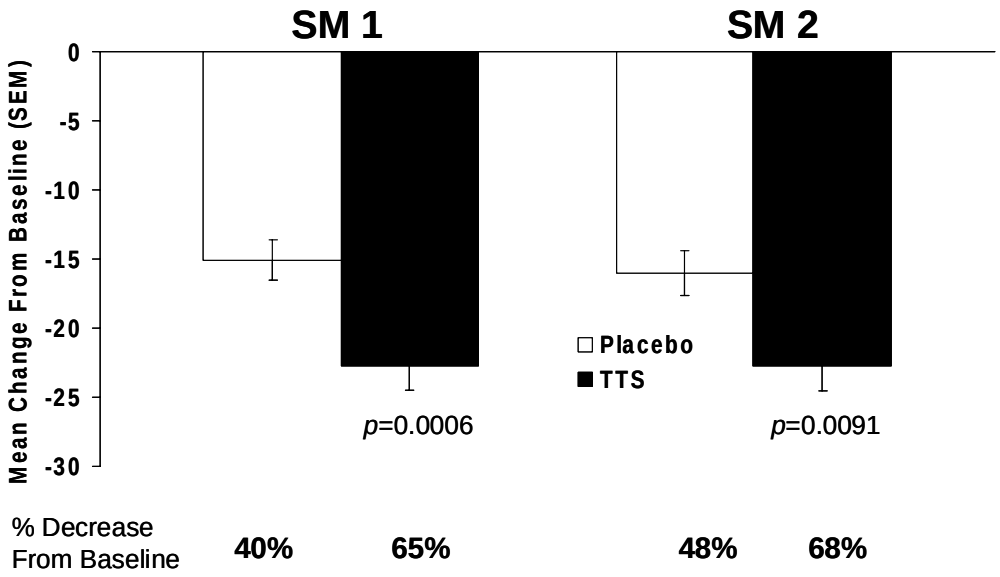
TTS=testosterone transdermal system

Figure 13
Change from Baseline in Sexual Desire Domain Score.
Phase III Studies



TTS=testosterone transdermal system

Figure 14
Change from Baseline in Personal Distress Scale
Phase III Studies

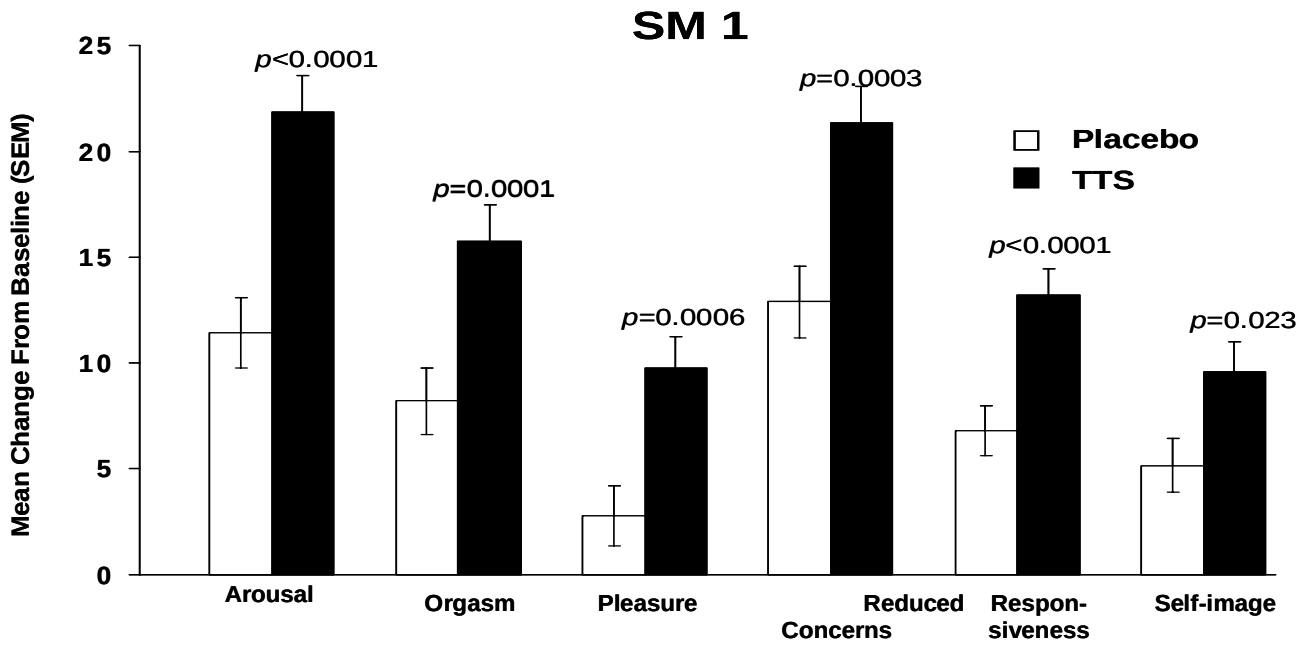


TTS=testosterone transdermal system

Other PFSF Endpoints

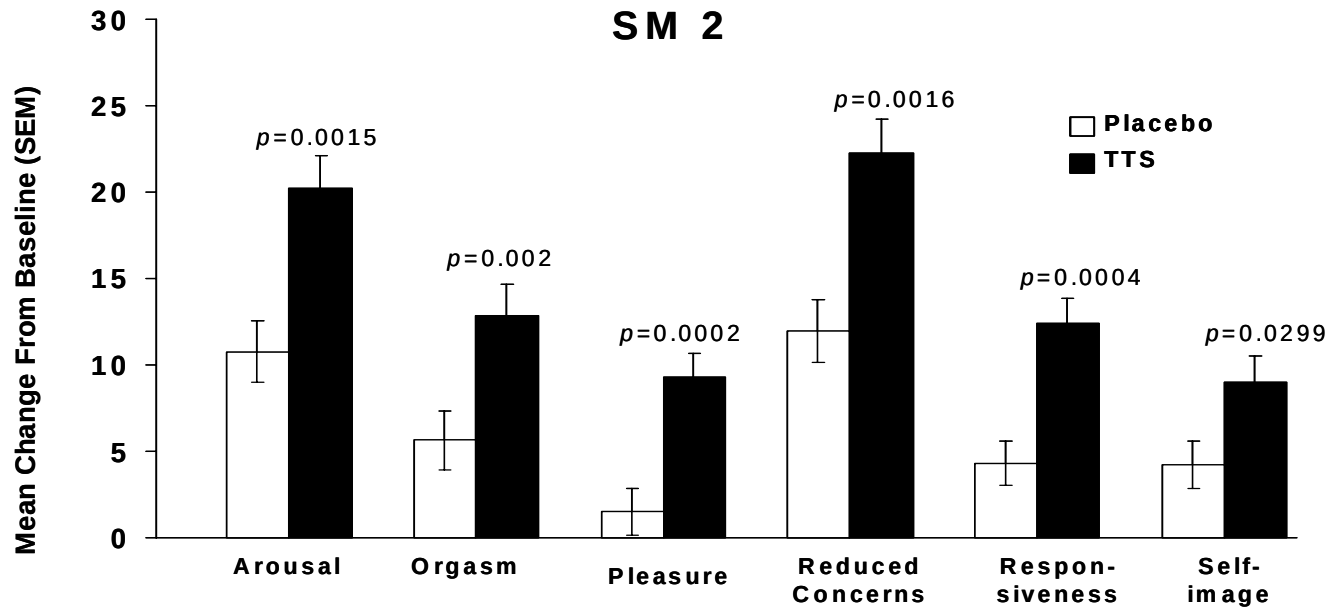
Patients treated with 300 mcg/day testosterone transdermal system had statistically significant increases in all other PFSF domains (i.e., sexual arousal, orgasm, sexual pleasure, sexual concerns, sexual responsiveness, and sexual self image) compared with placebo in Studies SM 1 and SM 2 (Figures 15 and 16). Note that an increase in the sexual concerns score indicated a decrease in patients' concerns related to sexuality.

Figure 15
Change from Baseline in PFSF Domains at Week 24: Study SM 1



Data shown corresponds to the mean change from baseline (+/-) 1 standard error.
For sexual concerns domain score, positive change indicates decrease in sexual concerns.
TTS = 300 mcg/day testosterone transdermal system.

Figure 16
Change from Baseline in PFSF Domains at Week 24: Study SM 2

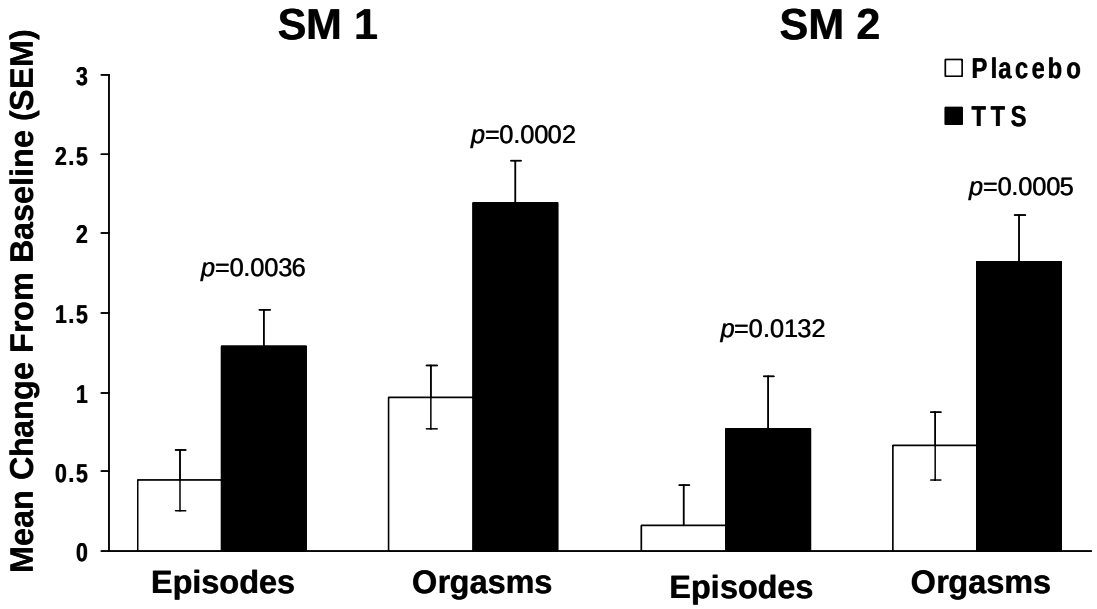


Data shown corresponds to the mean change from baseline (+/-) 1 standard error.
For sexual concerns domain score, positive change indicates decrease in sexual concerns.
TTS = 300 mcg/day testosterone transdermal system.

Other SAL Endpoints

Significant effects of testosterone treatment were also seen with regard to the other SAL endpoints, frequency of total sexual activity and frequency of orgasm (Figure 17).

Figure 17
Mean Change from Baseline in 4-week Frequency of Total Activities and of Orgasms in the Phase III studies.



TTS=testosterone transdermal system

3.2.5 Consistency of Treatment Effects Across Subpopulations

Efficacy was examined in a number of subpopulations defined on the basis of demographic and other characteristics at baseline (Figures 18 and 19).

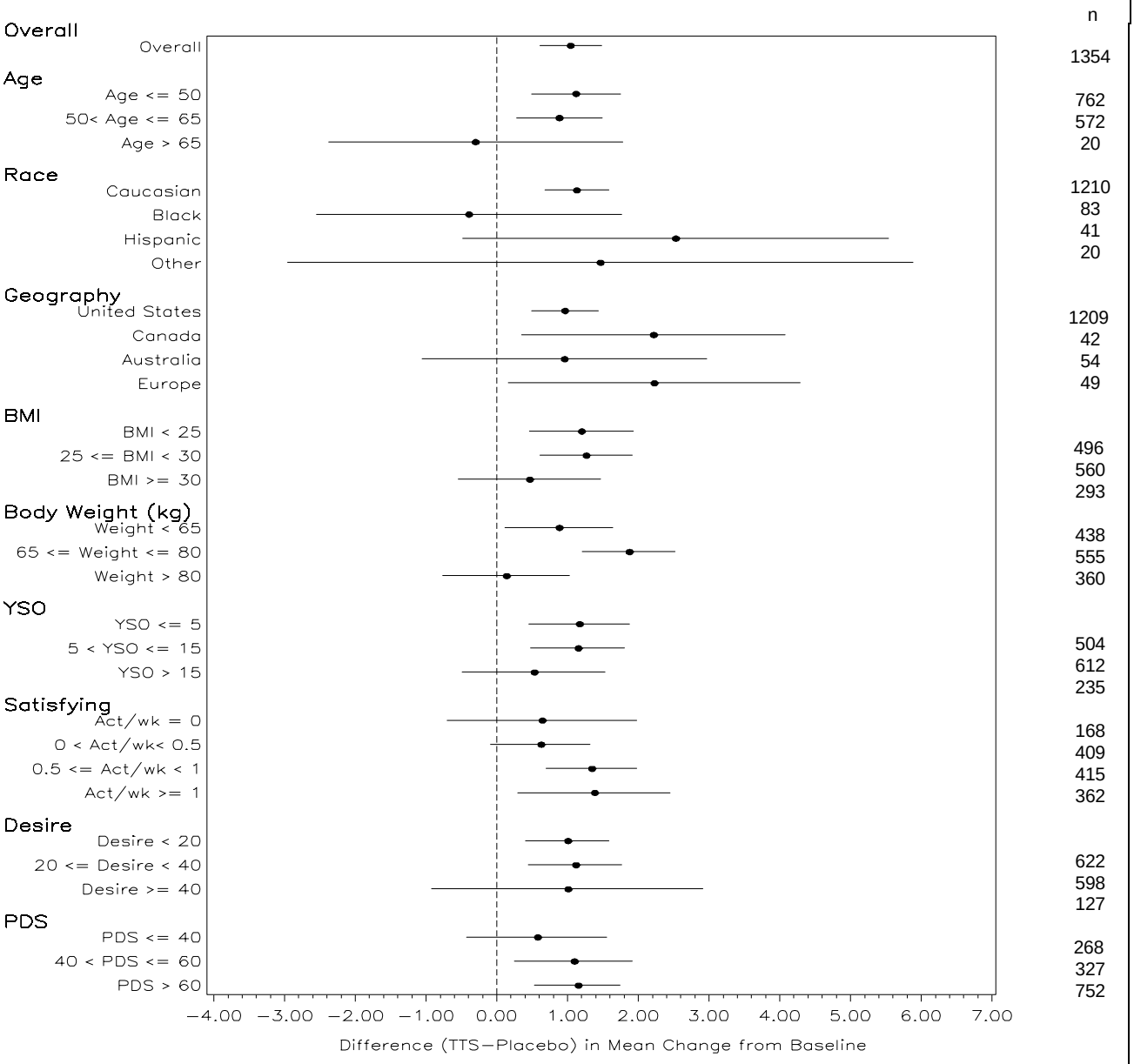
Subgroup analyses of the combined Phase IIb and Phase III studies in surgically menopausal women support the effectiveness of Intrinsa in a variety of countries, across a range of demographic and reproductive characteristics, disease severity, types of estrogen therapy, and baseline hormone concentrations. A generally consistent treatment effect across subpopulations is apparent in both total satisfying episodes and sexual desire.

The magnitude of the treatment effect was influenced by SHBG level, consistent with the fact that higher SHBG levels result in lower free testosterone levels. When patients were subdivided by route of administration of concomitant estrogen, a larger treatment effect was seen in patients using transdermal estrogen. This finding also can be attributed to affects of SHBG on free testosterone, as SHBG levels differ in patients on oral and transdermal estrogen. When users of oral estrogen products were further divided by type of estrogen [conjugated equine estrogens (CEE) vs. non-CEE], patients using CEE tended to have lower efficacy than patients using other

oral estrogens. The reasons for this difference may be in part a result of higher SHBG levels induced by CEE treatment.

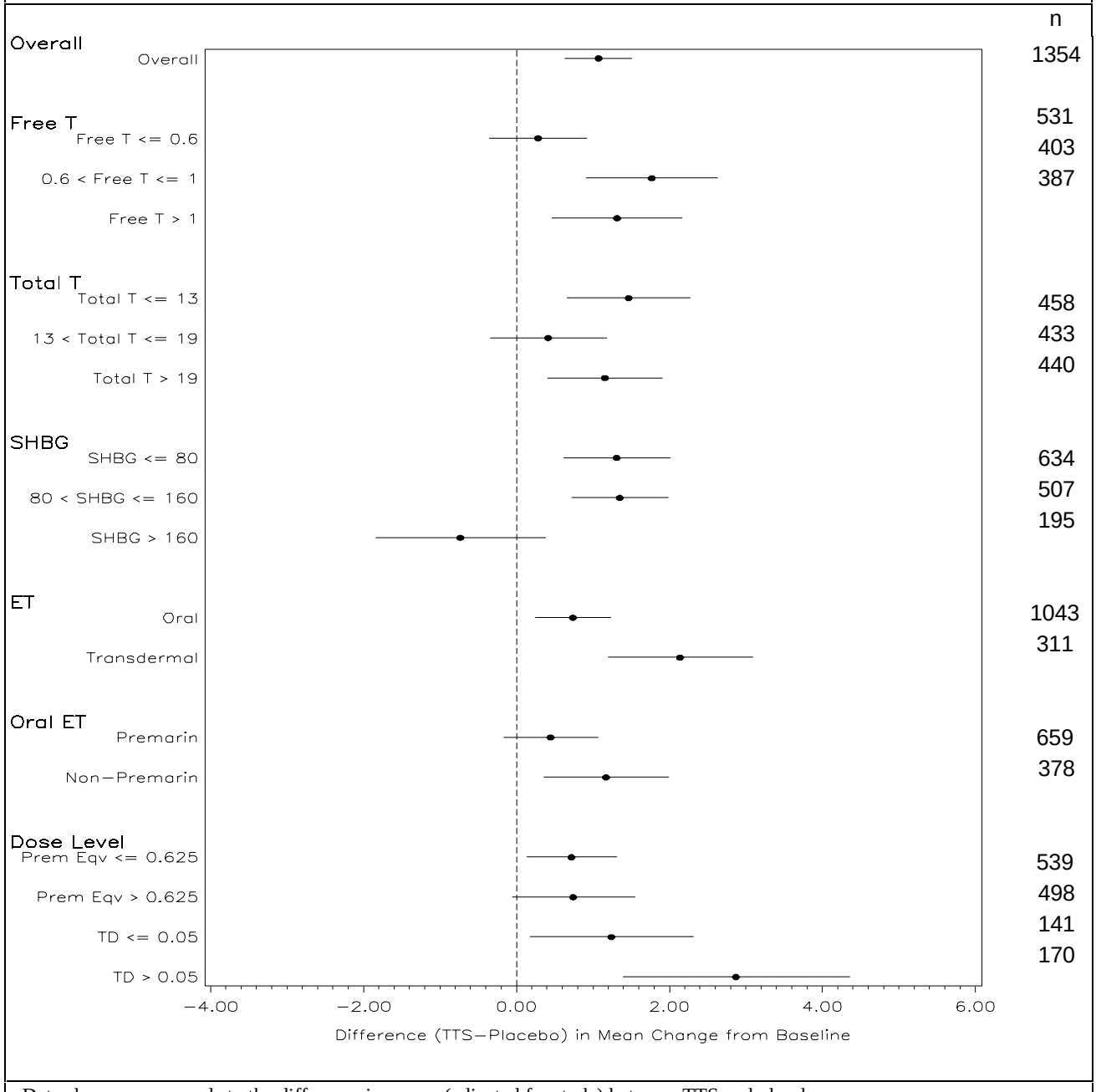
Figure 18
Differences Between TTS and Placebo in Mean Change from Baseline for 4-week Frequency of Total Satisfying Episodes at Week 24 by Subgroup: Combined Studies SM 1, SM 2, 1999068, 1999092

(Page 1 of 2)



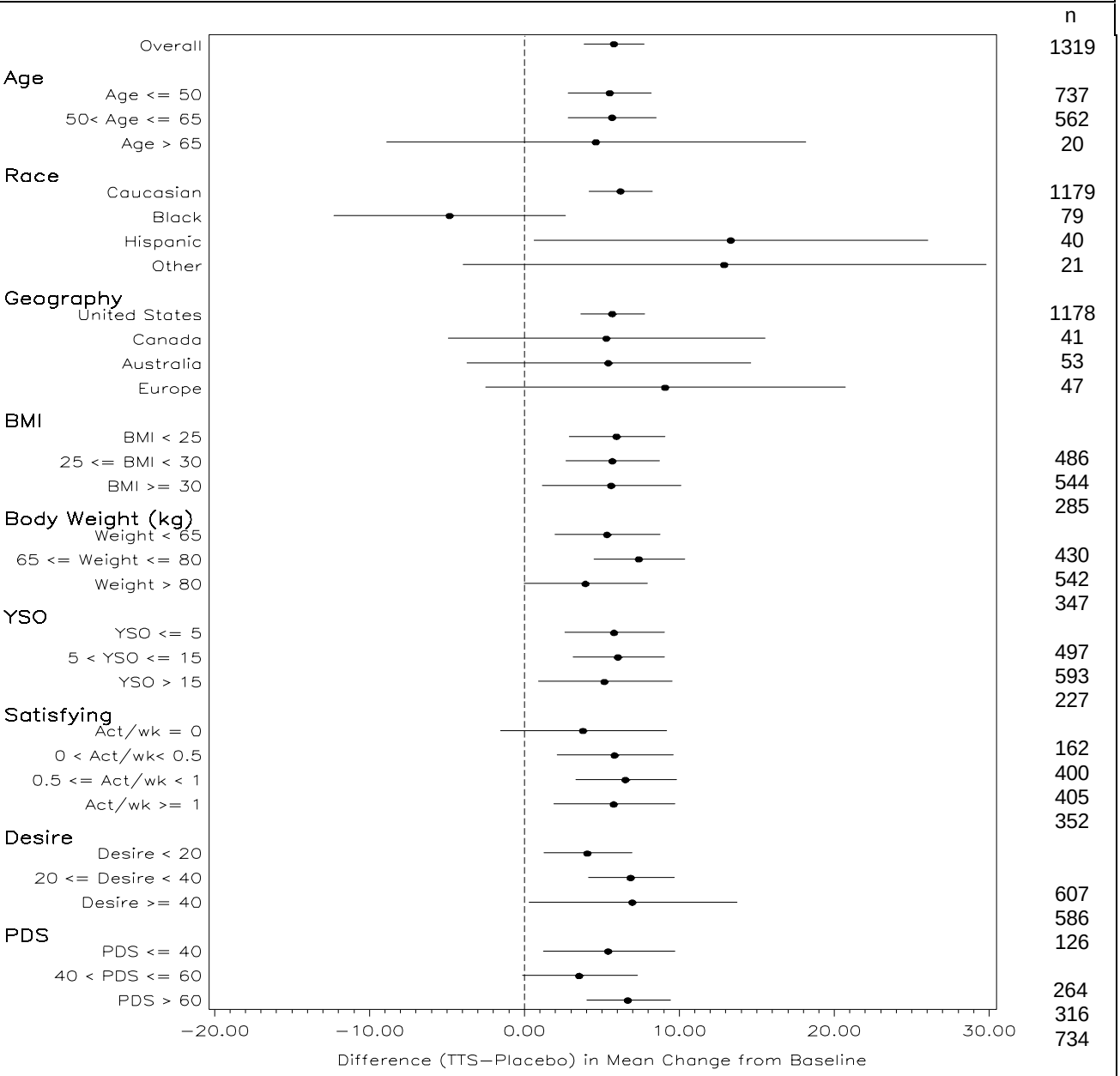
Data shown corresponds to the difference in means (adjusted for study) between TTS and placebo and the 95% confidence interval.
Subgroup definitions based on baseline data.
TTS = 300 mcg/day testosterone transdermal system; YSO=years since oophorectomy.

Figure 18
Differences Between TTS and Placebo in Mean Change from Baseline for 4-week Frequency of Total Satisfying Episodes at Week 24 by Subgroup: Combined Studies SM 1, SM 2, 1999068, 1999092Page 2 of 2)



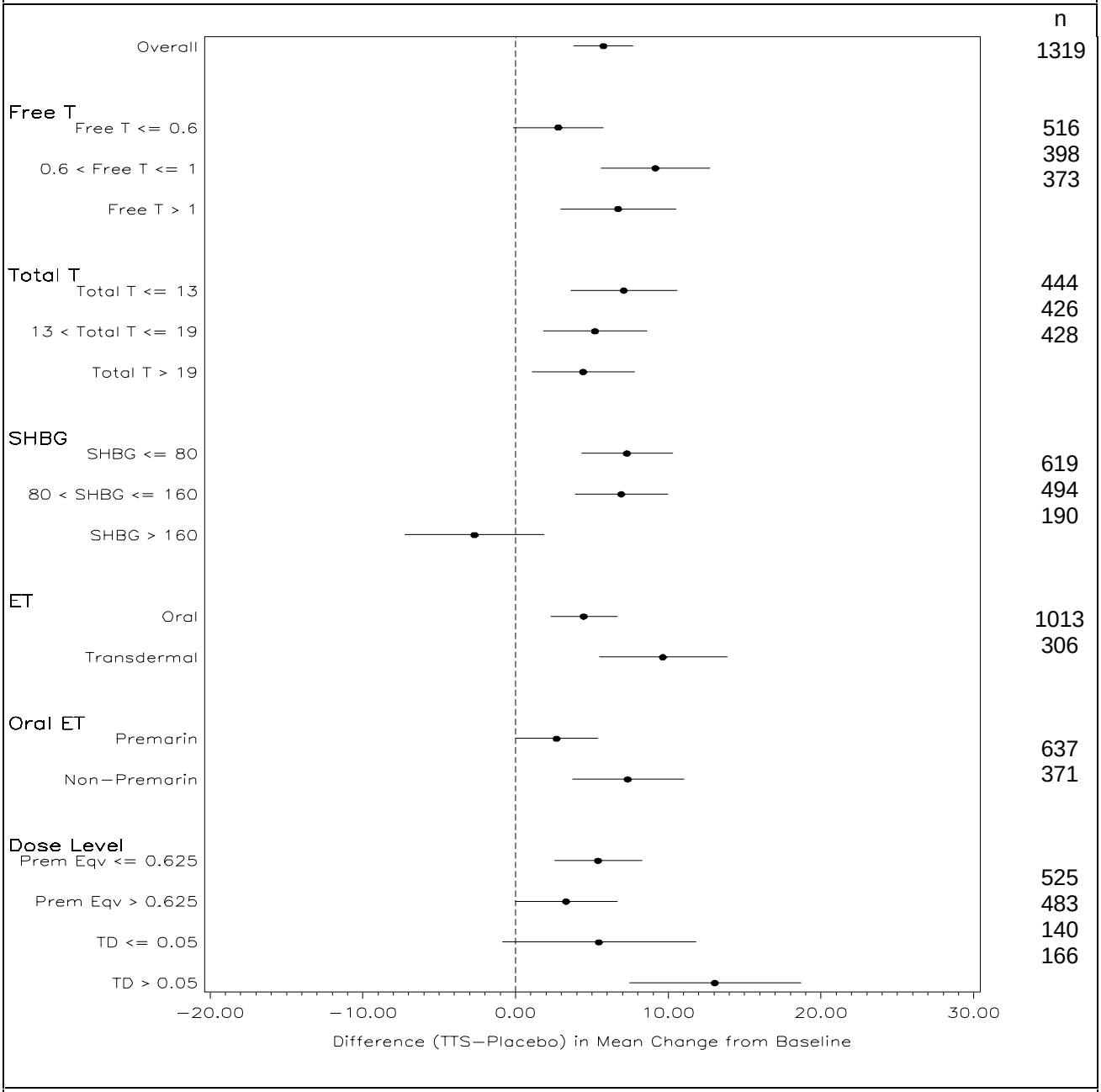
Data shown corresponds to the difference in means (adjusted for study) between TTS and placebo and the 95% confidence interval.
Subgroup definitions based on baseline data.
TTS = 300 mcg/day testosterone transdermal system.

Figure 19
Differences Between TTS and Placebo in Mean Change from Baseline for Sexual Desire at Week 24 by Subgroup: Combined Studies SM 1, SM 1, 1999068, 1999092
(Page 1 of 2)



Data shown corresponds to the difference in means (adjusted for study) between TTS and placebo and the 95% confidence interval.
Subgroup definitions based on baseline data.
TTS = 300 mcg/day testosterone transdermal system.

Figure 19
Differences Between TTS and Placebo in Mean Change from Baseline for Sexual Desire at Week 24 by Subgroup: Combined Studies SM 1, SM 1, 1999068, 1999092(Page 2 of 2)

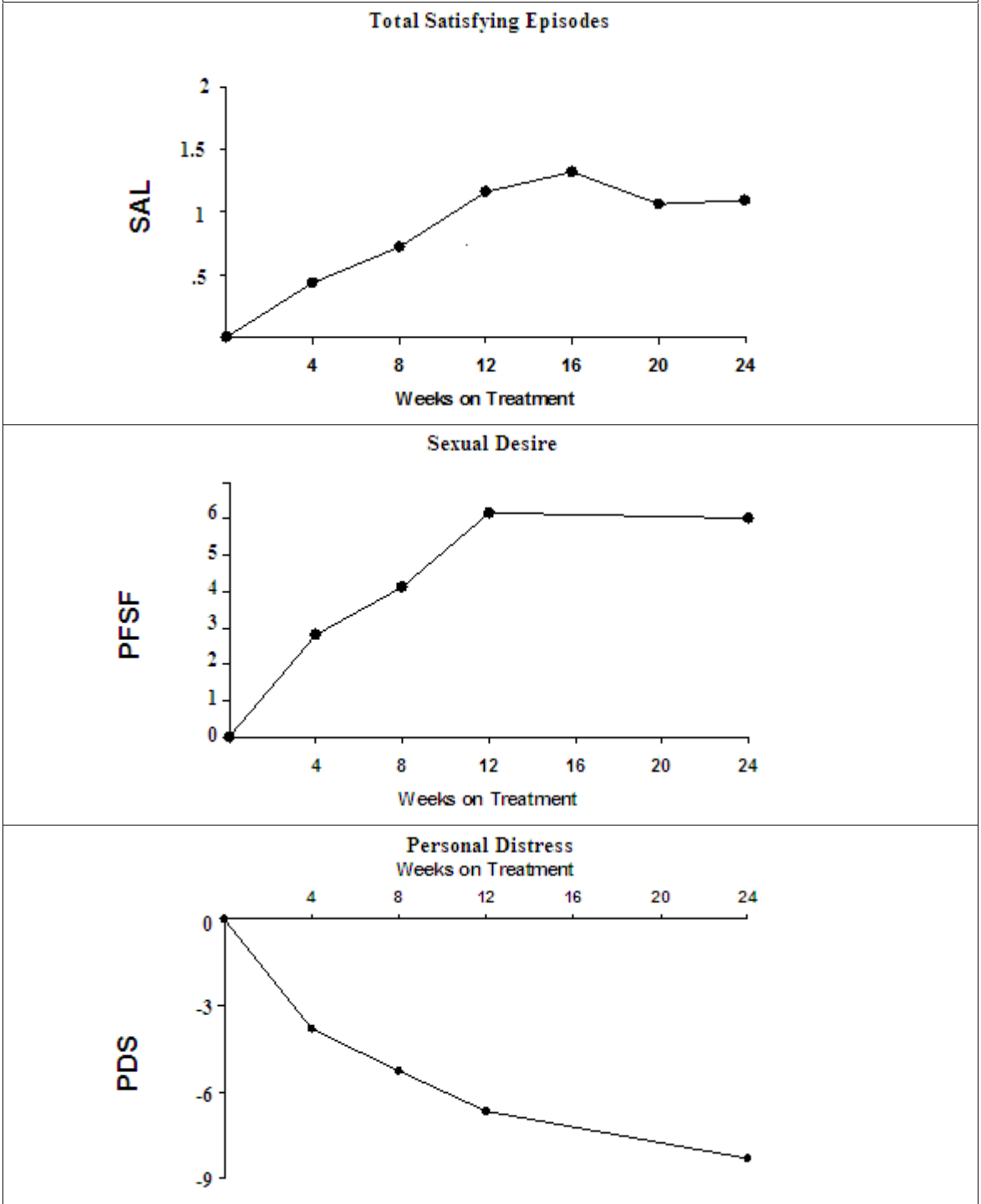


Data shown corresponds to the difference in means (adjusted for study) between TTS and placebo and the 95% confidence interval.
Subgroup definitions based on baseline data.
TTS = 300 mcg/day testosterone transdermal system.

3.2.6 Time to Onset of Effects

Overall, treatment benefits were seen as early as 4 weeks, and maximum effects in sexual desire and total satisfying episodes were seen by about 12 weeks. Beneficial effects were maintained for the remainder of the 24-week efficacy period (Figure 20). Decreases in distress were also seen by 4 weeks and distress continued to decline for the remainder of the 24-week efficacy period.

Figure 20
Time Course of Treatment Effects
Mean Differences, 300 mcg/day TTS versus Placebo:
Combined Studies SM 1 and SM 2



Values represent differences in least-squares means of 300 mcg/day TTS and placebo adjusted for study effect.

3.2.7 Clinical Relevance of Treatment Benefits

The clinical relevance study (Study CMKUS030993) used an anchoring technique to determine what minimum differences in study endpoints (frequency of satisfying sexual activity, desire, distress) were meaningful to patients. This approach ties the pivotal study outcome measures to the patients' perceptions of benefit. A significantly greater proportion of patients in the testosterone group reported experiencing an overall meaningful benefit compared with patients in the placebo group (52% vs. 31%). Receiver operating characteristics (ROC) analyses were used to quantify the minimum changes that were meaningful to patients. When these cutoffs were used as responder definitions and applied to the Phase III studies, the proportion of patients identified as responders was similar to the responders based on the patients' own perception of benefit. The results of this study indicate that patients receive clinically relevant improvements in sexual function with the 300 mcg/day testosterone transdermal system treatment.

Because women's sexuality is complex, a single endpoint may not adequately capture all aspects of sexuality. Based on the specific nature of HSDD, treatments for this condition would ideally increase sexual desire, decrease distress, and lead to an increase in the frequency of satisfying sexual activity.

In addition to demonstrating significant differences compared with placebo, it is also important that new therapies provide benefits that are meaningful to patients (i.e., are clinically relevant). A number of methodologies exist to estimate the minimum change in an endpoint that is meaningful to patients. One of the most well-established and widely used methods is the anchoring technique (Sloan et al., 2003). This approach ties pivotal study outcome measures to the patients' perceptions of benefit.

Because these studies involved new instruments, additional research was undertaken to provide perspective on what magnitude of change was meaningful to patients. A clinical relevance study (Study CMKUS030993) was designed to use an anchoring technique to determine the minimum differences in study endpoints that were meaningful to patients (e.g., the MCID, the minimum clinically important difference). The study data were collected in a series of one-on-one interviews conducted (in person or over the telephone) by a trained, experienced female interviewer using a structured interview guide that contained both open-ended and fixed-response (yes/no or scaled-response) questions.

The interviews began with an open-ended, qualitative session in which the interviewer elicited from each patient a full description of her sexual feelings and behaviors before entering the clinical study and then during the clinical study. Following this open-ended exploration, the patients were asked a series of fixed-response questions pertaining to potential benefits she might or might not have experienced while enrolled in the clinical study.

Patients (n=132; 12% of the Phase III study population) were invited to participate on the basis of the timing of their 24-week study visits and geographic locations, with as broad a representation of clinical sites as possible. All interviews were conducted no later than 2 weeks after patients completed or exited double blind treatment. The patients, interviewer, study site personnel, and the sponsor representatives who observed interviews or analyzed clinical data all remained blinded

to the patients' treatment assignments (active or placebo). This subgroup appeared to be representative of the overall study population on the basis of similar baseline demographic characteristics and disease severity.

The primary assessment in the clinical relevance study was based on the patients' answers (yes or no) to the following question, which was asked with reference to the patients' experiences during the double-blind portion of the studies:

> "Considering everything that we have talked about today, would you say that you experienced a meaningful benefit from the study patches?"

Patients were also asked, while still unaware of their treatment assignment, whether they would continue using the product if it were available.

Patients' Reports of Overall Benefit

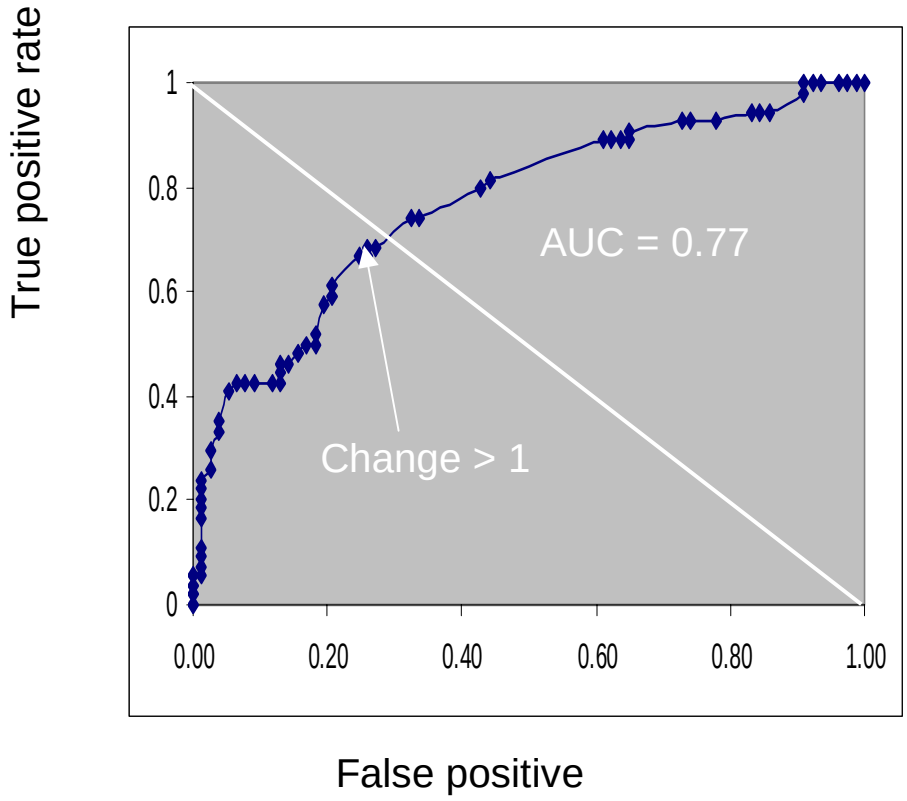
Following unblinding of the pivotal trials, analysis revealed that a significantly greater proportion of patients in the testosterone group reported experiencing an overall meaningful benefit compared with patients in the placebo group [TTS, 33 of 64 (51.6%); Placebo, 21 of 68 (30.9%); p=0.0254].

Determination of Minimum Clinically Important Difference (MCID)

The changes from baseline in frequency of total satisfying activity and desire observed in the Phase III trials for patients answering yes and no to this overall clinical relevance question were analyzed prior to breaking the blind. For completeness, similar analyses were also performed for distress, after unblinding. Receiver operating characteristics (ROC) analyses were used to establish the cutoffs in efficacy endpoints that best distinguished patients who reported an overall benefit ("responders') from those who did not.

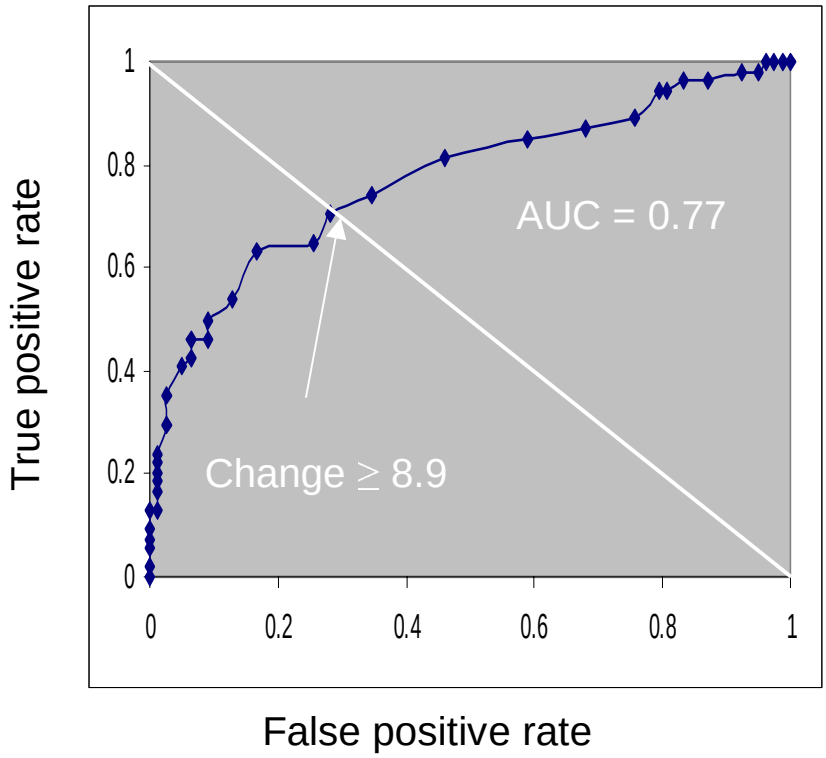
The MCID for an increase in total satisfying sexual activity as measured by the SAL was > 1 episode of activity/4 weeks (Figure 21). The MCID for an increase in sexual desire, as measured by the score for the desire domain of the PFSF, was ≥ 8.9 (Figure 22). For completeness, an ROC analysis was performed after unblinding of the Phase III data to determined the MCID for an change in personal distress score; this value was ≤ -20 (Figure 23).

Figure 21
ROC Curve For Change from Baseline in Frequency of Total Satisfying Sexual Activity.



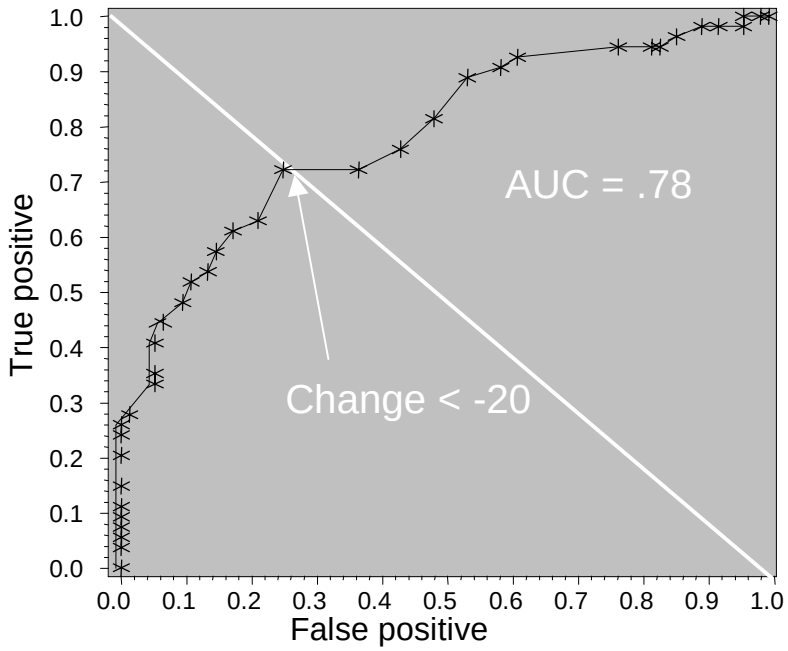
The MCID defined by the ROC analysis is shown by the intersection of the diagonal line with the curve (upper left corner).

Figure 22
ROC Curve For Change from Baseline in Sexual Desire Domain Score.



The MCID defined by the ROC analysis is shown by the intersection of the diagonal line with the curve (upper left corner).

Figure 23
ROC Curve For Change from Baseline in Personal Distress Scale.



The MCID defined by the ROC analysis is shown by the intersection of the diagonal line with the curve (upper left corner).

Application of Responder Cutoffs to Phase III Data

These responder definitions, which were based on the patients' own assessments of whether or not they received meaningful benefits from the study patches, were applied to the Phase III study results to examine the differences between treatment groups in the percentages of responders. Statistically significant differences between treatment groups were seen for all key endpoints in both Phase III studies (Table 11).

Table 11
Patients Classified as Receiving Clinically Meaningful Benefit in Phase III Studies Based on Responder Analysis

Study	Treatment		p-value
	Placebo	TTS	
Change from Baseline in Total Satisfying Episodes			
SM 1	34.8%	45.7%	0.0102
SM 2	25.1%	42.2%	<0.0001
Change from Baseline in Sexual Desire			
SM 1	34.6%	51.3%	<0.0001
SM 2	33.9%	49.2%	0.0005
Change from Baseline in Personal Distress*			
SM 1	39.1%	50.0%	0.0117
SM 2	39.1%	51.6%	0.0056

TTS=testosterone transdermal system
.A responder for total satisfying is defined as a patient with a change from baseline > 1. A responder for desire is defined as a patient with a change from baseline >= 8.9. A responder for distress was defined as a change from baseline<= -20.
*Unlike the cutoff values for total satisfying episodes and sexual desire, this responder definition was calculated after unblinding.

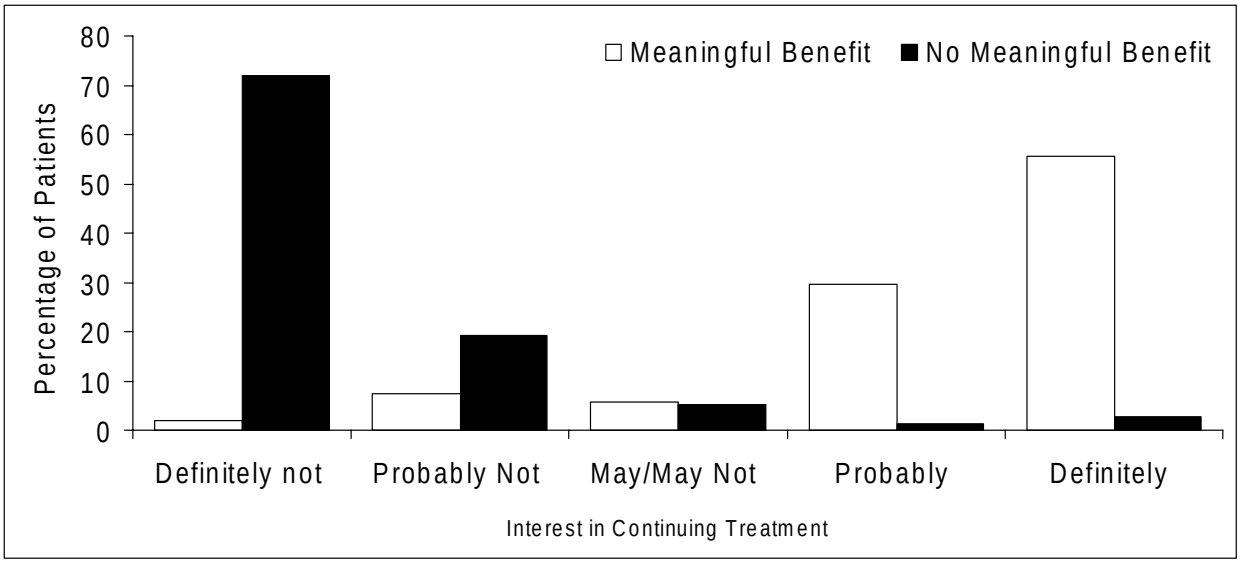
The similarity of the percentages of responders identified by asking a subset of patients about benefit directly and by applying the responder cut-offs to the entire set of study patients (Table 11) supports the appropriateness of the responder cut-offs as good estimates of minimal meaningful change.

For additional perspective, efficacy results for patients who reported meaningful benefit from study patches were compared with data for the age-matched, normal-libido control group in the validation studies of the psychometric instruments. Mean and median levels of total satisfying sexual activity, sexual desire, and personal distress in these women ranged from 58% to 88% of levels measured in the normal-libido women. These comparisons indicate that, whether response is determined directly by the patients themselves or by applying responder criteria, the change in endpoints for responders are typical of normal women in this age group, and do not reflect hypersexual behavior.

Patient Willingness to Continue Treatment

Most patients who reported experiencing an overall benefit indicated that they probably or definitely would continue treatment while most patients who reported they did not experience an overall benefit indicated they would definitely not or probably not continue (Figure 24).

Figure 24
Interest in Continuing Treatment in Patients Who Reported a Meaningful Benefit vs. Those Who Did Not—Clinical Relevance Study



3.2.8 Persistence of Benefit Following Discontinuation of Treatment

The persistence of benefit following treatment discontinuation was assessed in a substudy of Studies SM 1 and SM 2 (see Table 3 and Figure 11). In this study, a subset of patients were selected to participate in a 13-week, double-blind follow-up study during which they were randomly assigned to receive double-blind treatment with the testosterone patch or placebo. All patients in this substudy were responders during the earlier treatment period (self assessment). Of the 205 patients who participated in this substudy, 199 (97%) completed interviews with a trained sex therapist between Weeks 63-65. During this interview, the therapists assessed whether the patient had a noticeable decrease in desire during the 13-week period (primary endpoint), as well as other aspects of sexuality. Patients also reported their experiences directly. A similar percentage of patients in each treatment group completed these interviews.

A significantly higher percentage of patients in the placebo group had a noticeable decrease in desire for sexual activity from Week 52 to Week 65 compared with the testosterone group (Table 12). A similar pattern of response was seen for other variables.

These differences observed between the placebo and testosterone group in the 13-week, double-blind, follow-up study for assessment of persistence of benefit indicate that continuous testosterone treatment is needed for continued treatment benefits.

Table 12
Persistence of Benefit by Treatment Group

Question	Placebo N=102 n (%)	300 mcg/day TTS N=97 n (%)	p-value
Noticeable Decrease in Desire for Sexual Activity (Therapist)	64 (62.7)	42 (43.3)	0.0076
Noticeable Decrease in Overall Clinical Benefit (Therapist)	62 (60.8)	45 (46.4)	0.0503
Noticeable Decrease in Desire for Sexual Activity (Patient)	64 (62.7)	42 (43.3)	0.0077
Noticeable Decrease in Satisfying Sexual Activity (Patient)	48 (47.1)	25 (25.8)	0.0023
Noticeable Decrease in Desire to Initiate Sexual Activity (Patient)	61 (59.8)	37 (38.1)	0.0028
Noticeable Decrease in Willingness for Partner-initiated Sexual Activity (Patient)	33 (32.4)	23 (23.7)	0.2168
Noticeable Decrease in Anticipation of Sexual Activity (Patient)	55 (53.9)	32 (33.0)	0.0042
Noticeable Decrease in Overall Clinical Benefit (Patient)	64 (62.7)	40 (41.2)	0.0033

TTS = 300 mcg/day testosterone transdermal system.

3.3 Safety

The 300 mcg/day testosterone transdermal system demonstrated a favorable safety profile in surgically menopausal women with HSDD with up to 78 weeks of exposure. Overall adverse events were similar in the testosterone and placebo groups during the 6-month, placebo-controlled period of the Phase III surgical menopause studies. The most common adverse event in both treatment groups was application site reaction; most of these reactions were mild or moderate in severity and did not lead to study discontinuation. Small increases in the percentage of patients with acne and hirsutism reported as adverse events were seen in the testosterone group compared with placebo in one of the Phase III studies. These events were generally mild and did not result in discontinuation of treatment. No clinically important changes in laboratory parameters were observed with testosterone treatment. Two studies in naturally menopausal women, including one study that was double-blind and placebo-controlled for 12 months, are supportive of the favorable safety seen in surgically menopausal women.

3.3.1 Overview of Safety Studies

In designing the safety assessments for this clinical trial program, careful consideration was given to the known pharmacologic effects of testosterone and to potential adverse effects raised in the literature. As a result, special monitoring of various known androgenic effects in women (acne, alopecia, voice changes, hirsutism, clitoromegaly) was included in the trials. Special consideration was also given to potential effects of testosterone on the breast or cardiovascular system. All of these results are provided in some detail in this briefing document.

This section focuses on safety data from 2 Phase III studies (Studies SM 1 and SM 2) of the 300 mcg/day testosterone transdermal systems in surgically menopausal women with hypoactive sexual desire disorder (Table 13). These studies were double-blind and placebo-controlled during the first 6 months, followed by an additional safety follow-up during which all patients received testosterone, for total testosterone exposure of up to 78 weeks. In most cases, results in this section will show the results of the separate Phase III studies (Studies SM 1 and SM 2). Clinical laboratory parameters and open-label period safety data from both SM 1 and SM 2 were combined for analysis for ease of review.

Results of the Phase IIb studies in this population (Studies 1999068 and 1999092) were similar to those of the Phase III studies; these data were included in the analyses of safety in subpopulations, so as to have the largest possible sample (see Section 3.3.2.1). The Phase II and Phase III studies were also combined for the analysis of correlations between hormone concentrations and safety and efficacy results. Additional descriptions of these studies, including patient demographics and accountability, are provided in Section 3.2.

Supportive safety data are also available from 2 Phase III studies in naturally menopausal women with HSDD (Studies NM 1 and NM 2) (Table 13). A summary of these data is provided in Section 3.3.5.

Table 13
Selected Design Characteristics of Studies in Menopausal Women with HSDD

Study Number	Phase/ Region	Study Design	Concomitant Estrogen Therapy	Testosterone Dose Groups mcg/day (ITT Patients)
Phase III Studies—Surgically Menopausal Women with HSDD				
SM 1	III/ US, Canada, Australia	24-week randomized, DB, PC, efficacy and safety period followed by 28-week OL safety period in SM women	Oral or transdermal	0 (n = 279) 300 (n = 283)
SM 2	III/ US, Canada, Australia	24-week randomized, DB, PC, efficacy and safety period followed by 28-week OL safety period in SM women	Oral or transdermal	0 (n = 266) 300 (n = 266)
Phase II Studies—Surgically Menopausal Women with HSDD				
1999068	IIb/ US	24-week randomized, DB, PC, efficacy and safety period followed by 28-week DB, PC safety extension period in SM women. Dose ranging study.	Oral	0 (n = 119) 150 (n = 107) 300 (n = 110) 450 (n = 111)
1999092	IIb/ EU, Australia	24-week randomized, DB, PC, efficacy and safety in SM women	Transdermal	0 (n = 39) 300 (n = 37)
Phase III Studies--Naturally Menopausal Women with HSDD				
NM 1	III/ US, Canada, Australia	24-week randomized, DB, PC, efficacy and safety period in NM women	Oral estrogen with continuous progestin	0 (n = 273) 300 (n = 276)
NM 2	III/ US, Canada, Australia	52-week randomized, DB, PC, efficacy and safety study (24-week period for primary efficacy endpoint; 52-week DB, PC safety period) in NM women	Oral estrogen with continuous progestin	0 (n = 117) 300 (n = 241) (250 patients are still continuing and are not included in this analysis)

DB = double blind; PC = placebo controlled; OL = open label; SM = surgically menopausal; NM = naturally menopausal; ITT = intent-to-treat.

Safety assessments included adverse event collection, clinical laboratory parameters, vital signs and physical examination findings, and systematic assessments of potential androgenic adverse events, including acne and hirsutism. Patients were specifically queried about any change in voice or scalp hair growth and standardized assessment scales were used to evaluate facial hair and acne at each visit. At each visit, study personnel also examined the application site for any signs of skin reaction, and recorded any skin irritation reported by the patient.

The number of patients and the duration of exposure to the 300 mcg/day testosterone transdermal system in the clinical development program are consistent with the expectations defined in the

ICH Guideline on Extent of Population Exposure to Assess Clinical Safety for Drugs Intended for Long-term Treatment of Non-Life-Threatening Conditions (Table 14).

Table 14
Patient Exposure to Transdermal Testosterone
Phase IIb and Phase III Studies

Duration of Treatment	Surgical Menopause Studies ≥ 300 mcg/day n	Natural Menopause Studies 300 mcg/day n	Total
At least one dose	1288	517	1805
6 months	957	388	1345
12 months	494	136	630
18 months	127	0	127
Total exposure (patient-months)	10,742	3350	14,092

TTS=300 mcg/day testosterone transdermal system. Includes all patients exposed to the testosterone transdermal system in Studies 1999068, 1999092, SM 1 and its extension, SM 2 and its extension, NM 1 and NM 2 (interim safety analysis population). These data reflect status as of 28 June 2004 for on-going SM studies and 27 April 2004 for the on-going Study NM 2.

Safety of Other Doses

Higher (450 mcg/day) and lower (150 mcg/day) doses of the testosterone transdermal system were evaluated in a dose-ranging study (Study 1999068) which, along with the other Phase II studies, provided the efficacy and safety data that were the basis for selection of the 300 mcg dose for further testing in Phase III. No clear dose/response relationship for adverse events was observed across the range of doses tested in Study 1999068 (150 mcg/day, 300 mcg/day, 450 mcg/day). There was some evidence of an androgenic effect (e.g., increases in facial hair, slight decreases in HDL, and slight increases in LDL) with the 450 mcg/day dose; however, this effect was small and of uncertain clinical relevance. The 300 mcg dose was comparable to placebo for all safety parameters, including androgenic side effects (skin and hair), lipid profiles, carbohydrate metabolism, coagulation parameters, and renal and liver function parameters.

3.3.2 Safety in Surgically Menopausal Women

3.3.2.1 Summary of Adverse Events

The overall safety profile of the 300 mcg/day testosterone transdermal system was similar to placebo in both Phase III studies, as shown in Table 15.

Table 15 Summary of Adverse Events 24-Week, Double-Blind Period Studies SM 1 and SM 2				
	SM 1		SM 2	
	Placebo N=279 n (%)	TTS N=283 n (%)	Placebo N=266 n (%)	TTS N=266 n (%)
Any adverse event	222 (79.6)	220 (77.7)	197 (74.1)	198 (74.4)
Serious adverse event	7 (2.5)	7 (2.5)	6 (2.3)	5 (1.9)
Withdrawal due to adverse event	19 (6.8)	24 (8.5)	22 (8.3)	22 (8.3)
Most common adverse events				
Application site reaction	109 (39.1)	88 (31.1)	77 (28.9)	79 (29.7)
Upper respiratory tract infection	26 (9.3)	28 (9.9)	20 (7.5)	22 (8.3)
Headache	21 (7.5)	28 (9.9)	14 (5.3)	15 (5.6)
TTS=testosterone transdermal system				

The most common adverse events observed in the Phase III trials (≥2%) occurring at a higher incidence in the testosterone group than in the placebo group are provided in Table 16.

Table 16 Adverse Events at ≥2% Incidence and Higher in TTS than Placebo 24-Week, Double-blind Period Studies SM 1 and SM 2 (combined)		
Adverse Events	Placebo (N=545) n (%)	TTS 300 mcg/d (N=549) n (%)
Upper respiratory tract infection	46 (8.4)	50 (9.1)
Headaches	35 (6.4)	43 (7.8)
Hirsutism	32 (5.9)	40 (7.3)
Acne	28 (5.1)	37 (6.7)
Alopecias	16 (2.9)	23 (4.2)
Anxiety symptoms	13 (2.4)	15 (2.7)
Voice Deepening	12 (2.2)	15 (2.7)
Migraine headaches	8 (1.5)	15 (2.7)
Gastrointestinal and abdominal pains (excl oral and throat)	4 (0.7)	14 (2.6)
Nausea and vomiting symptoms	8 (1.5)	12 (2.2)
Influenza like illness	8 (1.5)	12 (2.2)
Gastroenteritis viral	9 (1.7)	11 (2.0)
Weight increased	8 (1.5)	11 (2.0)
Disturbances in initiating and maintaining sleep	8 (1.5)	11 (2.0)
Hypertension	8 (1.5)	11 (2.0)
TTS=testosterone transdermal system		

3.3.2.2 Androgenic Adverse Events

Few patients discontinued treatment as a result of androgenic adverse events during the 24-week, double-blind treatment period (Table 17).

Table 17
Withdrawals due to Androgenic Adverse Events
24-Week, Double-Blind Period
Studies SM 1 and SM 2

	SM 1		SM 2	
	Placebo N=279 n (%)	**TTS N=283 n (%)**	**Placebo N=266 n (%)**	**TTS N=266 n (%)**
Acne	0	0	0	2 (0.8)
Alopecia	1 (0.4)	1 (0.4)	2 (0.8)	4 (1.5)
Hirsutism	0	2 (0.7)	0	2 (0.8)
Voice deepening	0	0	0	2 (0.8)
Clitoromegaly	0	0	0	1 (0.4)

TTS=testosterone transdermal system

The percentages of patients reporting androgenic adverse events during the double-blind period was similar between treatment groups in Study SM 1, and increased in the testosterone group compared with the placebo group in Study SM 2 (Table 18). Most patients (78%) who reported androgenic adverse events reported only one type of event.

Table 18
Patients Reporting Androgenic Adverse Events
24-Week, Double-Blind Period
Studies SM 1 and SM 2

	SM 1		SM 2	
Patients with Adverse Events	**Placebo N=279 n (%)**	**TTS N=283 n (%)**	**Placebo N=266 n (%)**	**TTS N=266 n (%)**
Acne	17 (6.1)	17 (6.0)	11 (4.1)	20 (7.5)
Alopecia	9 (3.2)	9 (3.2)	7 (2.6)	14 (5.3)
Hirsutism	18 (6.5)	16 (5.7)	14 (5.3)	24 (9.0)
Voice deepening	8 (2.9)	7 (2.5)	4 (1.5)	8 (3.0)
Severity of Androgenic Adverse Events (as a proportion of events)				
Mild	51 (96.2)	50 (98.0)	39 (97.5)	65 (91.5)
Moderate	2 (3.8)	1 (2.0)	1 (2.5)	5 (7.0)
Severe	0	0	0	1 (1.4)

TTS=testosterone transdermal system

The one severe androgenic adverse event reported in the double-blind period of Study SM 2 was a woman in the TTS group who experienced hoarseness that was assessed by the investigator as severe and probably related to the study drug. This patient had resolution of the event following discontinuation of treatment. One patient in the testosterone group in study SM 1 reported signs

of clitoromegaly during the 24-week, double-blind period. On evaluation, the investigator noted proximal thickening in the clitoral area. The patient discontinued from the study and the event resolved 1 month later. The maximum serum free testosterone concentration recorded in this patient was 2.2 pg/mL [reference range in premenopausal women, 0.9 to 7.3 pg/mL].

Effects of treatment on acne and facial hair were evaluated using objective assessment performed during clinic visits. Most patients experienced no increase in these scores (Tables 19 and 20).

Table 19
Acne Clinical Assessments and Adverse Events
24-Week, Double-Blind Period
Studies SM 1 and SM 2

	SM 1		SM 2	
Change from Baseline	**Placebo N=279 n (%)**	**TTS N=283 n (%)**	**Placebo N=266 n (%)**	**TTS N=266 n (%)**
Acne Score Change*				
≤0	256 (98.1)	257 (97.3)	235 (98.7)	237 (97.5)
1-2	5 (1.9)	6 (2.7)	3 (1.3)	6 (2.5)
≥3	0	0	0	0
Adverse Events	17 (6.1)	17 (6.0)	11 (4.1)	20 (7.5)
TTS=testosterone transdermal system				
*Scale of Palatsi et al., 1984				

.

Table 20
Facial Hair Clinical Assessments and Adverse Events
24-Week, Double-Blind Period
Studies SM 1 and SM 2

	SM 1		SM 2	
	Placebo N=279 n (%)	**TTS N=283 n (%)**	**Placebo N=266 n (%)**	**TTS N=266 n (%)**
Chin hair*				
≤0	250 (95.8)	253 (95.8)	228 (95.8)	226 (93.0)
1-2	11 (4.2)	11 (4.2)	10 (4.2)	17 (7.0)
≥3	0	0	0	0
Upper lip hair*				
≤0	245 (93.9)	249 (94.3)	226 (95.0)	229 (94.2)
1-2	16 (6.1)	15 (5.7)	12 (5.0)	13 (5.3)
≥3	0	0	0	1 (0.4)
Adverse Events	18 (6.5)	16 (5.7)	14 (5.3)	24 (9.0)
TTS=testosterone transdermal system				
*Scale of Lorenzo, 1970.				

3.3.2.3 Androgenic Adverse Events in Subpopulations

Analyses to assess safety in subpopulations were designed based on the known pharmacologic effects of testosterone and the safety profile observed in the clinical studies. Because patients in

these studies were generally healthy except for HSDD, there were few patients with significant co-morbid conditions and no subpopulation analyses of patients with co-morbid conditions were performed. Subpopulations based on age, race, body mass index (BMI), weight, route of concomitant estrogen administration, baseline serum sex hormone binding globulin (SHBG) concentration, and geography were examined. These analyses did not indicate that any subpopulation examined was at increased risk of androgenic adverse events compared with the randomized population.

3.3.2.4 Assessment of Androgenic Adverse Events in Patients with Higher Hormone Levels

Four patients (all from Study SM 2) in the TTS group experienced relatively high maximum free testosterone serum concentrations (>20 pg/mL) during the 6-month, double-blind study period. Two of them did not report any androgenic adverse events during this period. Two patients with high maximum free testosterone levels reported androgenic adverse events during this period. One patient was a 49-year-old Caucasian woman who experienced mild facial hair growth approximately 3 months after randomization to testosterone. She also developed mild acne 1 week after her Week 24 visit. Her free testosterone level at Week 12 was 61.8 pg/mL, at Week 24 was 16.5 pg/mL and at Week 52 was 3.2 pg/ml. The patient completed the open-label period of the study and entered the treatment arm of the extension with the adverse events ongoing. The patient had no clinically relevant laboratory changes. The second patient was a 65-year-old Caucasian woman who experienced mild hirsutism on the chin approximately 3 months after randomization to testosterone. The patient withdrew consent due to lack of therapeutic effect after almost 6 months of treatment and the hirsutism resolved 1 month later. Her free testosterone serum concentration was 6.2 pg/mL at Week 12 and 30.4 pg/mL at her exit visit. The patient also reported adverse events of moderate anxiety and mild weight gain. She had no clinically relevant laboratory changes.

During the 28-week, open-label period, 7 patients (6 from Study SM 1; 1 from Study SM 2) had relatively high free testosterone serum concentrations (> 20 pg/mL). Two of these patients did not report any androgenic adverse events. One patient, a 35-year-old Caucasian woman, had a free testosterone level of 107.7 pg/mL at Week 52. She reported mild acne while receiving placebo in the double-blind period, and entered the open-label follow-up on testosterone. While in this period, she began taking a product containing methyltestosterone. Her adverse event of acne was ongoing at 52-weeks. A second patient, a 40-year old Caucasian woman, reported mild hirsutism 1 month after beginning testosterone open-label treatment; her serum testosterone at Week 52 was 24.2 pg/mL. She completed the open-label period with the event on-going and entered the 52-week study extension. A third patient, a 39-year-old Hispanic woman, had mild hirsutism 3 months after beginning open-label testosterone treatment; she had previously reported mild acne while on placebo during the double-blind period. Her free testosterone concentration at Week 52 was 24.1pg/mL. Hirsutism resolved with treatment on-going. A fourth patient had a free testosterone concentration of 63.1 pg/mL at Week 52, after 12 months of testosterone treatment. She reported mild hoarseness after 11 months of treatment and completed 12 months with the event on-going. She did not continue into the extension study, and her event resolved 1 month after completing the open-label period. The fifth patient, a 39-year-old Caucasian woman, experienced mild acne 9 months after being randomized to testosterone. Her free testosterone at

Week 52 was 23.7 pg/mL. The adverse event resolved 3 months later while treatment was on-going.

Further analysis of the relationships between serum hormone concentrations and androgenic adverse events can be found in section 4.5 of this document.

3.3.2.5 Other Adverse Events of Interest

A number of other adverse events were examined, either because they have been associated with androgen excess or they may indicate an interaction with the effects of the concomitant estrogen (Table 21). These adverse events were reported at similar incidence in the testosterone and placebo groups.

Table 21
Other Adverse Events
24-Week, Double-Blind Period
Studies SM 1 and SM 2

	SM 1		SM 2	
	Placebo N=279 n (%)	**TTS N=283 n (%)**	**Placebo N=266 n (%)**	**TTS N=266 n (%)**
Breast tenderness	7 (2.5)	7 (2.5)	9 (3.4)	6 (2.3)
Hot flushes	6 (2.2)	6 (2.1)	6 (2.3)	5 (1.9)
Weight gain	3 (1.1)	4 (1.4)	5 (1.9)	7 (2.6)
Anxiety	4 (1.4)	4 (1.4)	5 (1.9)	6 (2.3)
Edema	2 (0.7)	1 (0.4)	2 (0.8)	2 (0.8)
Aggression	2 (0.7)	1 (0.4)	2 (0.8)	1 (0.4)
Abnormal liver function tests	0	2 (0.7)	0	4 (1.5)

TTS=testosterone transdermal system

Breast safety and cardiovascular safety information can be found in sections 3.3.3 and 3.3.4 of this briefing document.

3.3.2.6 Serious Adverse Events

Few serious adverse events were reported in these studies. The serious events that were seen were due to a variety of causes and do not suggest any serious treatment-related safety concerns (Table 22). In the 6-month, double-blind study period, similar numbers of patients reported serious adverse events in the testosterone and placebo groups (Table 15). Two patients in the testosterone group reported serious adverse events assessed as possibly related to treatment by the investigators. These adverse events were a transient ischemic attack in 1 patient and a patient who reported an episode with tightness in chest, diarrhea, flushing, increased heart rate, nausea, tingling in roof of mouth, and diaphoresis. In both cases, the adverse events resolved while the patient was on study drug.

One patient, who was receiving placebo in Study SM 2, died during the study due to a basal ganglia hemorrhage.

Table 22
Serious Adverse Events
24-Week, Double-blind Period
Studies SM 1 and SM 2
(page 1 of 2)

Treatment Group Patient No. (partially obscured)	Age		Onset Day in Phase	AE Causality	AE Severity	AE Outcome	Action Taken
Study SM 1 DB							
Placebo							
39473xxx	51	Costochondritis	171	Doubtful	Severe	Ongoing	No Action Taken
65413xxx	59	Diverticulitis NOS	118	Doubtful	Severe	Recovered	No Action Taken
66813xxx	56	Coronary artery disease NOS	15	Doubtful	Severe	Ongoing	Drug Discontinued
67023xxx	49	Cholecystitis NOS	122	Doubtful	Severe	Recovered	No Action Taken
76863xxx	52	Gastric ulcer haemorrhage	22	Doubtful	Moderate	Recovered	No Action Taken
77163xxx	50	Fibula fracture	133	Doubtful	Moderate	Recovered	No Action Taken
77213xxx	51	Diverticulitis NOS	132	Doubtful	Moderate	Recovered	No Action Taken
		Hiatus hernia	132	Doubtful	Moderate	Recovered	No Action Taken
TTS							
67093xxx	53	Pneumonia NOS	82	Doubtful	Severe	Recovered	Drug Interrupted
70723xxx	38	Abdominal adhesions	7	Doubtful	Severe	Recovered	No Action Taken
76863xxx	48	Viral infection NOS	65	Doubtful	Severe	Recovered	No Action Taken
77033xxx	52	Transient ischaemic attack	37	Possible	Moderate	Recovered	Drug Discontinued
77263xxx	45	Chest tightness	71	Possible	Severe	Recovered	Drug Discontinued
		Diarrhoea NOS	71	Possible	Severe	Recovered	Drug Discontinued
		Flushing	71	Possible	Severe	Recovered	Drug Discontinued
		Heart rate increased	71	Possible	Severe	Recovered	Drug Discontinued
		Nausea	71	Possible	Severe	Recovered	Drug Discontinued
		Paraesthesia oral	71	Possible	Severe	Recovered	Drug Discontinued
		Sweating increased	71	Possible	Severe	Recovered	Drug Discontinued
		Throat tightness	71	Possible	Severe	Recovered	Drug Discontinued
77343xxx	51	Pneumonia aspiration	52	Doubtful	Severe	Recovered	No Action Taken
77363xxx	51	Herpes simplex	105	Doubtful	Severe	Recovered	No Action Taken

TTS=testosterone transdermal system. Patient numbers partially obscured for privacy.

Table 22
Serious Adverse Events
24-Week, Double-blind Period
Studies SM 1 and SM 2
(Page 2 of 2)

Treatment Group Patient No. (partially obscured)	Age		Onset Day in Phase	AE Causality	AE Severity	AE Outcome	Action Taken
Study SM 2 DB							
Placebo							
46394xxx	55	Blood pressure increased	35	Doubtful	Moderate	Recovered	Drug Interrupted
		Chest pain	35	Doubtful	Moderate	Recovered	Drug Interrupted
		Paraesthesia	35	Doubtful	Mild	Recovered	Drug Interrupted
52734xxx	52	Pelvic pain NOS	8	Doubtful	Moderate	Recovered	No Action Taken
66714xxx	55	Anxiety	116	Doubtful	Moderate	Ongoing	Drug Discontinued
		Back pain	116	Doubtful	Moderate	Recovered	Drug Discontinued
		Dyspnoea	116	Doubtful	Moderate	Recovered	Drug Discontinued
		Hypoaesthesia	116	Doubtful	Moderate	Recovered	Drug Discontinued
76924xxx	69	Sepsis NOS	129	Doubtful	Moderate	Recovered	No Action Taken
77084xxx	58	Cerebral haemorrhage	36	Doubtful	Severe	Patient Died	No Action Taken
77514xxx	55	Mesothelioma	68	Doubtful	Severe	Ongoing	Drug Discontinued
TTS							
46394xxx	54	Appendicitis	141	Doubtful	Severe	Recovered	Drug Interrupted
66784xxx	42	Catheter related infection	109	Doubtful	Severe	Recovered	No Action Taken
		Post procedural complication	42	Doubtful	Severe	Ongoing	Drug Discontinued
66954xxx	55	Cellulitis gangrenous	37	Doubtful	Severe	Recovered	No Action Taken
		Gangrene NOS	37	Doubtful	Severe	Recovered	No Action Taken
66954xxx	50	Salivary duct obstruction	43	Doubtful	Severe	Recovered	No Action Taken
76904xxx	49	Vertigo	14	Doubtful	Severe	Recovered	Drug Interrupted

TTS=testosterone transdermal system. Patient numbers partially obscured for privacy.

3.3.2.7 Adverse Events in Open-Label, Follow-up Period (Weeks 25-52)

In the following section, Placebo→TTS designates patients who were randomized to placebo for Weeks 0-24 and switched to testosterone for Weeks 25-52; TTS→TTS designates patients who were randomized to testosterone for Weeks 0-24 and continued on testosterone for Weeks 25-52. For simplicity of presentation, data from the 2 studies were combined for this presentation.

Seventy-six percent of patients randomized in Studies SM 1 and SM 2 completed the 24-week, double-blind period of the studies and entered the 28-week, open-label extension period during which all patients received 300 mcg/day testosterone. The patients in the open-label period were representative of the original randomized population, based on baseline demographic characteristics.

No new safety concerns were identified in the open-label period. Patients receiving their first 6 months of testosterone treatment (Placebo→TTS group) showed no meaningful difference in overall adverse events or serious adverse events, compared with patients receiving their second 6 months of testosterone treatment (TTS→TTS group) (Table 23). Withdrawals due to adverse events were higher in the TTS→TTS group than in the Placebo→TTS group.

Table 23
Summary of Adverse Events
Open-Label Period Weeks 25-52
Studies SM 1 and SM 2

	Placebo→TTS N=418 n (%)	TTS→TTS N=419 n (%)
Any adverse event	235 (56.2)	243 (58.0)
Serious adverse event	7 (1.7)	7 (1.7)
Withdrawal due to adverse event	25 (6.0)	35 (8.4)

Placebo→TTS is the group that received double-blind placebo treatment for 24 weeks, followed by open-label testosterone treatment for 28 weeks. TTS→TTS is the group that received double-blind testosterone for 24 weeks, followed by open-label testosterone for 28 weeks.

Few patients withdrew due to androgenic adverse events during the open-label period (Table 24); however, more testosterone patients withdrew due to hirsutism than placebo patients.

Table 24 Withdrawal due to Androgenic Adverse Events Open-Label Period Weeks 25-52 Studies SM 1 and SM 2		
	Placebo→TTS N=418 n (%)	TTS→TTS N=419 n (%)
Acne	4 (1.0)	3 (0.7)
Alopecia	3 (0.7)	5 (1.2)
Hirsutism	4 (1.0)	10 (2.4)
Voice deepening	2 (0.5)	1 (0.2)
Placebo→TTS is the group that received double-blind placebo treatment for 24 weeks, followed by open-label testosterone treatment for 28 weeks. TTS→TTS is the group that received double-blind testosterone for 24 weeks, followed by open-label testosterone for 28 weeks.		

A total of 14 patients experienced serious adverse events during this period (Table 25).

Table 25
Serious Adverse Events: Open-label Period Weeks 25-52, Studies SM 1 and SM 2

Treatment Group Patient Number (partially obscured)	Age[a]		Onset Day in Phase	Onset Day on Treatment	AE Causality	AE Severity	AE Outcome	Action Taken
Study SM 1 OL								
Placebo->TTS								
5308xxxx	55	Osteoarthritis NOS	156	156	Doubtful	Moderate	Recovered	No Action Taken
77253xxxx	40	Intervertebral disc herniation	41	41	Doubtful	Severe	Recovered	Drug Interrupted
77363xxxx	45	Small intestinal obstruction NOS	40	40	Doubtful	Severe	Recovered	No Action Taken
TTS->TTS								
39163xxxx	55	Arthritis NOS	15	184	Doubtful	Severe	Ongoing	No Action Taken
4115xxxx	48	Cholecystitis NOS	192	360	Doubtful	Severe	Recovered	Drug Interrupted
		Pancreatitis due to biliary obstruction	193	361	Doubtful	Severe	Recovered	Drug Interrupted
6541xxxx	43	Cholelithiasis	36	204	Doubtful	Severe	Recovered	No Action Taken
6714xxxx	56	Intestinal obstruction NOS	26	189	Doubtful	Moderate	Recovered	No Action Taken
7706xxxx	56	Chest pain (non-cardiac/non-pulmonary)	27	197	Doubtful	Severe	Recovered	No Action Taken
		Dyspnoea	27	197	Doubtful	Severe	Recovered	No Action Taken
7736xxxx	51	Atrial fibrillation	11	182	Doubtful	Severe	Recovered	No Action Taken
Study SM 2 OL								
Placebo->TTS								
6695xxxx	54	Cholelithiasis	63	63	Doubtful	Severe	Recovered	No Action Taken
7690xxxx	45	Abdominal pain NOS	127	127	Doubtful	Severe	Recovered	Drug Interrupted
7692xxxx	69	Pancreatitis acute	98	98	Doubtful	Severe	Recovered	No Action Taken
7722xxxx	62	Breast cancer metastatic	38	38	Doubtful	Severe	Ongoing	Drug Discontinued
TTS->TTS								
7729xxxx	38	Nerve injury	191	358	Doubtful	Severe	Ongoing	No Action Taken

Onset Day in Phase is the day the AE started relative to the start date of the open-label period.
Onset Day on Treatment is the day the AE started relative to the start date of the treatment.
Placebo->TTS is the group of patients randomized to placebo during the 24-week double-blind period who received active treatment during the 28-week open label period (Weeks 25-52).
TTS->TTS is the group of patients randomized to TTS during the 24-week double-blind period who received active treatment during the 28-week open label period (Weeks 25-52).
NOS = not otherwise specified; TTS = 300 mcg/day testosterone transdermal system.
[a] Age at screening.

3.3.2.8 Adverse Events in Open-Label, Follow-up Extension Studies (Weeks 53 to 78)

Safety data available through 28 June 2004 from the on-going extensions of the Phase III studies SM 1 and SM 2 in surgically menopausal women were submitted in a 90-Day Safety Update to the NDA.

A total of 321 (50%) out of 641 patients from both studies who completed Week 52 chose to continue into the 52-week safety extension studies (Weeks 53-104): Of these patients, 167 (52%) patients received between approximately 6 and 12 months of testosterone exposure (patients originally randomized to placebo for 6 months, followed by open-label testosterone, designated by Placebo→TTS) and 154 (48%) received between approximately 12 and 18 months of testosterone exposure (patients randomized to testosterone who continued to receive testosterone in the open-label periods, designated by TTS→TTS). A total of 257 (80%) patients completed through Week 78 as of 28-Jun-2004. For ease of interpretation, this update attributes all adverse events reported during the 13-week assessment of persistence of treatment benefit (double-blind period, Weeks 53-65) as though these occurred while the patients were receiving open-label TTS therapy, although 103 patients were receiving placebo during that time.

The interim safety analysis population was representative, in terms of demographic and anthropometric characteristics, of the intent-to-treat population during the first 52 weeks of both studies. Demographic and anthropometric characteristics of the groups were balanced at baseline.

The percentage of patients who reported adverse events and withdrew due to adverse events was similar between the groups (Table 26). A higher percentage of patients who received between 6 and 12 months of testosterone exposure reported serious adverse events compared with patients who received between 12 and 18 months of testosterone exposure. Overall, a low number of serious adverse events were reported and none were assessed as possibly or probably related to study drug by the investigators. In addition, the percentage of patients who had adverse events, had serious adverse events, and withdrew due to adverse events during Weeks 53-78 was similar compared with the 6-month treatment periods during the first year of the combined studies. There was no indication that more severe adverse events occurred with extended exposure to testosterone therapy.

Table 26
Summary of Adverse Events
Weeks 53-78 of Combined Studies SM 1 and SM 2
(Interim Safety Analysis Population)

	Placebo→TTS N=167 n (%)	TTS→TTS N=154 n (%)	Total N=321 n (%)
Patients[a]			
With Any Adverse Events	90 (53.9)	79 (51.3)	169 (52.6)
With Serious Adverse Events	5 (3.0)	1 (0.6)	6 (1.9)
Who Withdrew due to Adverse Events	9 (5.4)	8 (5.2)	17 (5.3)
Who Died	0	0	0

TTS = 300 mcg/day testosterone transdermal system.
Placebo->TTS is the group of patients who received placebo during the 24-week double-blind period and TTS during Weeks 25-52 and Weeks 53-78.
TTS->TTS is the group of patients who received TTS during the 24-week double-blind period and TTS during Weeks 25-52 and Weeks 53-78.

Six patients withdrew due to androgenic events during Weeks 53-78 (Table 27).

Table 27
Withdrawal due to Adverse Events
Weeks 53-78 of Combined Studies SM 1 and SM 2
(Interim Safety Analysis Population)

	Placebo→TTS N=167 n (%)	TTS→TTS N=154 n (%)	Total N=321 n (%)
Acne	2 (1.2)	0	2 (0.6)
Alopecia	0	4 (2.6)	4 (1.2)
Hirsutism	0	0	0
Voice deepening	0	0	0

TTS = 300 mcg/day testosterone transdermal system.
Placebo->TTS is the group of patients who received placebo during the 24-week double-blind period and TTS during Weeks 25-52 and Weeks 53-78.
TTS->TTS is the group of patients who received TTS during the 24-week double-blind period and TTS during Weeks 25-52 and Weeks 53-78.

Serious adverse events observed during this period are summarized in Table 28.

Table 28
Listing of Serious Adverse Events:
Weeks 53-78 of Combined Studies SM 1 and SM 2
(Interim Safety Analysis Population)

	Treatment Group						
Study	Patient numbers (obscured)	Age		Causality	Severity	AE Outcome	Action Taken
SM 1	Placebo->TTS						
	7721xxxx	45	Heart rate irregular	Doubtful	Moderate	Ongoing	Drug Interrupted
	7721xxxx	38	Biliary tract infection	Doubtful	Severe	Recovered	No Action Taken
	7726xxxx	52	Hypertension	Doubtful	Moderate	Ongoing	No Action Taken
SM 2	Placebo->TTS						
	7692xxxx	69	Chest pain	Doubtful	Severe	Recovered	No Action Taken
	7750xxxx	49	Breast cancer in situ	Doubtful	Severe	Ongoing	Drug Discontinued
	TTS->TTS						
	7722xxxx	59	Osteoarthritis	Doubtful	Severe	Ongoing	Drug Interrupted

Plc->TTS is the group of patients who received placebo during the 24-week double-blind period and TTS during Weeks 25-52 and Weeks 53-78.
TTS->TTS is the group of patients who received TTS during the 24-week double-blind period and TTS during Weeks 25-52 and Weeks 53-78.
TTS = 300 mcg/day testosterone transdermal system.
Patient numbers obscured for privacy.

The overall percentage of patients who experienced an application site adverse reaction was very low during Weeks 53 through 78 of the studies (3.7%). Only 1 patient (a patient in the Placebo→TTS) withdrew from the study due to an application site reaction. No cases of sensitization were reported during this period.

The number of markedly abnormal laboratory values was small in each of the 2 groups. No patients had markedly abnormal results for any renal or liver function parameter, or for total cholesterol, and less than 1% of patients had an abnormal finding for HDL cholesterol or glucose. Abnormal LDL-cholesterol was reported by 1 (0.8%) Placebo→TTS patient and 3 (2.3%) TTS→TTS patients; abnormal triglycerides were reported by 5 (3.7%) and 4 (3.1%), respectively, of patients in these groups.

In conclusion, patients treated for an additional 6 months of TTS therapy during Weeks 53-78 of Studies SM 1 and SM 2 (i.e., for up to a total of 18 months of treatment) continued to exhibit a favorable safety profile. The type and percentage of adverse events reported during Weeks 53-78, including their severity and causality, were very similar to those reported during the first year of both studies. No medically important treatment effects were observed in any laboratory parameter or vital sign with additional exposure to TTS during Weeks 53-78 of both studies (see sections .3.3.2.9 and 3.3.4.1 of this briefing document).

3.3.2.8 Application Site Reactions

Patients were evaluated by study personnel at each study visit for any sign of application site reaction. A rating scale of mild (expected symptoms such as erythema with or without itching, or itching alone, or other mild symptoms), moderate (moderate or severe erythema with any other symptoms such as papules or edema, or any more severe symptom in the absence of erythema), and severe (severe erythema with other severe symptoms such as profuse papules, serous exudates, etc.) was used to evaluate skin changes. Patient complaints about application site symptoms were also recorded as adverse events.

Application-site reactions reported as adverse events occurred at a similar incidence in both the placebo and testosterone groups during the 24-week, double-blind period of the combined Phase III studies (Table 29). Although more than 30% of patients experienced some application site reaction during the 6-month treatment period, the percentage of patients who withdrew from the studies due to these events was low. The percent of patients experiencing a severe application-site reaction was also low. The majority of application-site reactions were assessed as mild by the investigators.

Four patients during the double-blind study period (2 in the testosterone group and 2 in the placebo group) were identified by the investigator as cases of potential sensitization to the transdermal system, but no further testing was conducted to confirm the sensitization. Three of these patients withdrew from the study, and one patient continued.

Table 29
Summary of Application-site Reactions:
24-week Double-blind Period of Studies SM 1 and SM 2 (combined)

Parameter	Placebo N=545 n (%)	TTS N=549 n (%)
Patients		
With Any Adverse Event	186 (34.1)	167 (30.4)
With Serious Adverse Event	0	0
Who Withdrew due to Adverse Event	21 (3.9)	16 (2.9)
Who Died	0	0
Adverse Event Severity		
Mild	164 (79.2)	139 (76.4)
Moderate	40 (19.3)	37 (20.3)
Severe	3 (1.4)	6 (3.3)

TTS=testosterone transdermal system

The incidence of application-site reactions decreased in the open-label period. Severities were similar to those reported in the double-blind period and withdrawals due to application-site reactions remained low (<2%). No cases of potential sensitization were reported in the open-label study period.

Many application-site reactions occurred early in the study (in the first 28 days). The incidence decreased over time throughout the remaining 11 months of study.

The skin tolerability data from the Phase II and Phase III studies, as well as the cumulative irritation and wear study data, demonstrate that the testosterone transdermal system is very well tolerated in patients with up to 12 months of use. A very small percentage of patients exhibited severe reactions or discontinued therapy due to application-site reactions. Both the active and placebo transdermal systems were similarly well tolerated, indicating that testosterone is not a skin irritant in this setting.

3.3.2.9 Physical Examination Findings and Clinical Laboratory Assessments

Physical Examination Findings

Weight gain (mean of 0.2 to 0.3 kg after 24 weeks) was observed in the testosterone group in both Phase III trials; over the same period, the placebo patients lost about 0.2 kg (Table 30). Examination of patients who received testosterone during both the double-blind and open-label period showed that there was no mean weight gain in this group after 52 weeks (Figure 25).

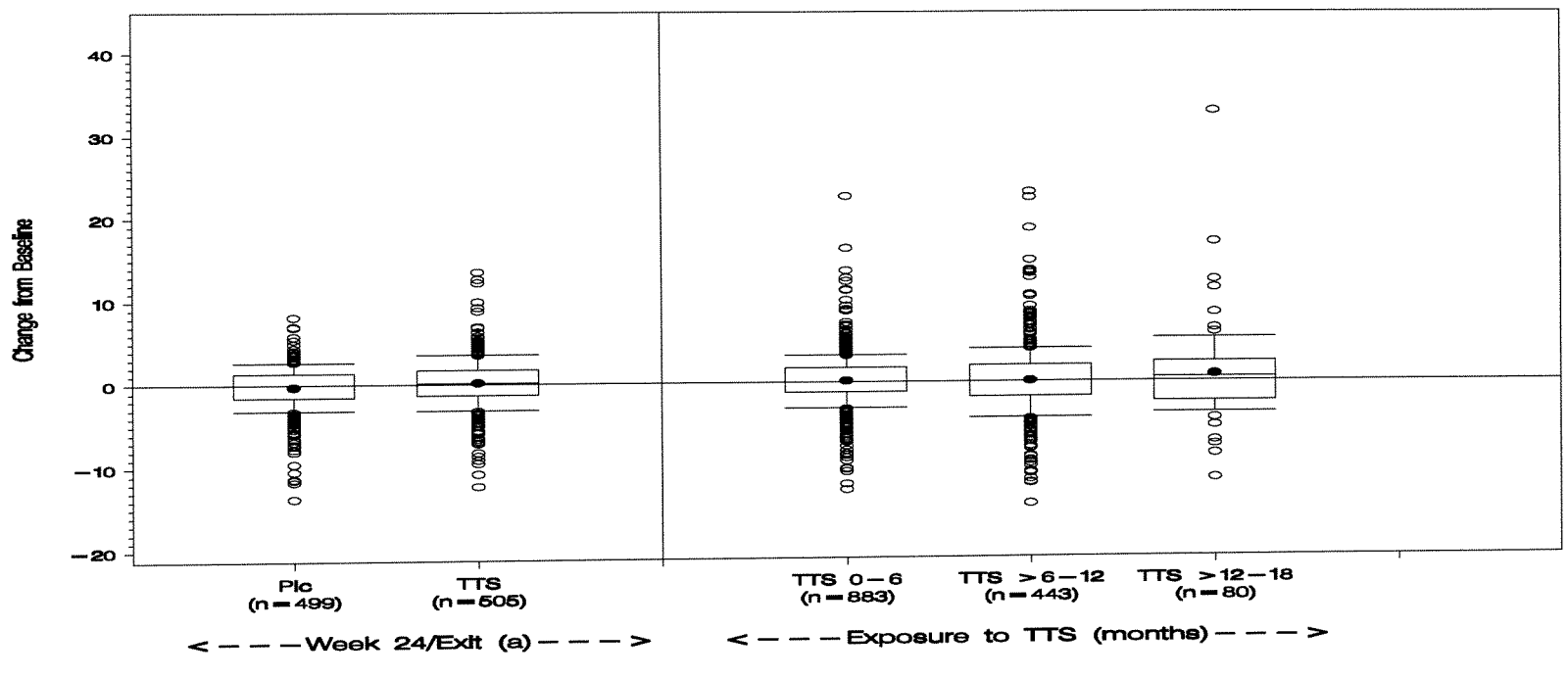
No changes in mean systolic or diastolic blood pressures were seen during the double-blind period or with open-label treatment up to 18 months total exposure (Table 30; Figures 26 and 27).

Table 30
Weight and Blood Pressure in 24-Week Double-Blind Period
Phase III Studies

	SM 1		SM 2	
Baseline Value **Change at Week 24/Exit**	**Placebo** **N=279**	**TTS** **N=283**	**Placebo** **N=266**	**TTS** **N=266**
Weight (kg)	75.93 [17.30] -0.24 [2.60] n=262	74.76 [16.23] 0.18 [2.92] n=264	75.00 [16.09] -0.19 [2.71] n=237	72.91 [14.77] 0.30 [3.12] n=241
Systolic blood pressure (mm HG)	120.7 [13.2] -0.2 [13.2] n=262	120.6 [13.5] 0.2 [12.6] n=264	120.9 [14.5] -0.9 [13.7] n=239	121.0 [14.4] 0.1 [12.1] n=241
Diastolic blood pressure (mm Hg)	76.1 [9.4] -1.2 [8.9] n=262	75.5 [8.4] -0.1 [8.9] n=264	75.3 [9.2] -0.3 [9.2] n=239	75.8 [9.6] 0.1 [9.1] n=241

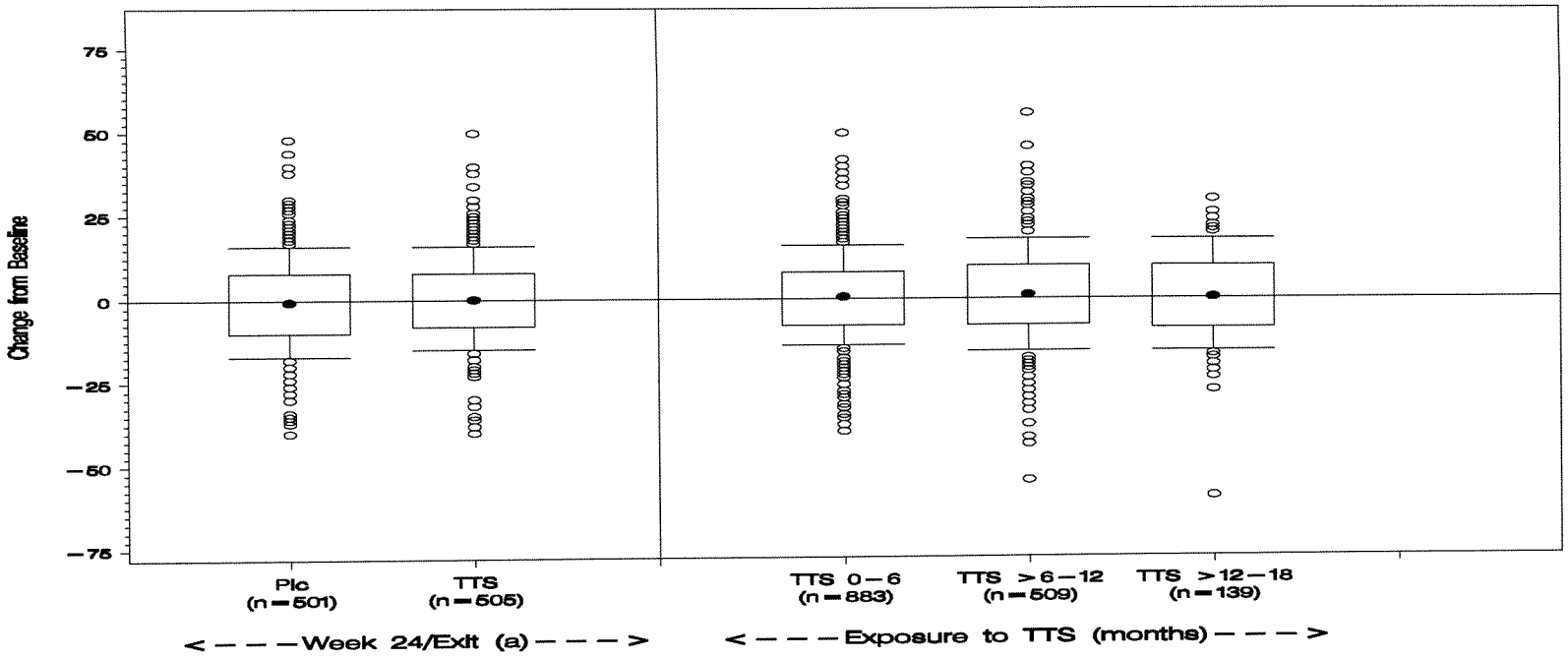
TTS=testosterone transdermal system
Values are means [standard deviation]. N=number of ITT patients. n=number of patients with values.

Figure 25
Change from Baseline in Weight (kg) in SM1 and SM2



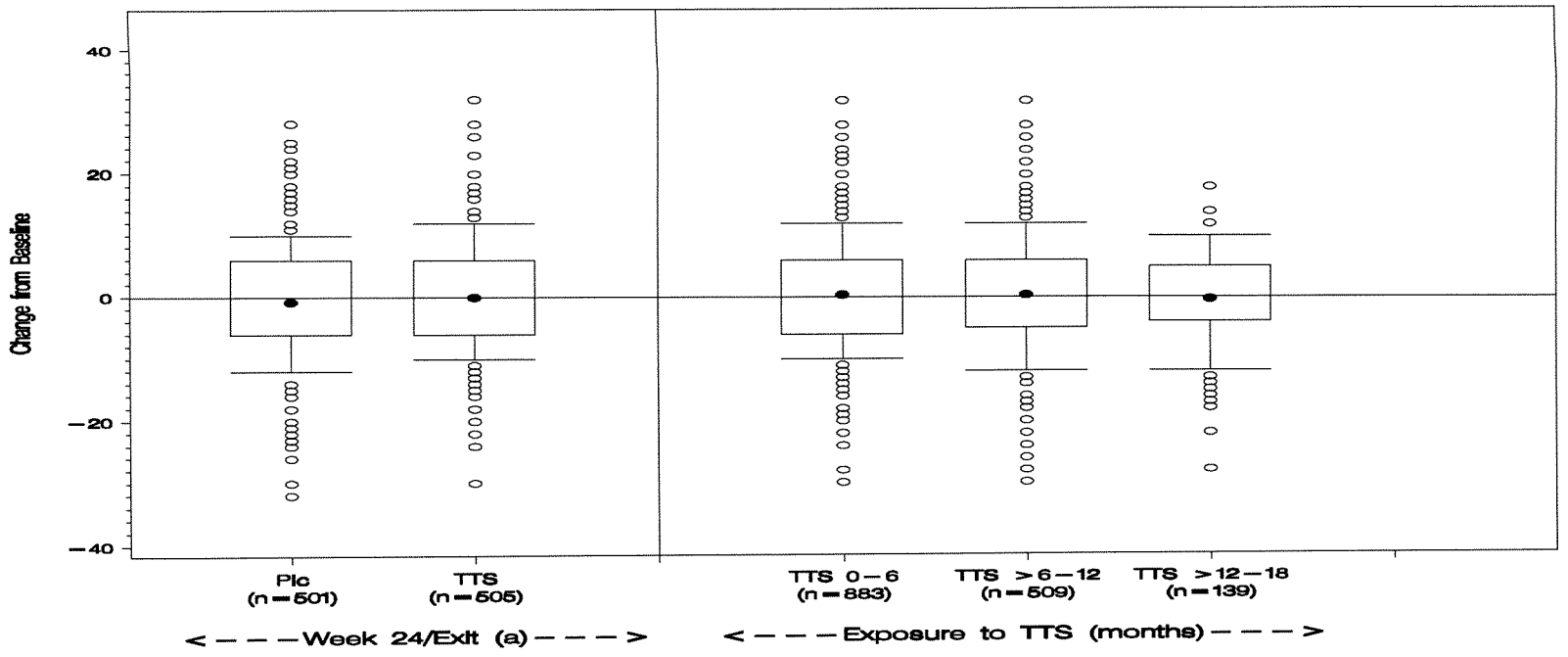
Plc = Placebo, TTS = 300 mcg/day testosterone transdermal system; number in brackets is number of patients with a value at that time-point.
(a) Includes exit evaluation if withdrawal was before 24 weeks.
Mean=dot; Median=central line; Box=interquartile range; Extreme value=circle; Lower whisker=10th Percentile; Upper whisker=90th Percentile.

Figure 26
Change from Baseline in Systolic Blood Pressure (mmHg) in SM1 and SM2



Plc = Placebo, TTS = 300 mcg/day testosterone transdermal system; number in brackets is number of patients with a value at that time-point.
(a) Includes exit evaluation if withdrawal was before 24 weeks.
Mean=dot; Median=central line; Box=interquartile range; Extreme value=circle; Lower whisker=10th Percentile; Upper whisker=90th Percentile.

Figure 27
Change from Baseline in Diastolic Blood Pressure (mmHg) in SM1 and SM2



Plc = Placebo, TTS = 300 mcg/day testosterone transdermal system; number in brackets is number of patients with a value at that time-point.
(a) Includes exit evaluation if withdrawal was before 24 weeks.
Mean=dot; Median=central line; Box=interquartile range; Extreme value=circle; Lower whisker=10th Percentile; Upper whisker=90th Percentile.

Clinical Laboratory Parameters

On the basis of known clinical laboratory changes associated with higher doses of testosterone in men with hypogonadism, an evaluation of clinical laboratory measurements of special interest was performed in both the Phase II and Phase III studies. This review included the following laboratory groupings: lipids, liver function tests, coagulation parameters, measures of carbohydrate metabolism, and hematology. Liver function tests and measures of carbohydrate metabolism are discussed in this section; lipids, hematologic parameters, and coagulation parameters are discussed in section 3.3.4.1 of this briefing document. There were no clinically significant changes in laboratory parameters with up to 78 weeks of testosterone treatment.

Review of all data, including individual cases of abnormal laboratory values, demonstrated no evidence of clinically important testosterone-associated changes in laboratory parameters during the 24-week, double-blind period or during subsequent open-label treatment for total exposures up to 78 weeks (18 months). Only 2 patients receiving testosterone withdrew because of laboratory abnormalities (elevated ALT and elevated fibrinogen). The patient with elevated ALT, a 46-year-old Caucasian, had a value of 54 IU/L at Week 24 while on testosterone. The event was assessed by the investigator as possibly related to treatment. A repeat test 7 weeks after treatment discontinuation showed an ALT of 54 IU/L. She was on concomitant lovastatin for hypercholesterolemia. The patient with elevated fibrinogen (522 mg/dL; normal 184-514 mg/dL) discontinued treatment after Week 24 while on testosterone. A repeat test performed 6 weeks after the first test and 2 days after drug discontinuation, was within normal limits (fibrinogen, 418 mg/dL). This patient was a heavy smoker.

Examination of changes in laboratory parameters by maximum serum free testosterone can be found in section 4.5 of this briefing document.

Liver Function Tests

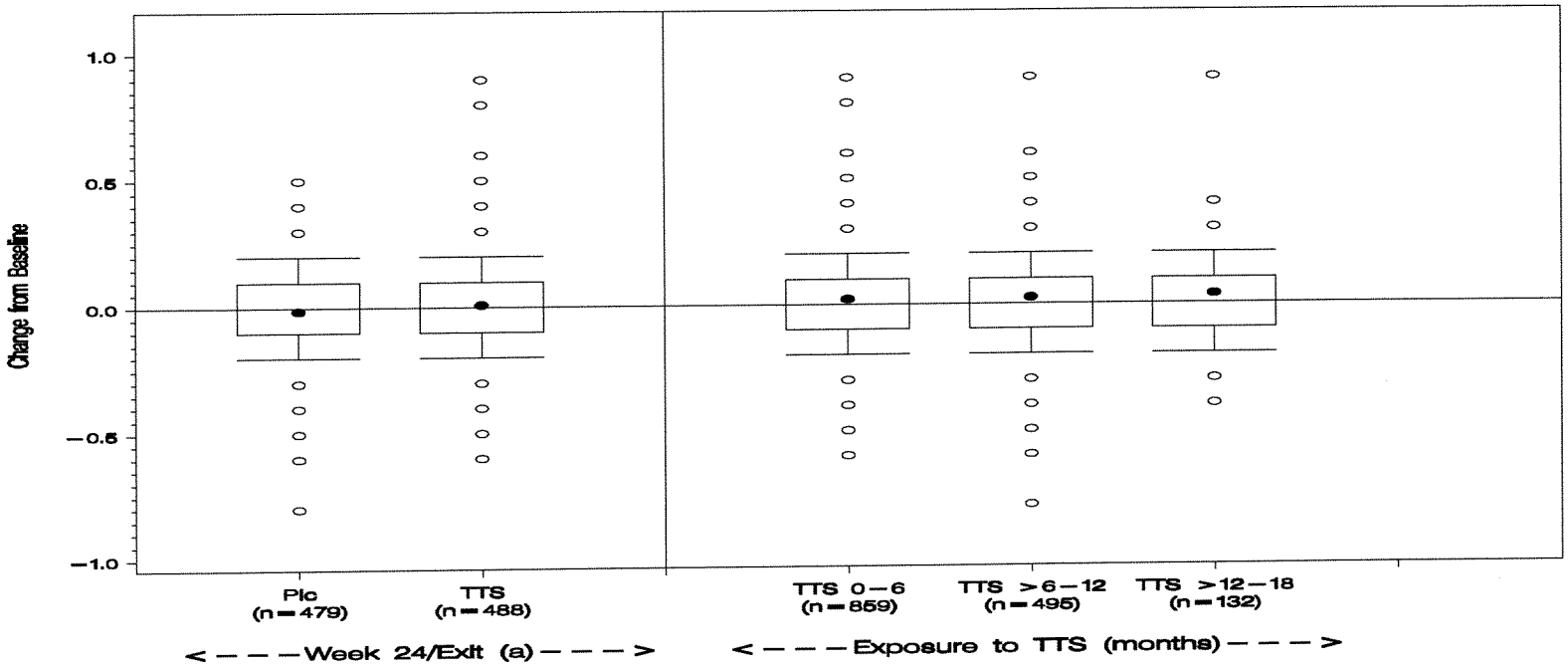
No differences between treatment groups in serum alkaline phosphatase, ALT, AST, or bilirubin during the double-blind period were noted in the Phase III studies (Table 31). There were no notable changes in these parameters with testosterone treatment for up to 18 months (Figures 28-30).

Table 31
Liver Function Tests during 24-Week Double-Blind Period
Phase III Studies

	SM 1		SM 2	
Baseline Value **Change at Week 24/Exit**	**Placebo** **N=279**	**TTS** **N=283**	**Placebo** **N=266**	**TTS** **N=266**
Alkaline phosphatase (U/L)	80.8 [23.4] -1.7 [12.1] n=252	79.5 [22.3] -1.0 [12.7] n= 260	79.2 [24.1] 0.0 [11.4] n=227	78.3 [22.9] -0.6 [18.3] n=228
ALT/SGPT (U/L)	22.3 [11.4] -0.2 [9.0] n= 252	21.1 [10.1] 0.4 [9.2] n=260	21.4 [9.1] 0.6 [8.4] n=227	20.7 [9.4] 0.8 [13.9] n= 228
AST SGOT (U/L)	22.4 [7.5] 0.0 [6.5] n=252	21.6 [5.9] 0.7 [6.4] n=260	22.2 [7.4] 0.6 [8.7] n= 227	21.6 [6.6] 0.8 [7.5] n=228
Bilirubin (mg/dL)	0.46 [0.22] -0.02 [0.17] n=252	0.45 [0.22] 0.01 [0.16] n=260	0.43 [0.20] 0 [0.15] n= 227	0.44 [0.23] 0 [0.18] n=228

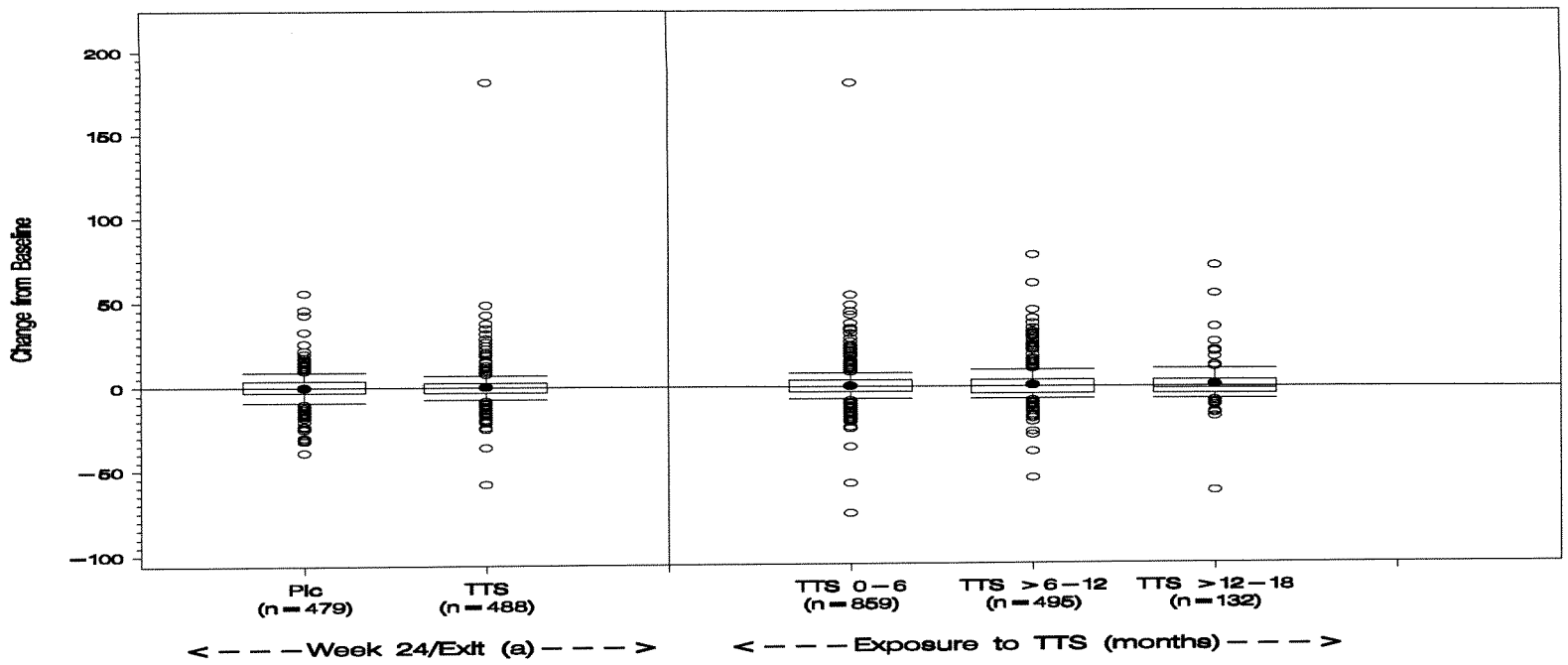
TTS=testosterone transdermal system
Values are means [standard deviation]. N=number of ITT patients. n=number of patients with values.

Figure 28
Change from Baseline in Total Bilirubin (mg/dL) in SM1 and SM2



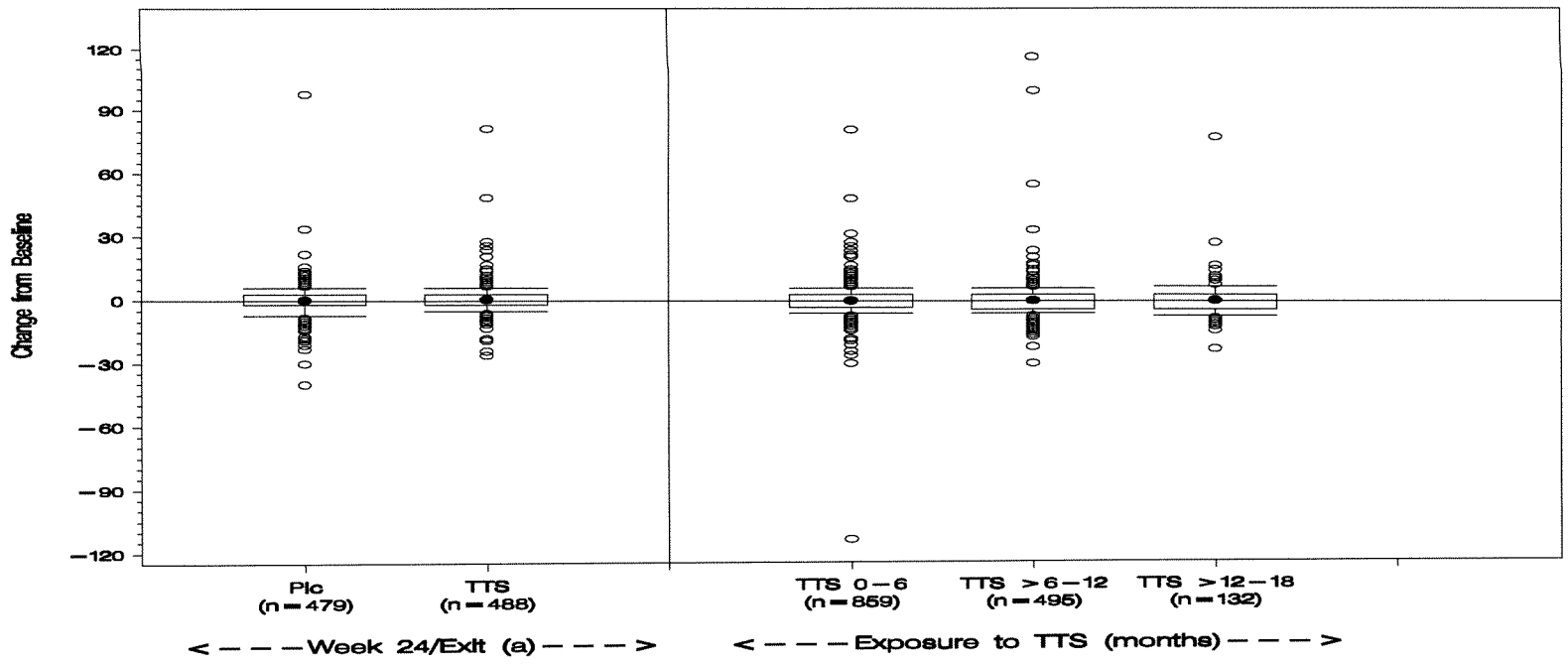
Plc = Placebo, TTS = 300 mcg/day testosterone transdermal system; number in brackets is number of patients with a value at that time-point.
(a) Includes exit evaluation if withdrawal was before 24 weeks.
Mean=dot; Median=central line; Box=interquartile range; Extreme value=circle; Lower whisker=10th Percentile; Upper whisker=90th Percentile.

Figure 29
Change from Baseline in Alanine Aminotransferase (SGPT) (U/L) in SM1 and SM2



Plc = Placebo, TTS = 300 mcg/day testosterone transdermal system; number in brackets is number of patients with a value at that time-point.
(a) Includes exit evaluation if withdrawal was before 24 weeks.
Mean=dot; Median=central line; Box=interquartile range; Extreme value=circle; Lower whisker=10th Percentile; Upper whisker=90th Percentile.

Figure 30
Change from Baseline in Aspartate Aminotransferase (SGOT) (U/L) in SM1 and SM2



Plc = Placebo, TTS = 300 mcg/day testosterone transdermal system; number in brackets is number of patients with a value at that time-point.
(a) Includes exit evaluation if withdrawal was before 24 weeks.
Mean=dot; Median=central line; Box=interquartile range; Extreme value=circle; Lower whisker=10th Percentile; Upper whisker=90th Percentile.

Carbohydrate Metabolism

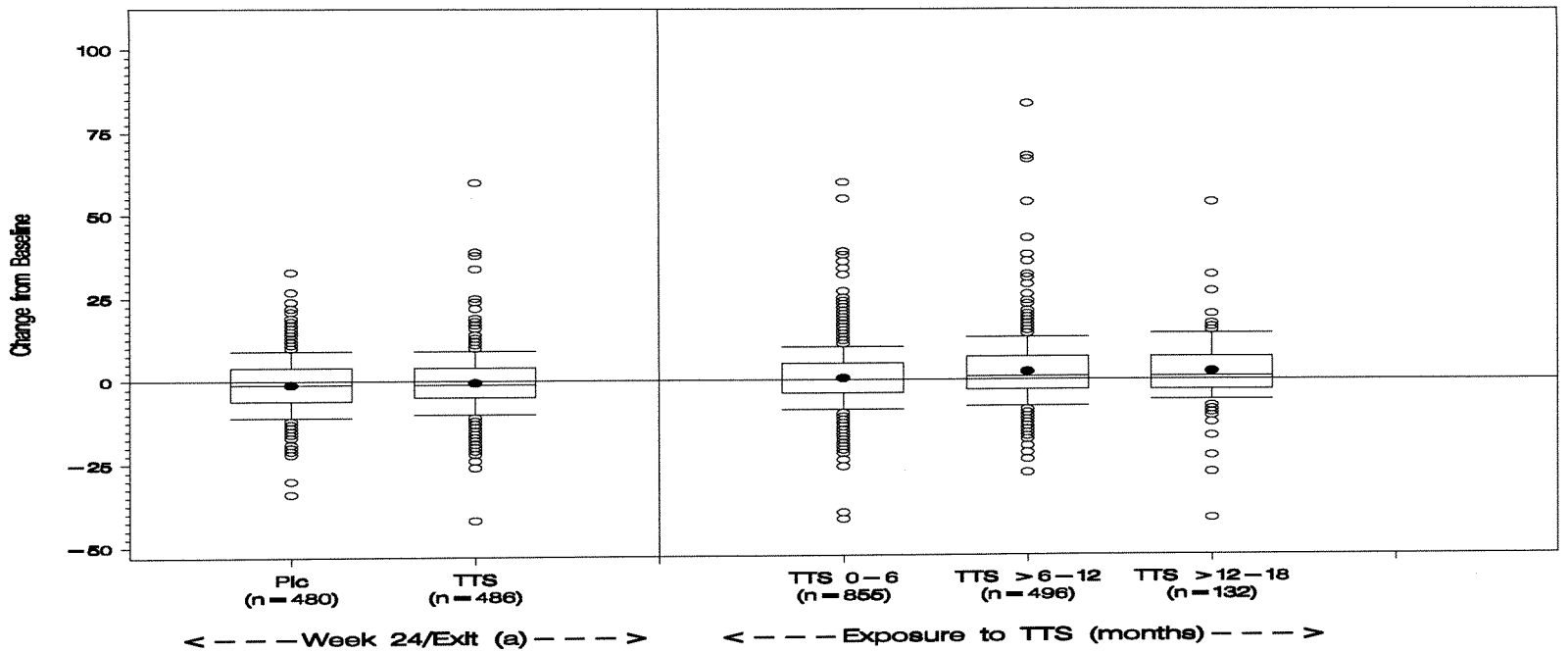
No changes between treatment groups were seen during the double-blind period in the Phase III studies (Table 32). No notable changes were seen with testosterone for total exposures of up to 18 months (Figures 31-33). No differences were noted in patients who had abnormal glucose values at baseline.

Table 32
Carbohydrate Metabolism during 24-Week Double-Blind Period
Phase III Studies

	SM 1		SM 2	
Baseline Value **Change at Week 24/Exit**	**Placebo** **N=279**	**TTS** **N=283**	**Placebo** **N=266**	**TTS** **N=266**
Glucose (mg/dL)	86.9 [8.6] -1.6 [8.6] n= 251	86.3 [8.4] -0.8 [9.2] n=258	86.0 [8.6] -0.4 [8.5] n=229	85.5 [8/7] -0.1 [8.8] n=228
HbA_{1c} (%)	5.31 [0.35] 0.03 [0.25] n= 247	5.32 [0.36] 0.02 [0.23] n=259	5.31 [0.39] 0.02 [0.24] n=228	5.32 [0.36] 0.05 [0.25] n=227
Insulin (mcU/mL)	9.3 [15.7] 0.2 [10.7] n=250	7.6 [6.1] 1.3 [5.2] n=259	8.2 [6.4] 1.5 [9.1] n=219	8.3 [7.3] 2.0 [13.1] n=222

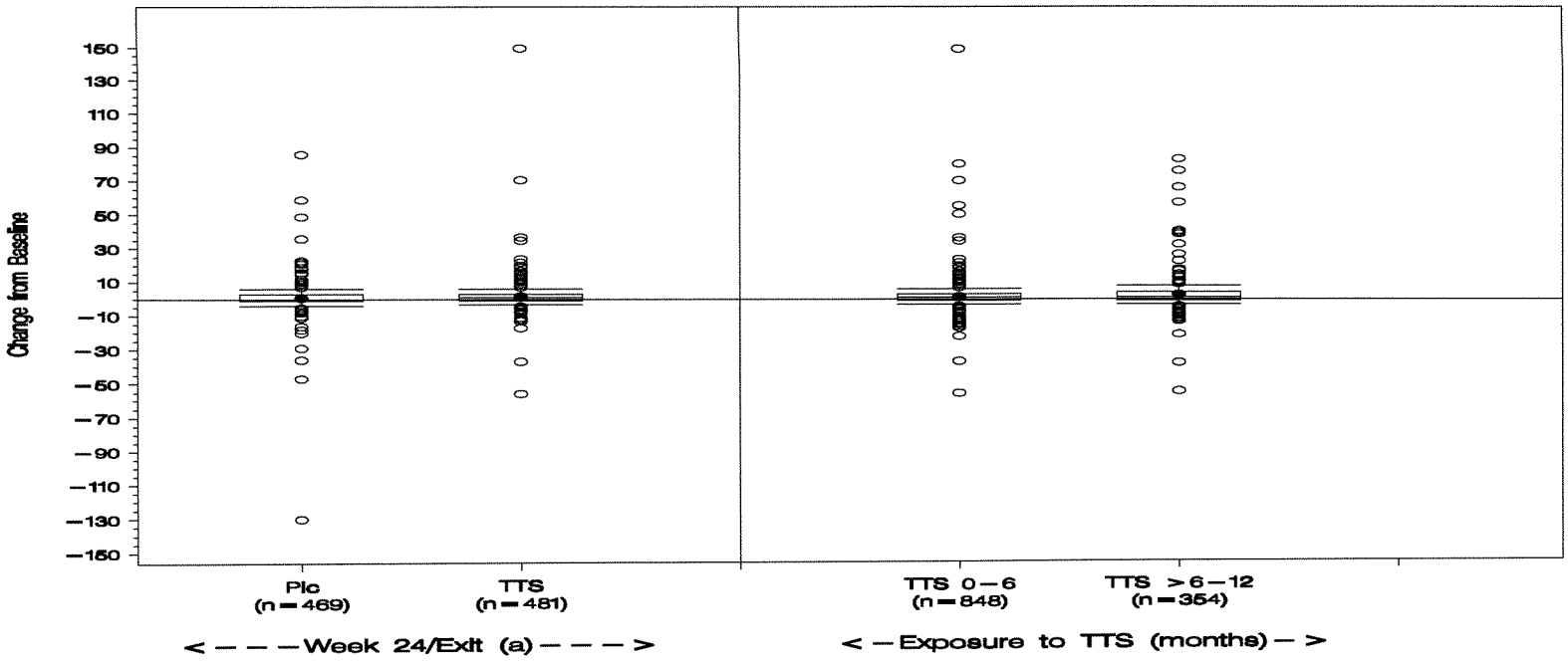
TTS=testosterone transdermal system
Values are means [standard deviation]. N=number of ITT patients. n=number of patients with values.

Figure 31
Change from Baseline in Glucose (mg/dL) in SM1 and SM2



Plc = Placebo, TTS = 300 mcg/day testosterone transdermal system; number in brackets is number of patients with a value at that time-point.
(a) Includes exit evaluation if withdrawal was before 24 weeks.
Mean=dot; Median=central line; Box=interquartile range; Extreme value=circle; Lower whisker=10th Percentile; Upper whisker=90th Percentile.

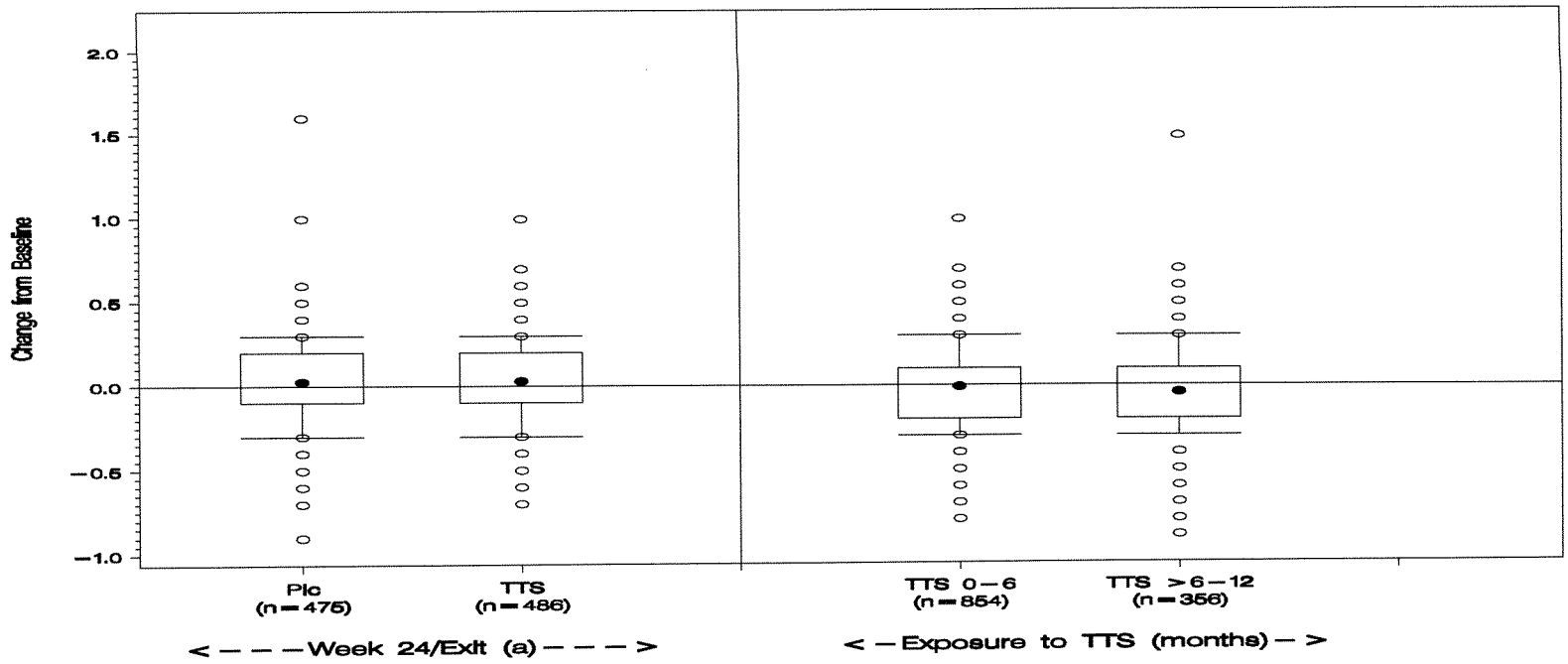
Figure 32
Change from Baseline in Insulin (uIU/mL) in SM1 and SM2



Plc = Placebo, TTS = 300 mcg/day testosterone transdermal system; number in brackets is number of patients with a value at that time-point.
(a) Includes exit evaluation if withdrawal was before 24 weeks.
Mean=dot; Median=central line; Box=interquartile range; Extreme value=circle; Lower whisker=10th Percentile; Upper whisker=90th Percentile.

Source: ~/UPDATE90/ADVISRY/SFTY/REPORT/finlbox.sas; SAS 8.2 program run 25OCT04:09:47 by tf6225; data taken from HCDW on I16JUL04.

Figure 33
Change from Baseline in Hemoglobin A1C (%) in SM1 and SM2



Plc = Placebo, TTS = 300 mcg/day testosterone transdermal system; number in brackets is number of patients with a value at that time-point.
(a) Includes exit evaluation if withdrawal was before 24 weeks.
Mean=dot; Median=central line; Box=interquartile range; Extreme value=circle; Lower whisker=10th Percentile; Upper whisker=90th Percentile.

Markedly Abnormal Laboratory Values

Few patients experienced markedly abnormal laboratory values while receiving testosterone treatment, and the number of patients with such values was similar in both treatment groups (Table 33).

Table 33
Markedly Abnormal Laboratory Values during 24-Week Double-Blind Period
Studies SM 1 and SM 2 (combined)

	SM 1 and SM 2	
	Placebo N=545 n	**TTS N=549 n**
Total cholesterol*	1	1
HDL cholesterol*	0	0
LDL cholesterol*	7	5
ALT	0	1
AST	1	0
Bilirubin	0	0
Fasting glucose	0	0
Fasting insulin	16	13
HgbA1C	0	0
Hemoglobin*	0	0

TTS=testosterone transdermal system. Values are numbers of patients. A measurement was defined as markedly abnormal if it was outside the limit and in excess of the percent change from baseline noted for each parameter: total cholesterol, > 280 mg/dL and increased by >30% ; HDL cholesterol, <34 mg/dL and decreased by >30%; LDL cholesterol, >160 mg/dL and increased by >30%; ALT, ≥ 3X the upper limit of normal and increased by >30%; AST, ≥ 3X the upper limit of normal and increased by >30%; bilirubin, ≥ 2.0 mg/dL and increased by >50%; fasting glucose, > 140 mg/dL and increased by >15% or <50 mg/dL and decreased by >15%; insulin, >25 µIU/mL and increased by >30%; HgbA1C, >6.1% and increased by >30%; hemoglobin, ≤ 9.5 g/dL and decreased by>30%.
*Group changes in these parameters are discussed in the cardiovascular safety section of this document (section 3.3.4.1).

Review of all clinical laboratory data, including individual cases of abnormal laboratory values, demonstrated no evidence of clinically important testosterone-associated changes in laboratory parameters with up to 78 weeks of transdermal testosterone treatment.

3.3.3 Breast Safety

The relationship between testosterone and breast cancer risk is not clear. Significant data exist that support the biologic plausibility for a protective effect of testosterone on breast tissue. In vitro studies have shown that testosterone can inhibit the stimulatory effects of estrogen, reverse ERa/ERb, and down regulate Myc expression in rhesus breast tissue (Dimitrikakis et al, 2003). Flutamide (a testosterone antagonist) was shown to increase mammary epithelial proliferation in these animals. Testosterone has been shown to either decrease the number of progressing tumors or increase the number of complete responses in a variety of in vivo models of mammary carcinoma (Dauvois et al, 1989, Dauvois et al 1991, Jayo et al, 2000). In the clinic, exogenous testosterone has been used as a treatment for advanced breast cancer and may increase the effectiveness of anti-estrogen therapy. Women afflicted with hyperandrogenic states, such as PCOS, do not show a consistent increase in breast cancer (Gammon and Thompson, 1991). Breast atrophy is often seen in congenital adrenal hyperplasia along with other signs of virilization. A recently published study by Dimitrakakis et al. observed no increased risk of breast cancer with the addition of exogenous testosterone to standard hormone therapy among postmenopausal women (mean duration of follow-up, 5.8 years); in fact, breast cancer rate in testosterone users was closest to that reported for hormone therapy never users (Dimitrakakis et al., 2004). Epidemiologic studies examining the relationship between endogenous testosterone and breast cancer risk have yielded equivocal results (The Endogenous Hormones and Breast Cancer Collaborative Group, 2002).

3.3.3.1 Incidence of Breast Cancer in the Clinical Trials

Four cases of breast malignancy were recorded during the testosterone transdermal system trials (Table 34). One case was in a placebo patient in a Phase II study (1999068). Three cases were observed during the open-label period in patients who had received between 5 and 37 weeks of testosterone treatment. No cases of breast cancer were observed in the studies in naturally menopausal women (which included some patients who had up to 52 weeks of testosterone treatment).

Based on the 1-year rate of breast cancer for 49-year-old (the mean age of the Phase III patients) white women (Reis et al., 2004), the number of events in the Phase III trials was not higher than expected.

Table 34. Breast Cancer Cases in the Clinical Trials

Age/Study	Gail risk 5 yr, %; lifetime, %*	Diagnosis	E/P Receptor +/-	Nodes	Treatment	Time on E	Time on TTS	Mammogram
50/1999068	1.1 10.3	Invasive ductal carcinoma, grade III	-	-	Surgery	1.25 yrs	0 (placebo)	+ at baseline
50/SM 2	1.8 15.9	Ductal carcinoma in situ	-	-	Surgery/Radiation	2 yrs	24 weeks Placebo→TTS	+ (was – at baseline)
63/SM 2	3.6 14.5	Metastatic adenocarcinoma	-	+ 6/10	Chemo/Radiation	16 yrs	5 weeks Placebo→TTS	- (palpable axillary mass)
56/SM 1	0.9 5.98	Tubulolobular carcinoma	+	-	Surgery/Radiation	11 yrs	37 weeks Placebo→TTS	+ (scattered fibroglandular densities at baseline; 6 month follow-up suggested)

Placebo→TTS indicates placebo during 24-week, double-blind period, followed by testosterone during the open-label period.
*>1.7%, 5-year risk considered high.

3.3.3.2 Effects of Testosterone on Cell Proliferation and Breast Density

A 6-month, randomized, double blind, placebo-controlled, study was conducted at the Karolinska University Hospital in Sweden to assess the effects of the 300 mcg/day testosterone transdermal system on mammographic breast density and breast tissue proliferation in naturally menopausal women on continuous combined estrogen and progestin therapy. All patients were given continuous combined treatment, with 2 mg estradiol and 1 mg norethisterone acetate, and randomly assigned to a testosterone treatment with the 300 mcg/day testosterone patch or a placebo patch. Two independent primary endpoints, breast epithelial proliferation (%Ki67 reactive epithelial and stromal cells obtained by fine needle aspiration) and mammographic breast density, were assessed in this study at baseline and after 6 months of treatment.

Of the 99 patients randomly assigned to treatment during the study, 88 (89%) completed the study. Demographic characteristics (age, race, height, weight, and BMI) were similar among the treatment groups at baseline. The average age of patients was 55 years (range: 45 to 65 years).

Paired samples containing sufficient cellular material for epithelial analysis were obtained from 43 patients (22 placebo, 21 testosterone). The mean (SEM) change from baseline in %Ki67 positive cells at 6 months was 2.32 (0.56) in the placebo group and 0.53 (0.65) in the testosterone group. A statistically significant treatment difference of -1.78 was seen based on unadjusted baseline values ($p=0.04$). While directionally consistent, mean values adjusted for baseline values did not reach significance (LSMean change -1.36, $p=0.08$). Additionally, Ki67 reactivity in the stromal cell component was decreased in patients receiving testosterone treatment compared to those receiving placebo (mean difference of -9.1, $p=0.06$, $n=14$). Taken together, these data suggest that the 300 mcg/day testosterone transdermal system diminishes epithelial and stromal cell proliferation in women exposed to 2 mg estradiol and 1 mg norethisterone acetate for a period of 6 months.

A total of 87 mammograms of the left breast were evaluable. There was no statistically significant difference in breast density at month 6 between the two treatment groups, whether using the Wolfe classification, the percentage of dense parenchyma, or the digitized assessment of breast density, even after adjusting on baseline values.

Overall, proliferation data from paired biopsy samples suggested a protective effect on the breast following six months administration of 300 mcg/day testosterone transdermal patch in women on concomitant oral hormone replacement therapy containing 2 mg of estradiol and 1 mg of norethisterone acetate in continuous combination. Breast density appeared unaffected by addition of transdermal testosterone over this time period. These data provide reassurance that the testosterone transdermal system does not exert a negative effect on breast tissue density and may have favourable effects on factors known to be predictive of breast cancer risk.

3.3.4 Cardiovascular Safety

The relationship between androgens and cardiovascular risk factors is complex, with both positive and negative effects observed, depending on gender and the dose, type, and route of administration of androgen. Mechanisms by which exogenous testosterone may worsen or lessen cardiovascular risk include changes in serum lipid levels, blood pressure, vascular reactivity,

viscosity, macrophage functions, and platelet functions (Basaria and Dobs, 2004; Wu and von Eckardstein, 2003).

No long-term, prospective data are available to evaluate the effects of exogenous, low-dose transdermal testosterone administration in women on cardiovascular morbidity or mortality, and limited, short-term data are available regarding changes in cardiovascular risk factors. In women, transdermal testosterone preparations appear to have neutral effects on lipids (Basaria and Dobs, 2004; Shifren, 2000), as opposed to methyltestosterone, which has negative effects on HDL cholesterol (Barrett-Connor et al., 1999; Basaria, et al 2002; Lobo, et al., 2003). Short-term androgen replacement in women does not adversely affect the vascular system (Basaria and Dobs, 2004). A retrospective study of 293 female-to-male transsexuals [age range, 17 to 70 years; mean, 34 years] found no increase in cardiovascular mortality or morbidity compared with the general female population (van Kesteren et al., 1997). These patients had been treated with oral testosterone undecanoate (160 mg/day) or intramuscular testosterone (250 mg every 2 weeks) for durations of 2 months to 41 years (total exposure 2418 patient-years)

3.3.4.1 Effects of Transdermal Testosterone on Laboratory Parameters Relevant to Cardiovascular Safety in Clinical Trials

Testosterone treatment through 78 weeks showed no clinically concerning effect on laboratory parameters related to cardiovascular safety [serum lipids, coagulation parameters (through 52 weeks), hematology parameters] or on blood pressure (see section 3.3.2.9 of this briefing document). Analyses of the relationship between changes in laboratory parameters and serum free testosterone levels can be found in section 4.5 of this briefing document.

Lipids

No clinically meaningful differences were noted in total cholesterol, HDL cholesterol, LDL cholesterol, or triglyceride levels between TTS-treated patients and the placebo-treated patients during the 24-week double-blind period (Table 35). No notable changes in these parameters were seen with up to 18 months of testosterone exposure (Figures 34-36).

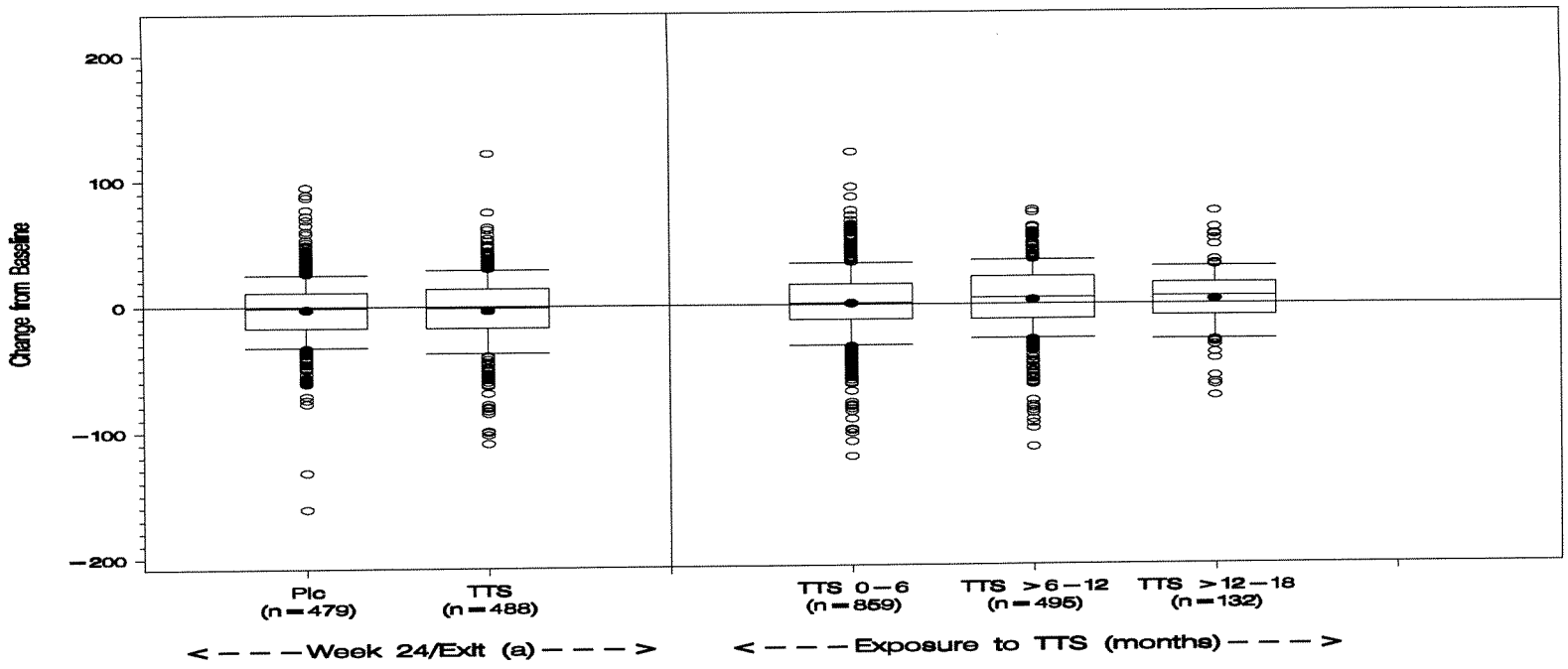
Testosterone was not associated with an increase in the percentage of patients experiencing markedly abnormal laboratory values for total cholesterol, HDL cholesterol, or LDL cholesterol (see Table 33 of this briefing document).

Table 35
Serum Lipids During 24-Week Double-Blind Period
Phase III Studies

	SM 1		SM 2	
Baseline Value **Change at Week 24/Exit**	**Placebo** **N=279**	**TTS** **N=283**	**Placebo** **N=266**	**TTS** **N=266**
Total cholesterol (mg/dL)	215 [34] -2.9 [26] n=252	217 [39] -2.8 [26] n=260	217 [37] -1.9 [26] n=227	219 [40] -3.6 [28] n=228
HDL cholesterol (mg/dL)	64 [16] 1.6 [10] n=252	61 [15] 0.4 [9] n=260	65 [18] 1.2 [9] n= 227	63 [19] 0.8 [10] n=228
LDL cholesterol (mg/dL)	122 [31] -2.7 [23] n=252	125 [34] -0.1 [23] n=260	124 [32] -2.1 [22] n= 227	125 [37] -2.3 [25] n=228
Triglycerides (mg/dL)	150 [75] -9 [59] n=252	156 [82] -17 [63] n=260	148 [80] -9 [65] n=227	155 [92] -13 [54] n=228

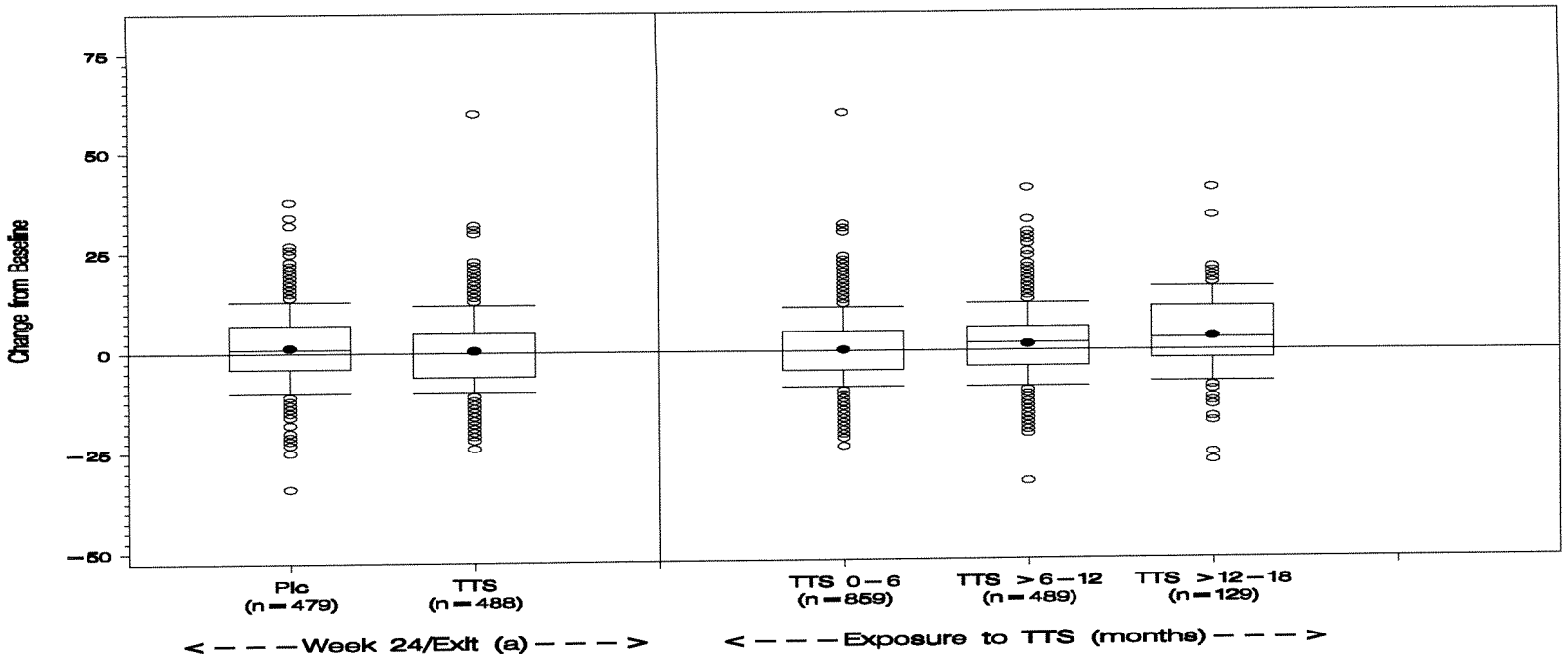
TTS=testosterone transdermal system
Values are means [standard deviation]. N=number of ITT patients. n=number of patients with values.

Figure 34
Change from Baseline in Total Cholesterol (mg/dL) in SM1 and SM2



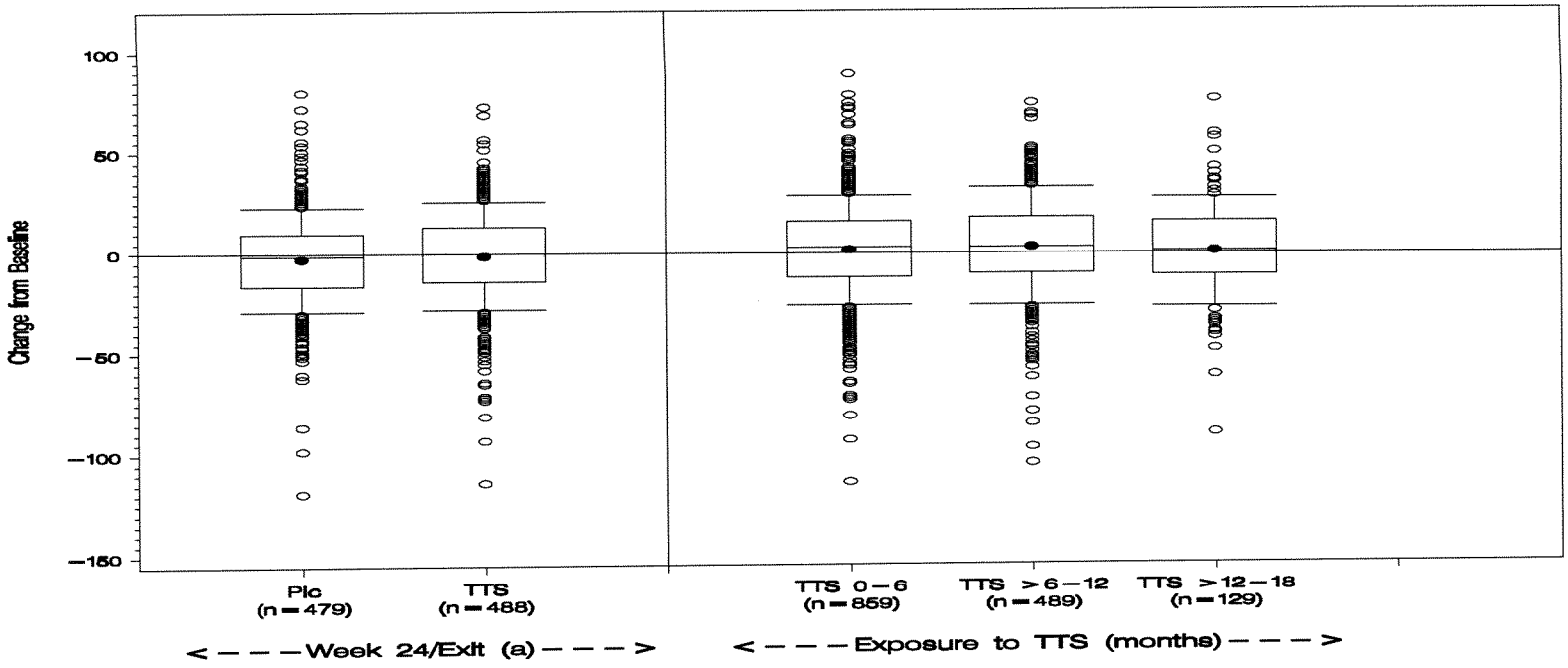
Plc = Placebo, TTS = 300 mcg/day testosterone transdermal system; number in brackets is number of patients with a value at that time-point.
(a) Includes exit evaluation if withdrawal was before 24 weeks.
Mean=dot; Median=central line; Box=interquartile range; Extreme value=circle; Lower whisker=10th Percentile; Upper whisker=90th Percentile.

Figure 35
Change from Baseline in HDL-Cholesterol (mg/dL) in SM1 and SM2



Plc = Placebo, TTS = 300 mcg/day testosterone transdermal system; number in brackets is number of patients with a value at that time-point.
(a) Includes exit evaluation if withdrawal was before 24 weeks.
Mean=dot; Median=central line; Box=interquartile range; Extreme value=circle; Lower whisker=10th Percentile; Upper whisker=90th Percentile.

Figure 36
Change from Baseline in LDL-Cholesterol (mg/dL) in SM1 and SM2



Plc = Placebo, TTS = 300 mcg/day testosterone transdermal system; number in brackets is number of patients with a value at that time-point.
(a) Includes exit evaluation if withdrawal was before 24 weeks.
Mean=dot; Median=central line; Box=interquartile range; Extreme value=circle; Lower whisker=10th Percentile; Upper whisker=90th Percentile.

Source: ~/UPDATE90/ADVISRY/SFTY/REPORT/finlbox.sas; SAS 8.2 program run 25OCT04:09:47 by tf6225; data taken from HCDW on I16JUL04.

Coagulation Parameters

Coagulation parameters were measured only in Study SM 1. No meaningful differences were noted between groups during the double-blind treatment period (Table 36) or with total testosterone exposure of up to 52 weeks (the last measurements taken for these parameters) (Figures 37-43).

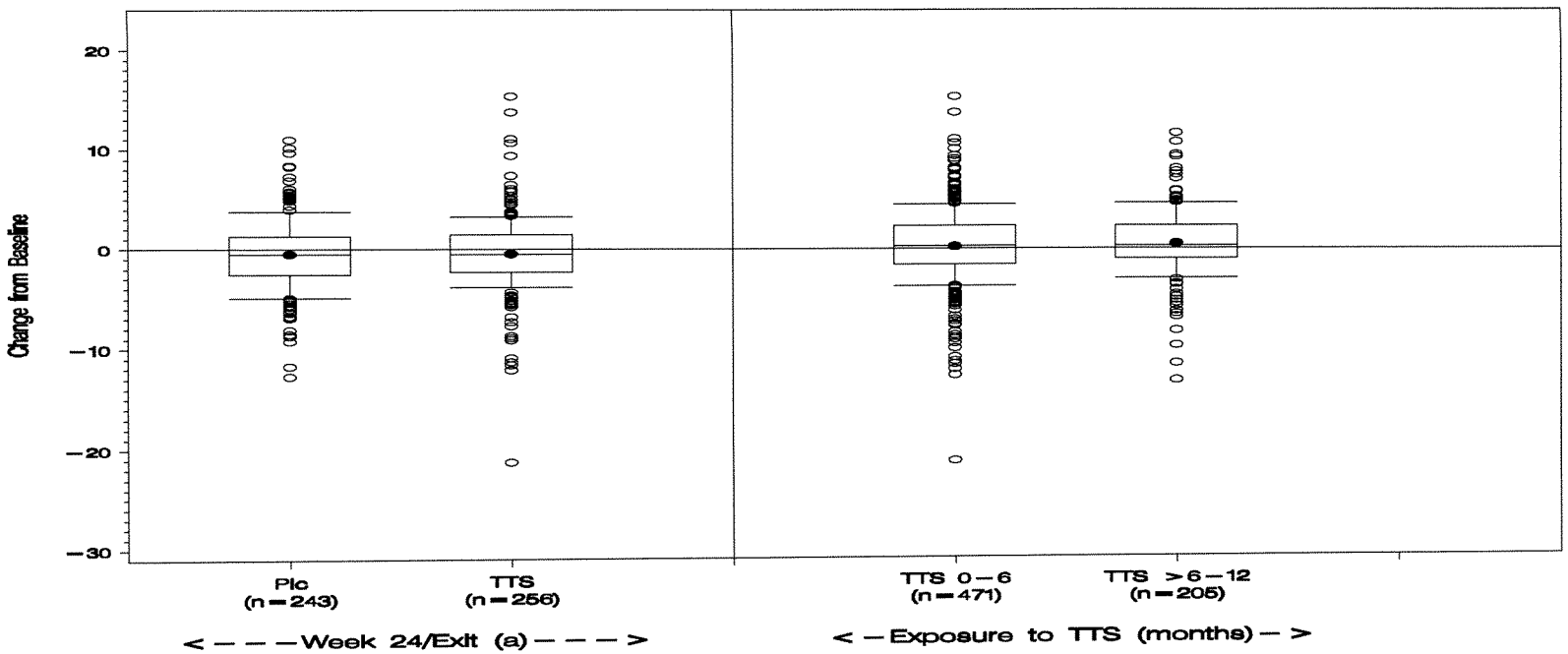
Table 36
Coagulation Parameters during 24-Week Double-Blind Period
Study SM 1

	SM 1	
Baseline Value **Change at Week 24/Exit**	**Placebo** **N=279**	**TTS** **N=283**
PT (sec)	10.9 [0.7] -0.2 [1.0] n=242	10.8 [0.6] -0.1 [0.9] n=254
APTT (sec)	29.2 [3.8] -0.5 [3.6] n=243	29.4 [4.2] -0.4 [3.8] n=256
Fibrinogen (mg/dL)	381.3 [95.9] 11.4 [90.1] n=241	386.9 [85.5] 9.7 [79.2] n=255
PAI activity (U/mL)	8.4 [10.2] -0.6 [9.0] n=230	7.6 [9.9] -0.6 [9.6] n=239
PAI antigen (ng/mL)	22.1 [17.3] 1.5 [19.9] n= 230	21.9 [19.1] -1.6[19.2] n=239
tPA antigen (ng/mL)	5.6 [3.3] 1.3 [3.3] n=247	5.5 [5.5] 1.1 [5.6] n=260
ATIII (functional)	104.0 [12.4] 1.8 [13.9] n=241	105.0 [11.1] 1.4 [12.6] n=254

TTS=testosterone transdermal system
Values are means [standard deviation]. N=number of ITT patients. n=number of patients with values.

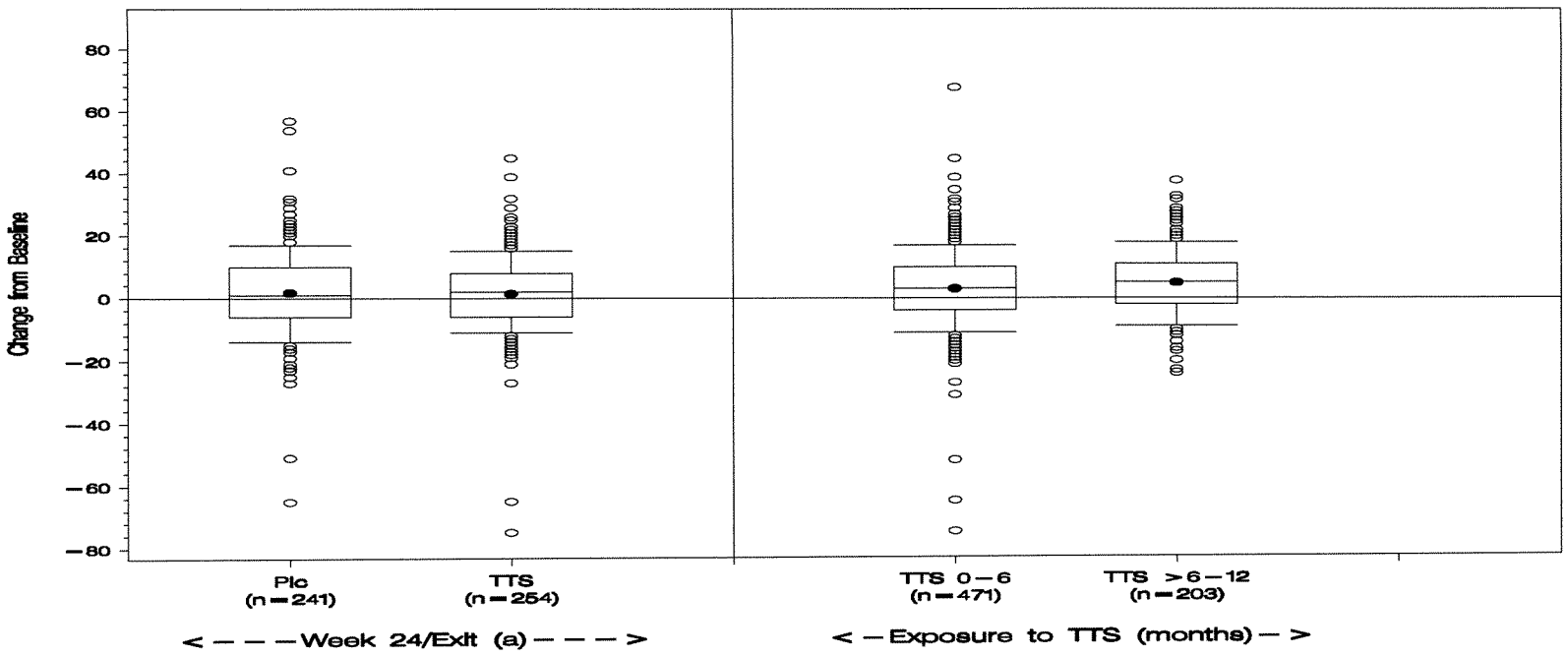
One patient with elevated fibrinogen (522 mg/dL; normal 184-514 mg/dL) discontinued treatment after Week 24 while on testosterone. A repeat test performed 6 weeks after the first test and 2 days after drug discontinuation, was within normal limits (fibrinogen, 418 mg/dL). This patient was a heavy smoker.

Figure 37
Change from Baseline in Activated Partial Thromboplastin Time (sec) in SM1



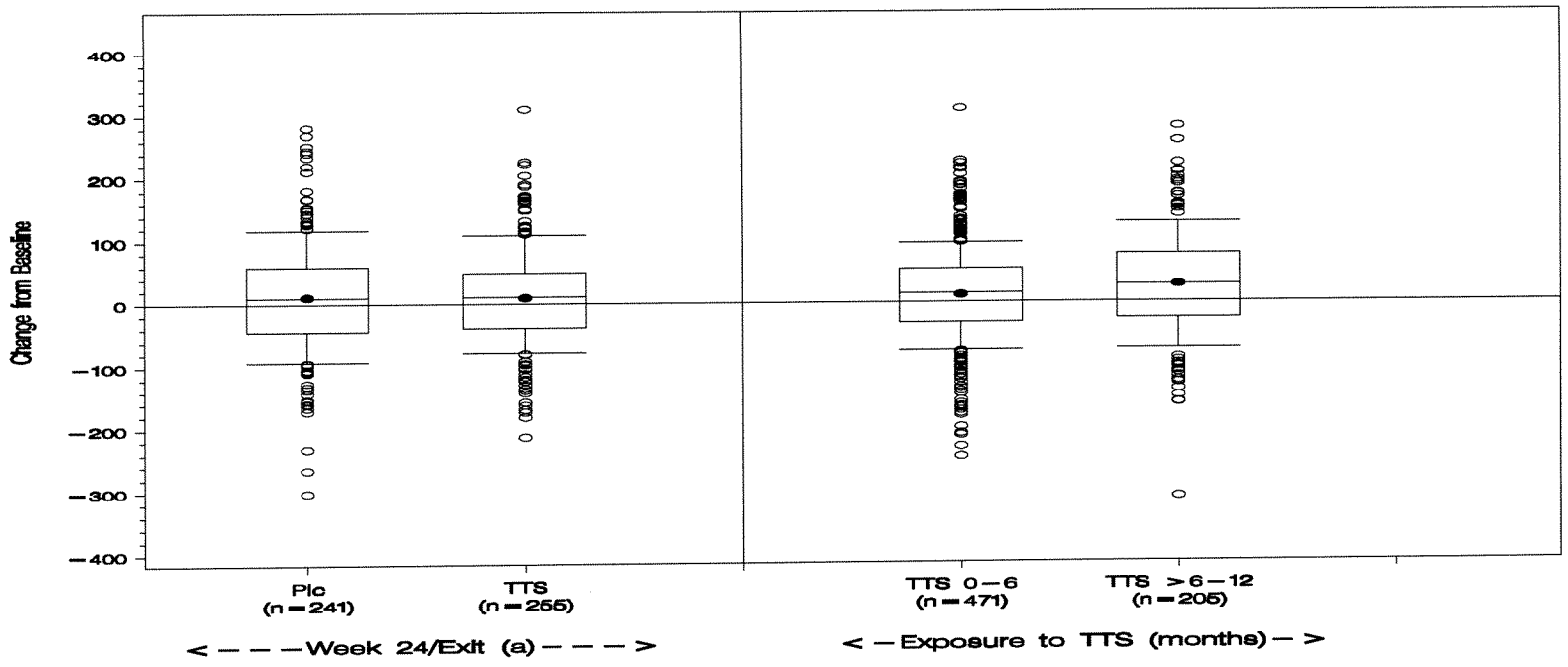
Plc = Placebo, TTS = 300 mcg/day testosterone transdermal system; number in brackets is number of patients with a value at that time-point.
(a) Includes exit evaluation if withdrawal was before 24 weeks.
Mean=dot; Median=central line; Box=interquartile range; Extreme value=circle; Lower whisker=10th Percentile; Upper whisker=90th Percentile.

Figure 38
Change from Baseline in Antithrombin III (%) in SM1



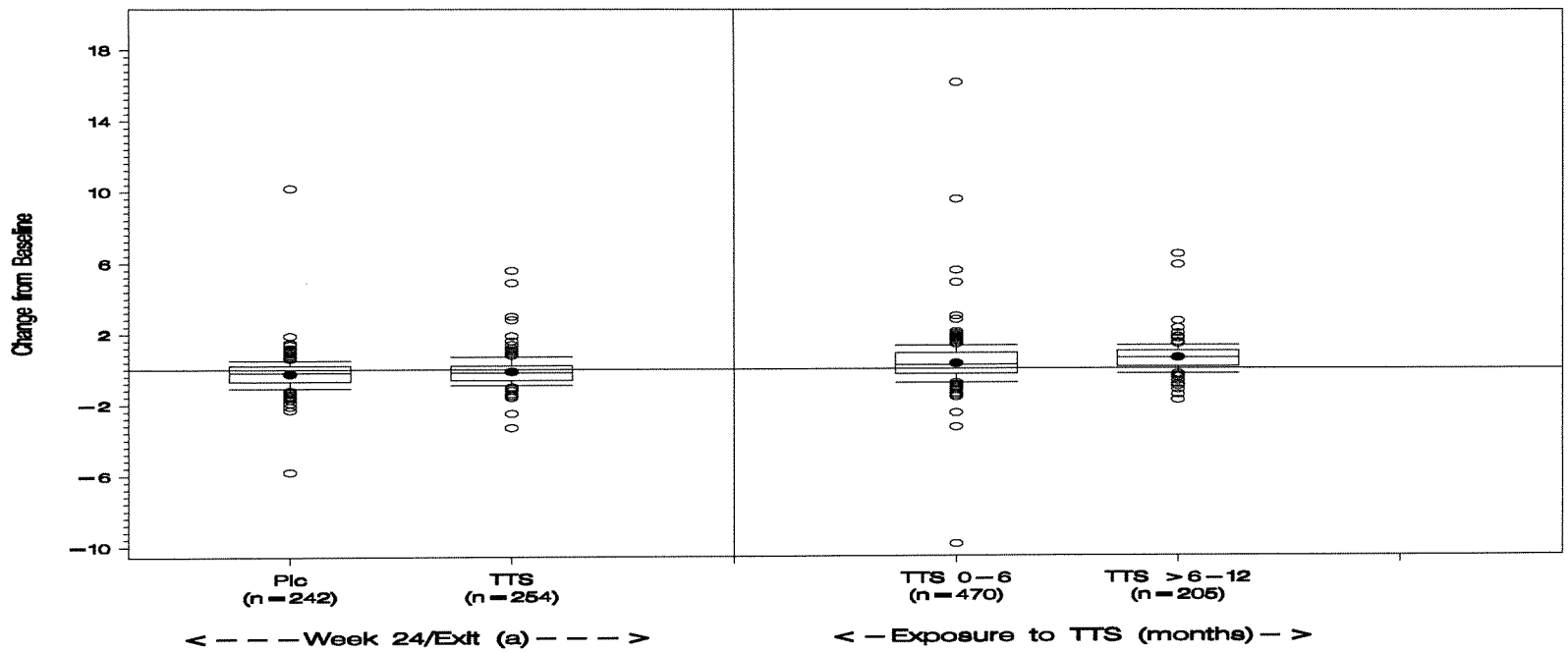
Plc = Placebo, TTS = 300 mcg/day testosterone transdermal system; number in brackets is number of patients with a value at that time-point.
(a) Includes exit evaluation if withdrawal was before 24 weeks.
Mean=dot; Median=central line; Box=interquartile range; Extreme value=circle; Lower whisker=10th Percentile; Upper whisker=90th Percentile.

Figure 39
Change from Baseline in Fibrinogen (mg/dL) in SM1



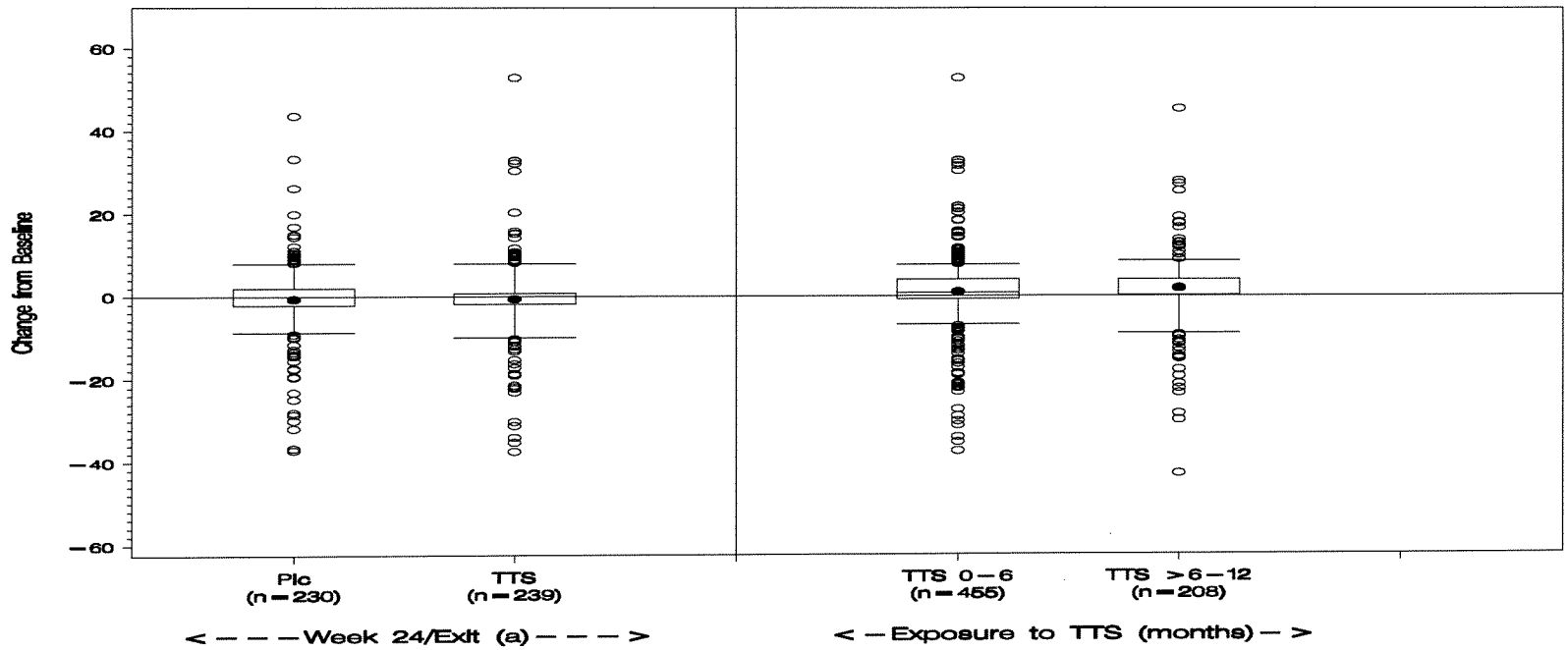
Plc = Placebo, TTS = 300 mcg/day testosterone transdermal system; number in brackets is number of patients with a value at that time-point.
(a) Includes exit evaluation if withdrawal was before 24 weeks.
Mean=dot; Median=central line; Box=interquartile range; Extreme value=circle; Lower whisker=10th Percentile; Upper whisker=90th Percentile.

Figure 40
Change from Baseline in Prothrombin Time (sec) in SM1



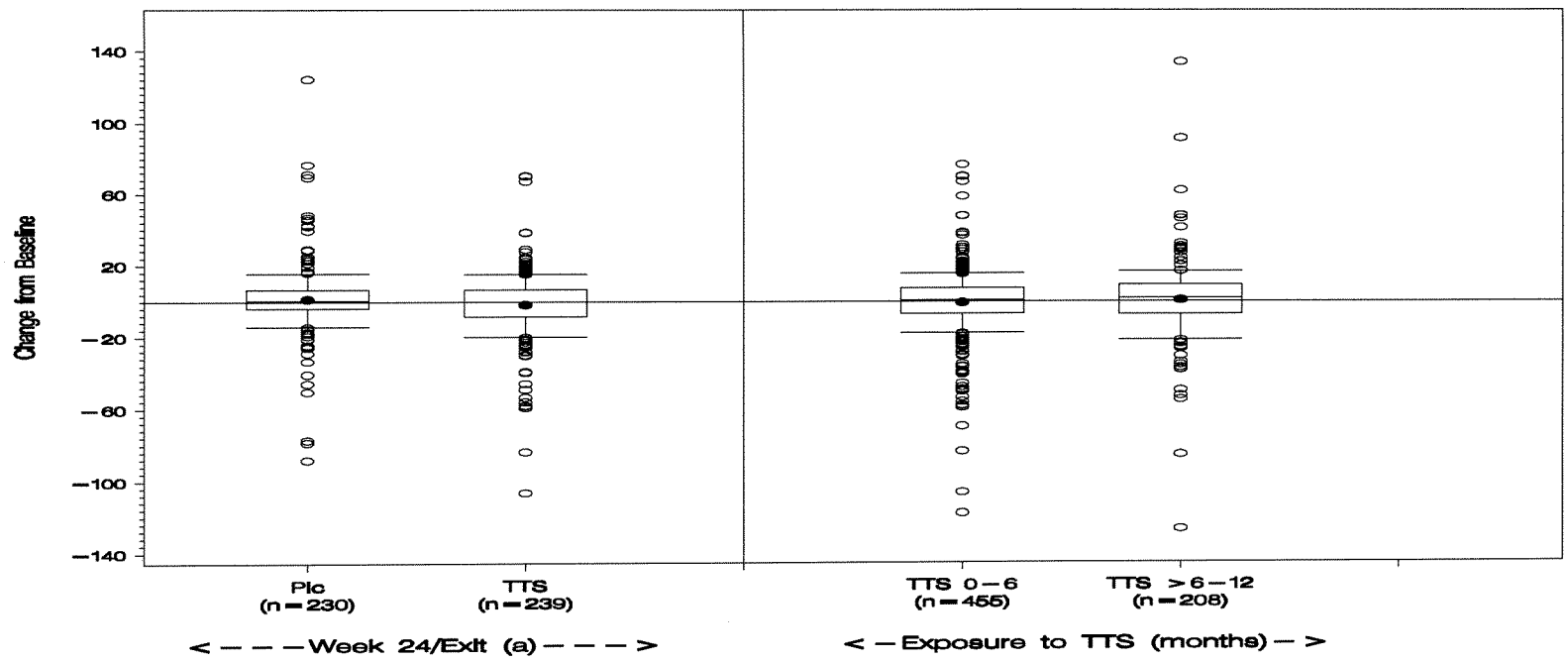
Plc = Placebo, TTS = 300 mcg/day testosterone transdermal system; number in brackets is number of patients with a value at that time-point.
(a) Includes exit evaluation if withdrawal was before 24 weeks.
Mean=dot; Median=central line; Box=interquartile range; Extreme value=circle; Lower whisker=10th Percentile; Upper whisker=90th Percentile.

Figure 41
Change from Baseline in Plasminogen Activator Inhibitor-1 Activ. (U/mL) in SM1



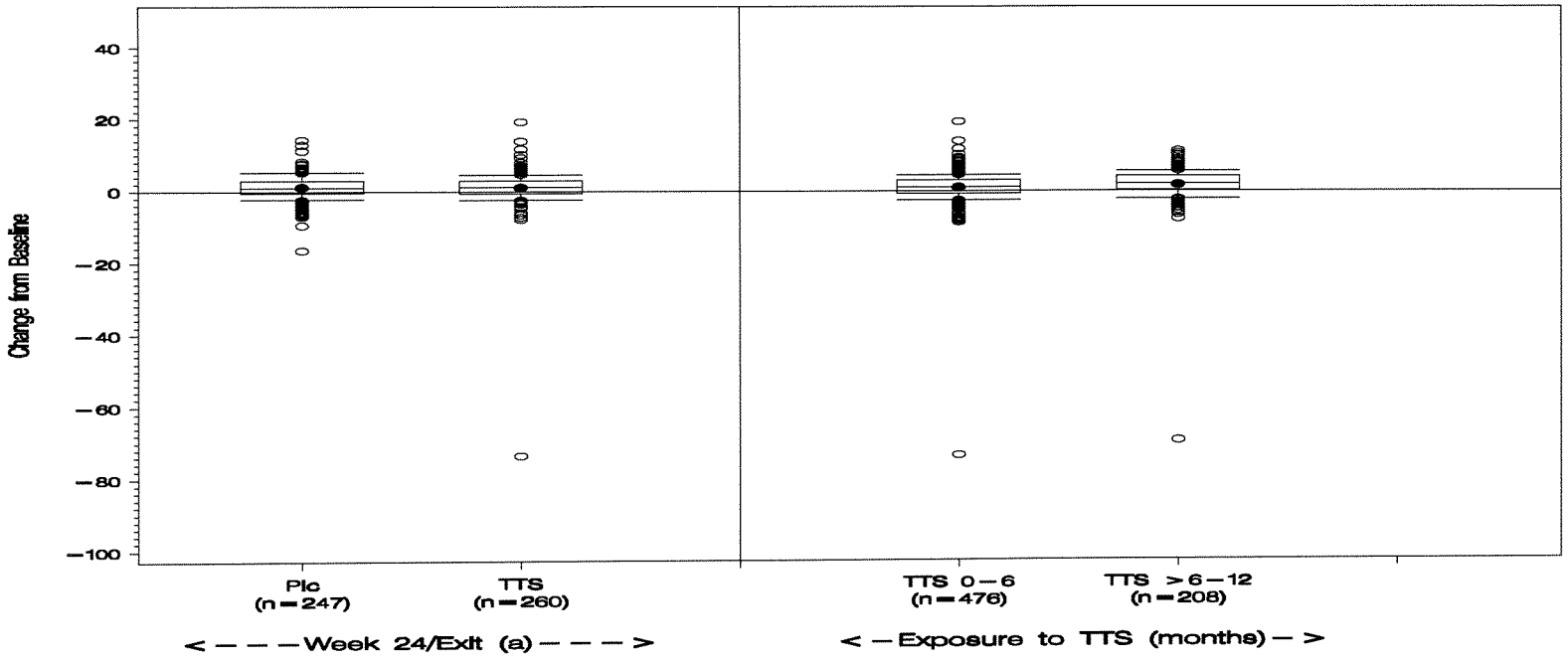
Plc = Placebo, TTS = 300 mcg/day testosterone transdermal system; number in brackets is number of patients with a value at that time-point.
(a) Includes exit evaluation if withdrawal was before 24 weeks.
Mean=dot; Median=central line; Box=interquartile range; Extreme value=circle; Lower whisker=10th Percentile; Upper whisker=90th Percentile.

Figure 42
Change from Baseline in Plasminogen Activator Inhibitor-1 Antig. (ng/mL) in SM1



Plc = Placebo, TTS = 300 mcg/day testosterone transdermal system; number in brackets is number of patients with a value at that time-point.
(a) Includes exit evaluation if withdrawal was before 24 weeks.
Mean=dot; Median=central line; Box=interquartile range; Extreme value=circle; Lower whisker=10th Percentile; Upper whisker=90th Percentile.

Figure 43
Change from Baseline in Tissue Plasminogen Activator Antigen (ng/mL) in SM1



Plc = Placebo, TTS = 300 mcg/day testosterone transdermal system; number in brackets is number of patients with a value at that time-point.
(a) Includes exit evaluation if withdrawal was before 24 weeks.
Mean=dot; Median=central line; Box=interquartile range; Extreme value=circle; Lower whisker=10th Percentile; Upper whisker=90th Percentile.

Hematologic Parameters

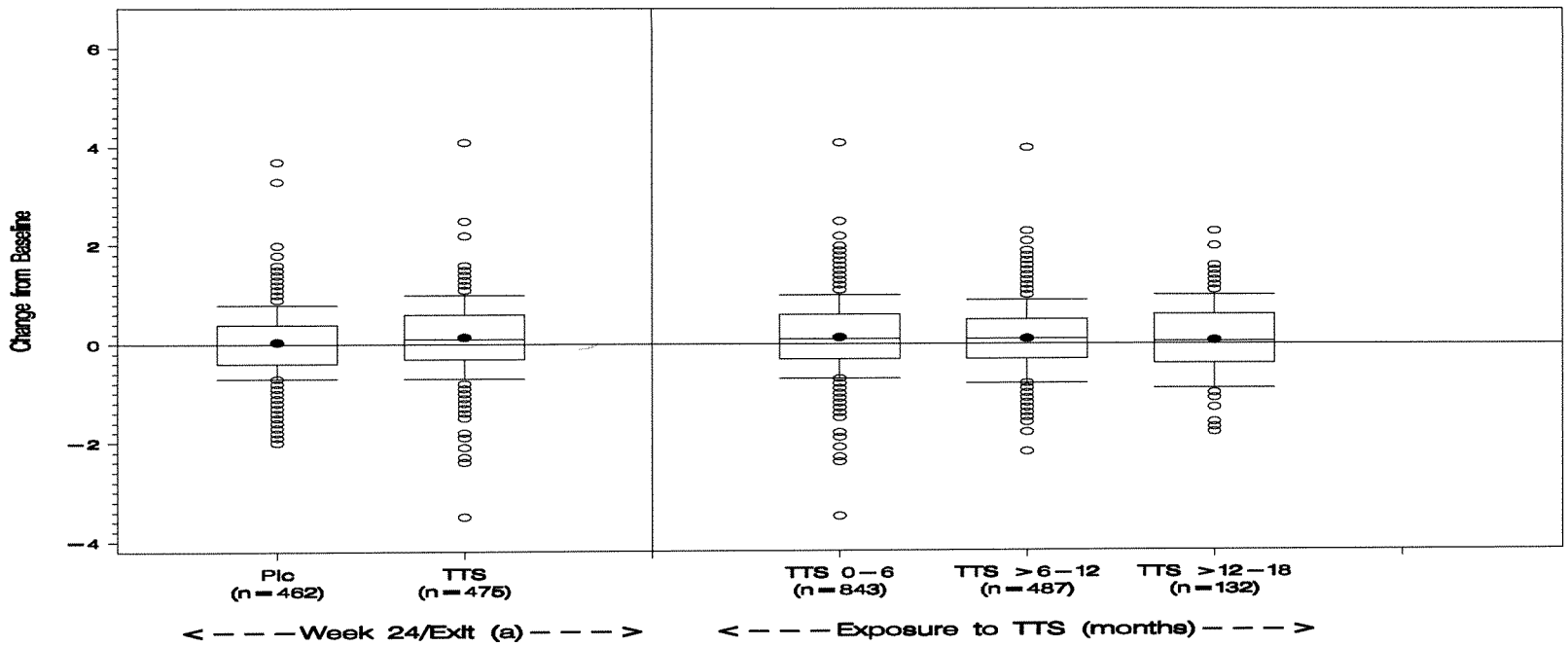
Hemoglobin increased by approximately 0.1 g/dL on average in the testosterone group by Week 24 of the double-blind period in the Phase III studies (Table 37), but did not change after that time with continuing treatment up to 78 weeks (Figure 44). Review of a scatter plot (Figure 45) showed no evidence that patients with higher baseline levels were more likely to experience increases. No patient in either treatment group experienced a markedly abnormal value for hemoglobin in the double-blind period (see Table 33). Hematocrit showed no clinically significant change from baseline in any treatment group in any individual study.

Table 37
Hematology Parameters during 24-Week Double-Blind Period
Phase III Studies

	SM 1		SM 2	
Baseline Value **Change at Week 24/Exit**	**Placebo** **N=279**	**TTS** **N=283**	**Placebo** **N=266**	**TTS** **N=266**
Hematocrit (%)	39.9 [2.5] 0.11 [2.18] n=240	39.8 [2.7] 0.48 [2.22] n=252	40.2 [2.5] 0.25 [1.93] n=218	40.2 [3.2] 0.46 [2.22] n=221
Hemoglobin (g/dL)	13.5 [0.9] 0.01 [0.69] n=241	13.4 [0.9] 0.14 [0.75] n= 252	13.6 [0.9] 0.09 [0.63] n=221	13.6 [1.1] 0.16 [0.72] n=223
Platelet count (x1000/mcL)	263.0 [53.3] -6.5 [26.1] n=235	264.7 [53.2] -6.2 [29.4] n=249	262.0 [55.0] -4.8 [26.7] n= 215	266.3 [58.8] -1.9 [31.5] n= 218

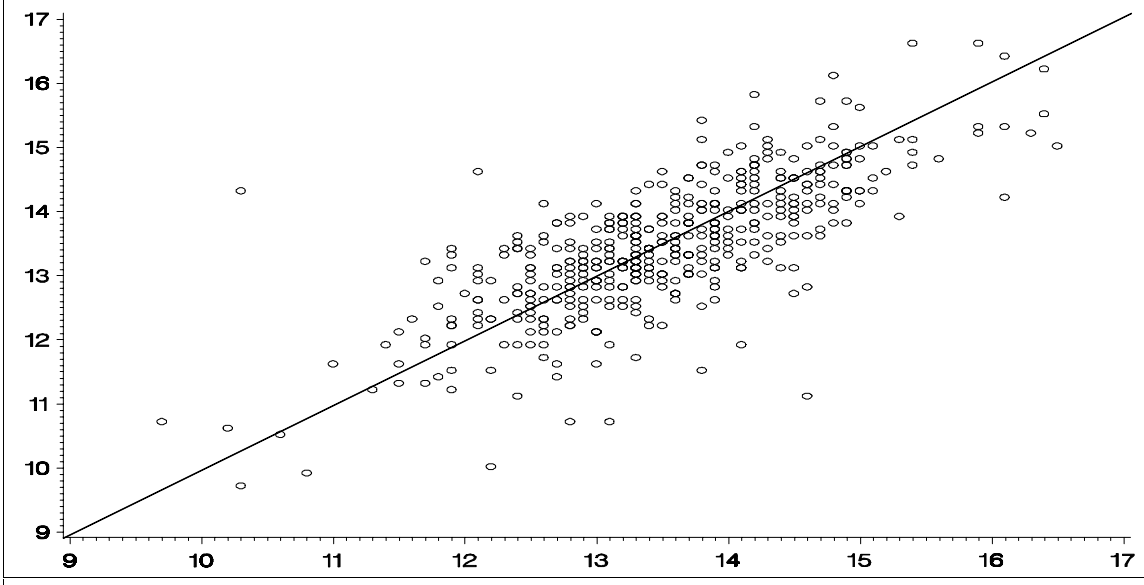
TTS=testosterone transdermal system
Values are means [standard deviation]. N=number of ITT patients. n=number of patients with values.

Figure 44
Change from Baseline in Hemoglobin (g/dL) in SM1 and SM2



Plc = Placebo, TTS = 300 mcg/day testosterone transdermal system; number in brackets is number of patients with a value at that time-point.
(a) Includes exit evaluation if withdrawal was before 24 weeks.
Mean=dot; Median=central line; Box=interquartile range; Extreme value=circle; Lower whisker=10th Percentile; Upper whisker=90th Percentile.

Figure 45
Changes in Hemoglobin (g/dL) at 24 Weeks with Testosterone Treatment.
Studies SM 1 and SM 2 (combined).



Y-axis is value at 24 weeks; X-axis is baseline value.

Few patients had markedly abnormal laboratory values for any of these parameters, and there was no increase in the incidence of such values with testosterone treatment (see Table 33).

3.3.5 Safety in Naturally Menopausal Women

Two studies of the 300 mcg/day testosterone transdermal system have been conducted in naturally menopausal women with HSDD. Safety data from these studies support the favorable safety profile observed in surgically menopausal women with HSDD; no additional safety or tolerability concerns were identified.

The protocols for the studies in naturally menopausal women with HSDD were similar to those of the studies in surgically menopausal women with regard to most endpoints and assessments (Table 38). FDA has requested available safety data from these studies as part of their review of the NDA in surgically menopausal women.

Table 38
Selected Design Characteristics of Studies in Surgically Menopausal Women with HSDD

Study Number	Phase/ Region	Study Design	Concomitant Estrogen Therapy	Testosterone Dose Groups mcg/day (ITT Patients)
Pivotal Phase III Studies				
NM 1 (2002006)	III/ US, Canada, Australia	24-week randomized, DB, PC, efficacy and safety period in NM women	Oral estrogen with continuous progestin	0 (n = 273) 300 (n = 276)
NM 2 (2002005)	III/ US, Canada, Australia	52-week randomized, DB, PC, safety period in NM women. This study is on-going.	Oral estrogen with continuous progestin	0 (n = 117) 300 (n = 241) (another 250 patients are still continuing and are not included in this analysis)

3.3.5.1 Safety in NM 1

The NM 1 Study (Study 2002006) was a multicenter, randomized, 24-week, double-blind, placebo-controlled, parallel-group study conducted in naturally menopausal women with HSDD on concomitant oral continuous estrogen and progestin therapy. This study was virtually identical in study design to that of the first 24 weeks of the SM 1 and SM 2 studies.

In addition to the major inclusion criteria previously described for Studies SM 1 and SM 2, patients had to be 40 to 70 years old with no spontaneous menstrual periods for 1 year (if post-hysterectomy, the patient must have had at least 1 ovary and a screening follicle-stimulating hormone level > 30 IU/L) and had to be receiving a stable dose of oral continuous estrogen and progestin therapy for at least 3 months prior to screening with the intention of maintaining that regimen. Patients who had had a hysterectomy were not permitted to take progestin therapy.

Patients were randomized in a 1:1 ratio to receive placebo or 300 mcg/day testosterone transdermal systems for 24 weeks and had to maintain their stable dose of estrogen and progestin (only estrogen if patients had no uterus) throughout the study.

Safety was evaluated as described for Studies SM 1 and SM 2, except for the addition of assessments of vaginal bleeding. Serum samples were analyzed for determination of free, total, and bioavailable testosterone; SHBG; free and total estradiol; and estrone.

A total of 549 patients were enrolled in the U.S. (46 clinical sites), Canada (8 clinical sites), and Australia (4 clinical sites) and 433 (79%) completed the 24-week study (Table 39).

Table 39
Disposition of Patients
Study NM 1

Parameter	Placebo (N=273) n (%)	TTS (N=276) n (%)
Randomized To Treatment		
Completed	209 (77)	224 (81)
Discontinued	64 (23)	52 (19)
Reason For Discontinuation		
Adverse Event	19 (7)	22 (8)
Protocol Violation	8 (3)	5 (2)
Voluntary Withdrawal	32 (12)	19 (7)
Lost to Follow-up	5 (2)	6 (2)

TTS = 300 mcg/day testosterone transdermal system.

Demographic characteristics of the population were balanced between treatment groups at baseline (Table 40).

Table 40
Baseline Characteristics of Patients
Study NM 1

Parameter	Placebo (N=273)	TTS (N=276)
Age (years)—mean (SD)	54 (4.9)	53.9 (4.8)
Race/Ethnicity—n (%)		
Indian (American)	1 (<1)	1 (<1)
Asian (Oriental)	1 (<1)	0
Black	8 (3)	10 (4)
Caucasian	256 (94)	260 (94)
Hispanic	6 (2)	5 (2)
Indonesian	1 (<1)	0
Baseline Weight (kg)—mean (SD)	69 (12.06)	69.4 (13.68)
Baseline Height (cm)—mean (SD)	163.3 (6.56)	163.8 (5.96)
Baseline Body Mass Index—mean (SD)	25.7 (4.32)	25.8 (4.98)
Relationship Length with Partner (years)—mean (SD)	20.4 (12.4)	20.1 (12.1)
Marital Status—n (%)		
Married to Partner	221 (81)	218 (79)
Not Married to Partner	52 (19)	58 (21)

TTS = 300 mcg/day testosterone transdermal system.

Adverse Events

Treatment with the 300 mcg/day testosterone transdermal system was well tolerated in this study, and no serious safety concerns were identified (Table 41).

Table 41
Summary of Adverse Events (Including Application-site-Reactions)
Study NM 1

Parameter	Placebo N=273 n (%)	TTS N=276 n (%)
Patients		
With Any Adverse Events	199 (72.9)	218 (79.0)
With Serious Adverse Events	4 (1.5)	7 (2.5)
Who Withdrew from Study Due to Adverse Events	19 (7.0)	22 (8.0)
Who Died	0	2 (0.7)*

TTS=testosterone transdermal system
*Both deaths occurred in motor vehicle accidents and were also considered serious adverse events.

The adverse event profile of the 300 mcg/day testosterone transdermal system in naturally menopausal women in Study NM 1 was similar to that observed in the surgically menopausal population.

Few clinically meaningful differences between treatment groups were seen among adverse events that were reported in the testosterone group by $\geq$ 2% of patients and at higher incidence than in the placebo group (Table 42). Most differences between groups were small and not clinically meaningful. More patients reported hirsutism, acne, and migraines in the testosterone group than in the placebo group. Only 1 of the 8 patients in the testosterone group and 0 of the patients in the placebo group withdrew from the study due to migraines. Of patients in the testosterone group reporting migraines, 3 had a history of migraines and 2 had a history of headaches.

Table 42
Adverse Events at ≥ 2% Incidence and Higher in TTS than Placebo
Study NM 1

Adverse Event	Placebo N=273 n (%)	TTS N=276 n (%)
Hirsutism	17 (6.2)	29 (10.5)
Nasopharyngitis	15 (5.5)	18 (6.5)
Acne	9 (3.3)	16 (5.8)
Sinusitis	8 (2.9)	13 (4.7)
Urinary tract infections	11 (4.0)	13 (4.7)
Headache	10 (3.7)	12 (4.3)
Vulvovaginal signs and symptoms	6 (2.2)	9 (3.3)
Influenza	6 (2.2)	8 (2.9)
Migraine headaches	2 (0.7)	8 (2.9)
Pharyngolaryngeal pain	6 (2.2)	8 (2.9)
Cough	2 (0.7)	7 (2.5)
Vaginosis fungal	4 (1.5)	6 (2.2)
Back pain	4 (1.5)	6 (2.2)
Nasal congestion and inflammations	2 (0.7)	6 (2.2)
Hypertension	4 (1.5)	6 (2.2)

Table displays adverse events reported by > 2% of patients in either treatment group in which the incidence for TTS was higher than placebo.
TTS = 300 mcg/day testosterone transdermal system

Consistent with the safety findings in the combined studies in surgically menopausal patients, few serious adverse events were reported in Study NM 1 in naturally menopausal women (Table 43). Four patients (1.5%) in the placebo group and 7 patients (2.5%) in the testosterone group reported serious adverse events. All of the serious adverse events were considered doubtfully related to study drug by the investigators. Three of the 7 patients in the testosterone group and 2 of the 4 patients in the placebo group recovered while remaining on study drug.

Table 43
Listing of Serious Adverse Events
Study NM 1

Treatment Group Patient Number (partially obscured)	Age		Onset Day of AE	Causality	Severity	AE Outcome	Action Taken
Placebo							
18696xxx	51	Colon cancer NOS	115	Doubtful	Severe	Ongoing	Drug Discontinued
65416xxx	49	Cholecystitis NOS	58	Doubtful	Severe	Recovered	No Action Taken
77236xxx	51	Anxiety	137	Doubtful	Severe	Recovered	No Action Taken
77546xxx	55	Non-small cell lung cancer metastatic	97	Doubtful	Severe	Ongoing	Drug Discontinued
TTS							
53166xxx	56	Myocardial infarction	144	Doubtful	Severe	Recovered	Drug Discontinued
66816xxx	55	Adnexa uteri mass	65	Doubtful	Moderate	Recovered	No Action Taken
66946xxx	59	Road traffic accident	102	Doubtful	Severe	Patient Died	Drug Discontinued
67026xxx	68	Malignant melanoma	152	Doubtful	Mild	Ongoing	No Action Taken
76906xxx	49	Road traffic accident	20	Doubtful	Severe	Patient Died	Drug Discontinued
76946xxx	51	Intervertebral disc disorder NOS	169	Doubtful	Moderate	Recovered	No Action Taken
77546xxx	49	Arrhythmia NOS	132	Doubtful	Severe	Recovered	No Action Taken

TTS=testosterone transdermal system; AE=adverse event. . Patient numbers partially obscured for privacy

Withdrawals Due to Adverse Events

There were no apparent differences between naturally menopausal patients (Study NM 1) and surgically menopausal patients in the combined studies with regard to the incidence or type of adverse events associated with withdrawal. The incidence of patient withdrawal due to adverse events was low and similar in both the testosterone (14 patients, 5.1%) and placebo (11 patients, 4.0%) groups during the 6-month study in naturally menopausal women. The adverse events associated with these withdrawals also were similar in both treatment groups. The adverse event most commonly associated with withdrawal was application-site reaction (testosterone, 10 patients, 3.6%; placebo, 8 patients, 2.9%). Overall, few patients withdrew from the study due to androgenic adverse events (1.5% [4/273] in the placebo group; 0 in the testosterone group).

Vaginal Bleeding Reported as Adverse Events

Patients were evaluated at each visit for an increase in frequency or worsening in severity of vaginal bleeding since beginning treatment. The incidence of vaginal bleeding reported as an adverse event (combined reports of metrorrhagia, uterine hemorrhage, and vaginal hemorrhage) was higher in the placebo group (6.6% [18/273]) compared with the testosterone group (2.9% [8/276]).

Androgenic Adverse Events

A higher percentage of patients in the testosterone group experienced androgenic adverse events compared with placebo (Table 44). This difference was a result of increased reporting of acne and hair growth (hirsutism) in the testosterone group. There was no difference between treatment groups in the percentage of patients experiencing alopecia or voice deepening.

Table 44
Summary of Androgenic Adverse Events
Study NM 1

Parameter	Placebo N=273 n (%)	TTS N=276 n (%)
Patients		
With Any Adverse Events	35 (12.8)	51 (18.5)
Acne	11 (4.0)	18 (6.5)
Alopecia	8 (2.9)	4 (1.4)
Hirsutism	17 (6.2)	29 (10.5)
Voice Deepening	7 (2.6)	8 (2.9)
Who Withdrew from Study Due to Adverse Events	4 (1.5)	0
Severity of Adverse Events (as a proportion of total events)		
Mild	46 (97.9)	63 (92.6)
Moderate	1 (2.1)	5 (7.4)
Severe	0	0

TTS=testosterone transdermal system

One patient in the testosterone group reported clitoral enlargement during the study. This patient, a 52 year-old Black woman, reported clitoral enlargement that began 2 months after first TTS application. The study drug was discontinued 5 days later, and the event resolved 20 days after that. The clitoral enlargement was not confirmed by physical examination. According to the investigator, the event was mild and possibly related to study drug. The patient was receiving concomitant oral conjugated estrogen. The patient removed the transdermal system prior to having her hormone levels drawn; therefore, a maximum postbaseline serum free testosterone concentration was not available.

No clinically relevant changes from baseline or between groups were noted for physical examinations during the study. No markedly abnormal findings were seen. No clinically relevant mean changes from baseline or between groups were noted for any vital sign, clinical laboratory parameter, or weight.

3.3.5.2. Safety in Study NM 2—Interim Data

The NM 2 Study is an ongoing Phase III, double-blind, parallel-group, placebo-controlled, multinational, multicenter study that randomized naturally menopausal women with hypoactive sexual desire disorder (HSDD) concurrently taking approved oral continuous estrogen and progestin therapy to either TTS or placebo (2:1 ratio) for 52 weeks. A total of 360 patients either completed 52 weeks of treatment (n = 202) or discontinued from the study as of 27-Apr-2004 (n = 158). Two of these patients did not receive study drug and were excluded from the Interim Safety Analysis Population, resulting in a total of 358 (117 placebo; 241 TTS) patients assessed in this safety summary. An additional 250 patients continue to receive blinded treatment during the first year of the study and are not included in this interim safety analysis.

Demographic and anthropometric characteristics of the treatment groups were balanced at baseline (Table 45).

Table 45 Baseline Characteristics: 52-week Double-blind Period Study NM 2 (Interim Safety Analysis Population)		
	Placebo	TTS
Parameter	(N=117)	(N=241)
Age (years)—mean (SD)	54.9 (5.3)	53.9 (5.2)
Race/Ethnicity—n (%)		
Indian (American)	0	1 (<1)
Asian (Oriental)	0	1 (<1)
Black	5 (4)	4 (2)
Caucasian	106 (91)	227 (94)
Greek	0	1 (<1)
Hispanic	5 (4)	6 (2)
Indian (Asian)	1 (1)	0
Portuguese	0	1 (<1)
Marital Status—n (%)		
Married to Partner	103 (88)	204 (85)
Not Married to Partner	14 (12)	37 (15)
Relationship Length with Partner (years)—mean (SD)	22.8 (12.5)	20.3 (12.6)
TTS=testosterone transdermal system. TTS group contains more patients due to 2:1 randomization scheme.		

The extent of exposure to the investigational transdermal systems was similar between the treatment groups. Fifty-six percent of the interim safety analysis population had approximately 52 weeks of exposure. The remainder of the population discontinued treatment early; 36% of the population had ≤ 24weeks of exposure.

Overall Summary of Adverse Events

The overall incidence of adverse events was similar between the treatment groups (Table 46).

Table 46 Summary of Adverse Events (Including Application-site Reactions): 52-week Double-blind Period NM 2 (Interim Safety Analysis Population)		
	Placebo N=117 n (%)	TTS N=241 n (%)
Patients		
With Any Adverse Events	93 (79.5)	196 (81.3)
With Serious Adverse Events	8 (6.8)	8 (3.3)
Who Withdrew from Study Due to Adverse Events	15 (12.8)	31 (12.9)
Who Died	0	0
TTS=testosterone transdermal system. TTS group contains more patients due to 2:1 randomization scheme.		

Summary of Adverse Events that Occurred at an Incidence of > 2%

Adverse events that occurred at an incidence of ≥ 2% in the TTS group and were reported in a higher percentage of TTS patients than placebo patients are summarized in Table 47.

Table 47
Adverse Events at ≥ 2% Incidence and Higher in TTS than Placebo:
52-week Double-blind Period
Study NM 2
(Interim Safety Analysis Population)

Adverse Event	**Placebo N=117 n (%)**	**TTS N=241 n (%)**
Nasopharyngitis	10 (8.5)	23 (9.5)
Hirsutism	8 (6.8)	19 (7.9)
Alopecias	5 (4.3)	15 (6.2)
Acne	5 (4.3)	14 (5.8)
Sinusitis	6 (5.1)	13 (5.4)
Fungal infections	4 (3.4)	11 (4.6)
Back pain	4 (3.4)	11 (4.6)
Arthralgia	1 (0.9)	9 (3.7)
Cough	1 (0.9)	9 (3.7)
Diarrhoea	2 (1.7)	8 (3.3)
Influenza	2 (1.7)	8 (3.3)
Bronchitis	0	8 (3.3)
Abdominal pain	0 (0.0)	7 (2.9)
Weight increased	1 (0.9)	7 (2.9)
Breast signs and symptoms	3 (2.6)	7 (2.9)
Vulvovaginal signs and symptoms	2 (1.7)	7 (2.9)
Dental and oral soft tissue infections	2 (1.7)	6 (2.5)
Non-site specific injuries	1 (0.9)	6 (2.5)
Hypercholesterolaemia	2 (1.7)	6 (2.5)
Rash	2 (1.7)	6 (2.5)
Intervertebral disc disorders	0	5 (2.1)
Sinus headache	1 (0.9)	5 (2.1)
Hoarseness	2 (1.7)	5 (2.1)
Dermatitis and eczema	2 (1.7)	5 (2.1)

TTS=testosterone transdermal system. TTS group contains more patients due to 2:1 randomization scheme.

Serious Adverse Events

Eight patients (6.8%) in the placebo group and 8 (3.3%) in the testosterone group reported serious adverse events. All but one of the serious adverse events (elevated liver enzymes in one patient) were considered doubtfully related to study drug by the investigators (Table 48). Eleven of the 16 patients recovered while remaining on study drug.

Table 48
Listing of Serious Adverse Events: 52-week Double-blind Period
Study NM 2
(Interim Safety Analysis Population)

Patient No. (partially obscured)	Age		Onset Day of AE	Causality	Severity	AE Outcome	Action Taken
39015xxx	58	Aseptic necrosis bone	382	Doubtful	Severe	Recovered	No Action Taken
39165xxx	62	Colitis ulcerative	18	Doubtful	Mild	Ongoing	No Action Taken
51635xxx	58	Contusion	157	Doubtful	Severe	Recovered	Drug Discontinued
		Joint sprain	157	Doubtful	Severe	Recovered	Drug Discontinued
		Muscle strain	157	Doubtful	Severe	Recovered	Drug Discontinued
51825xxx	51	Acute myocardial infarction	126	Doubtful	Severe	Recovered	Drug Discontinued
		Bundle branch block right	126	Doubtful	Moderate	Recovered	Drug Discontinued
66795xxx	54	Intervertebral disc disorder	74	Doubtful	Moderate	Recovered	No Action Taken
66825xxx	56	Concussion	91	Doubtful	Severe	Recovered	No Action Taken
66905xxx	66	Crohn's disease	339	Doubtful	Severe	Ongoing	No Action Taken
66955xxx	49	Neuralgia	36	Doubtful	Severe	Recovered	Drug Interrupted
66955xxx	54	Complex partial seizures	98	Doubtful	Severe	Ongoing	No Action Taken
76925xxx	61	Bundle branch block right	267	Doubtful	Severe	Recovered	No Action Taken
		Supraventricular tachycardia	267	Doubtful	Severe	Recovered	No Action Taken
77035xxx	62	Syncope	164	Doubtful	Severe	Ongoing	No Action Taken
77085xxx	53	Angina pectoris	93	Doubtful	Severe	Recovered	No Action Taken
77225xxx	61	Alanine aminotransferase increased	175	Possible	Mild	Recovered	Drug Discontinued
77225xxx	56	Asthenia	119	Doubtful	Severe	Recovered	Drug Interrupted
		Heart rate increased	119	Doubtful	Severe	Recovered	Drug Interrupted
		Hyperhidrosis	119	Doubtful	Severe	Recovered	Drug Interrupted
		Nausea	119	Doubtful	Severe	Recovered	Drug Interrupted
77445xxx	58	Myocardial infarction	25	Doubtful	Severe	Recovered	Drug Discontinued
77515xxx	53	Biliary cirrhosis primary	188	Doubtful	Moderate	Ongoing	Drug Discontinued

Treatment group is not identified because the blind is being maintained at the patient level. Patient numbers partially obscured for privacy

The percentage of patients who withdrew from the study due to adverse events was low and similar in both treatment groups (approximately 13% in each group). The most commonly reported adverse event that led to study withdrawal was application site reaction (3.4% [4/117] in the placebo group; 5.4% [13/241] in the testosterone group). Overall, few patients withdrew from the study due to androgenic adverse events (0.9% [1/117] in the placebo group; 2.5% [6/241] in the testosterone group).

A higher percentage of patients in the testosterone group experienced androgenic adverse events compared with placebo (Table 49). One (0.4%) patient in the testosterone group and 1 (0.9%) placebo patient reported clitoral enlargement during the study; both of these events resolved while the patient remained on study treatment.

Table 49
Summary of Androgenic Adverse Events: 52-week Double-blind Period
Study NM 2
(Interim Safety Analysis Population)

	Placebo N=117 n (%)	TTS N=241 n (%)
Patients		
With Any Adverse Events	17 (14.5)	50 (20.7)
Acne	5 (4.3)	17 (7.1)
Alopecia	5 (4.3)	15 (6.2)
Hirsutism	8 (6.8)	19 (7.9)
Voice Deepening	5 (4.3)	7 (2.9)
Who Withdrew from Study Due to Adverse Events	1 (0.9)	6 (2.5)
Severity of Adverse Event (as a proportion of events)		
Mild	20 (83.3)	54 (84.4)
Moderate	4 (16.7)	10 (15.6)
Severe	0	0

TTS=testosterone transdermal system. TTS group contains more patients due to 2:1 randomization scheme.

Endometrial biopsy data are being collected to evaluate the effects of transdermal testosterone on endometrial hyperplasia. Paired biopsy samples (baseline and week 52) have been evaluated for 293 patients. Two cases of hyperplasia (simple hyperplasia without atypia) have been noted. These data remain blinded to treatment. However, this would represent a maximum 1% rate of hyperplasia assuming both cases are due to TTS treatment (randomization 2:1). There is no evidence to suggest that 1 year of exposure of 300 mcg/day of transdermal testosterone contributes to a hyperplastic endometrial response when evaluated by direct histological observation.

There were no clinically relevant changes in any of the measured laboratory parameters (liver and renal function tests, carbohydrate metabolism, lipid profile, hematology) with testosterone treatment.

4. Biopharmaceutics and Clinical Pharmacology

Testosterone is widely distributed in the body. In women, testosterone circulates in blood either bound to sex hormone binding globulin (SHBG, 65-80%), bound to albumin (20-30%), or as the free hormone (0.5-2%), which along with the albumin-bound component constitutes the bioavailable testosterone. The proposed product contains a total of 8.4 mg of testosterone and systemically delivers a nominal dose of 300 mcg/day. The mean serum concentrations of free and total testosterone attained peak concentrations within 24-36 hours after system application and remained in a relatively narrow range (difference between C_{max} and C_{avg} is approximately 30%) over the entire wear period. Once the system was removed, the serum concentrations of testosterone dropped rapidly (within 12 hours) to near baseline values. In efficacy and safety studies, treatment with the 300 mcg/day testosterone transdermal system increased serum free testosterone to within the normal premenopausal range. Increases in serum testosterone concentrations seen at 24 weeks were maintained through 52 weeks of treatment. Treatment with testosterone did not change either serum estradiol or SHBG levels. Among patients receiving testosterone transdermal treatment, patients receiving oral concomitant estrogen had higher SHBG levels and lower free testosterone levels than patients on transdermal concomitant estrogen. Statistically significant correlations were observed between serum free testosterone levels and efficacy measures. No statistically significant relationships between serum free testosterone levels and the risk of androgenic adverse events, except for hirsutism.

4.1 Pharmacology of Testosterone

Whether endogenously produced or exogenously administered, testosterone is widely distributed in the body and subject to the same pharmacokinetic processes. In women, testosterone circulates in blood either bound to sex hormone binding globulin (SHBG, 65-80%), bound to albumin (20-30%) or as the free hormone (0.5-2%), which along with the albumen-bound testosterone component constitutes bioavailable testosterone. The affinity of testosterone binding to SHBG is high, thus it is reported that testosterone bound to SHBG does not provide significant contribution to the pharmacologic activity.

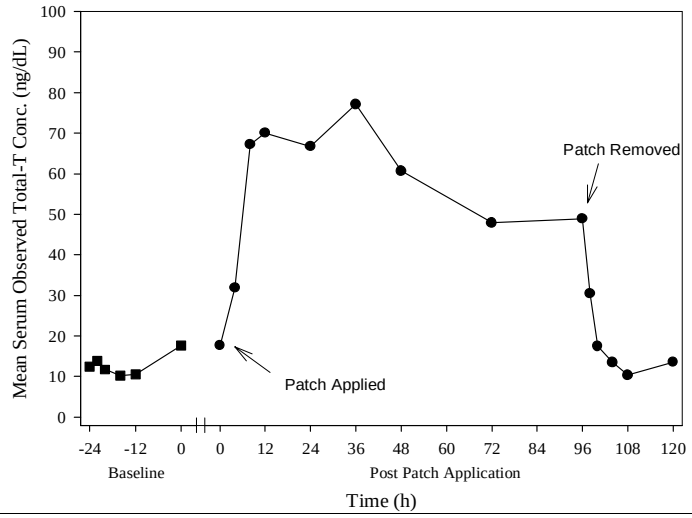
The concentrations of free testosterone are inversely related to serum SHBG concentrations. Because oral estrogen administration results in delivery of a greater amount of estrogen to the liver, subjects taking oral estrogen frequently have a higher SHBG concentration in blood, and a lower free testosterone concentration than subjects using transdermal estrogen. (Mazer & Shifren 2003) Unlike other oral androgenic hormones (e.g., methyltestosterone) that are known to depress the hepatic synthesis of SHBG, the 300 mcg/day testosterone transdermal system does not affect serum SHBG concentrations over 52 weeks of therapy.

Testosterone is extensively metabolized in the body by various enzyme systems, including Cytochrome P450 3A4 (CYP3A4), aromatase, and 5-alpha-reductase. The active metabolites of testosterone are estradiol and DHT. Testosterone is metabolized to DHT by steroid 5-alpha-reductase in many tissues including skin, and to estradiol by aromatase in tissues. Metabolites may be conjugated and excreted in urine or feces.

4.2 Delivery of Testosterone from 300 mcg/day Testosterone Transdermal System

An open label, single-dose study was conducted to evaluate the delivery of testosterone from the transdermal system. Subjects were surgically menopausal women aged 40 to 70 years and in good general health who had been on a stable dose of oral estrogen therapy for at least 3 months prior to screening. The subjects had a mean age of 53.1 (range: 40 to 69) years. The duration of exposure to testosterone was 4 days for each subject. The mean total testosterone serum concentration-time profile is shown in Figure 46.

Figure 46
Mean Total Testosterone Serum Concentrations over Time
(2003003)



The mean serum concentrations of free and total testosterone attained peak concentrations within 24-36 hours after system application. The concentrations remained in a relatively narrow range (difference between C_{max} and C_{avg} is approximately 30%) over the entire wear period. Once the system was removed, the serum concentrations of testosterone dropped rapidly (within 12 hours) to near baseline values since testosterone has a relatively short elimination half-life (approximately 2 hours). These results support no skin depot formation from the transdermal systems.

The amount of drug delivered via transdermal systems can be estimated by relating the systemic exposure to the dose using clearance principles or by using the depletion method. Of the two methodologies, the dose estimated from systemic exposure would provide a more relevant association to the clinical action. Systemic exposure has been shown to correlate with clinical efficacy and is the basis for bioequivalence assessments. This methodology is applicable to all forms of transdermal delivery (gels, sprays, buccal formulations, transdermal system) and allows direct comparison of clinically meaningful exposure levels. Dose calculations based on systemic exposure are independent of various formulation differences across different transdermal system technologies. The mean dose delivered from the 300 mcg/day testosterone transdermal system based on systemic exposure was 289 mcg/day (95% confidence interval 249 to 329 mcg/day); therefore, the proposed labeled dose for the 28-cm^2 TTS is 300 mcg/day.

The bioavailability of transdermal systems can be affected by the application site on the body because of differences in skin thickness, regional blood flow, and in the distribution of adipose tissue under the skin at different sites of the body. The results of a bioavailability study using a 14-cm^2 testosterone transdermal system indicated a reduction (12-20%) in serum testosterone concentrations for application on the buttocks compared to abdominal application. Based on this observation, all subsequent studies utilized application on the abdomen and the package insert specifies the abdomen as the application site.

4.3 Hormone Data from Safety and Efficacy Studies

Reference Ranges

The testosterone transdermal system is intended to provide testosterone therapy for women with HSDD, achieving testosterone concentrations compatible with a woman's physiology. In that respect, a reference range of testosterone serum concentrations in women with functional ovaries provides a useful context for comparison of the testosterone concentrations in surgically menopausal women with HSDD who have been treated with the testosterone transdermal system.

Because previous reference ranges were based upon relatively small numbers of women, additional bioanalytical work was undertaken to define appropriate reference ranges for serum hormones in women. The population used to define the reference ranges of androgens consisted of 161 premenopausal women from 18 to 49 years of age with functional ovaries. This was considered the appropriate group to define the reference ranges for the following reasons:

1. Unlike naturally and surgically menopausal women, premenopausal women have functional ovaries and regular menstrual cycles. This would account for androgens from all intrinsic sources (ovarian and adrenal).
2. The age range of 18 to 49 years describes the typical age distribution for normally cycling women. Since it is known that androgens decline with age, generating reference ranges from this entire age group would be representative of the normal cycling population.
3. Testosterone production in premenopausal women is approximately 100 to 400 mcg/day. Therefore the serum testosterone concentration range in the premenopausal population provides a useful comparison for serum testosterone concentrations produced by systemic delivery of 300 mcg/day of testosterone using the transdermal system.

This study provided the reference ranges that are used on serum hormone concentration plots in this section.

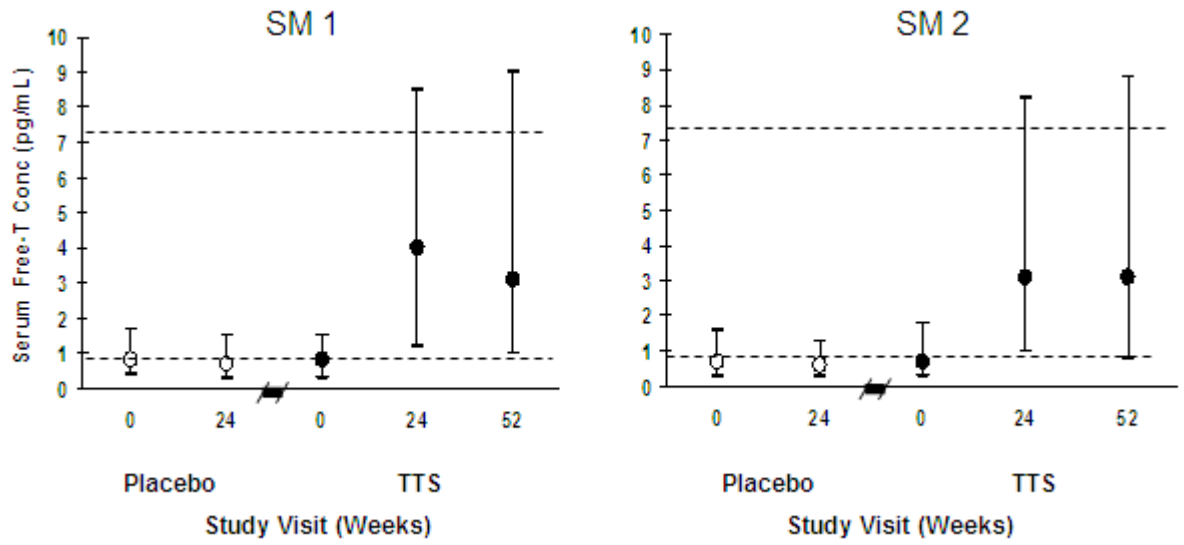
Serum Hormone Concentrations in Phase III Studies

The serum levels of hormones were measured at baseline and after 24 and 52 weeks of treatment in the Phase III studies (Studies SM 1 and SM 2). Baseline serum free testosterone concentrations were low for all patients.

These studies showed that treatment with the 300 mcg/day testosterone transdermal system increased median serum free testosterone levels from baseline values to within the premenopausal reference range (Figure 47). Bioavailable testosterone (Figure 48) and total testosterone (Figure 49) levels were also increased. Changes in free, bioavailable, and total testosterone seen at 24

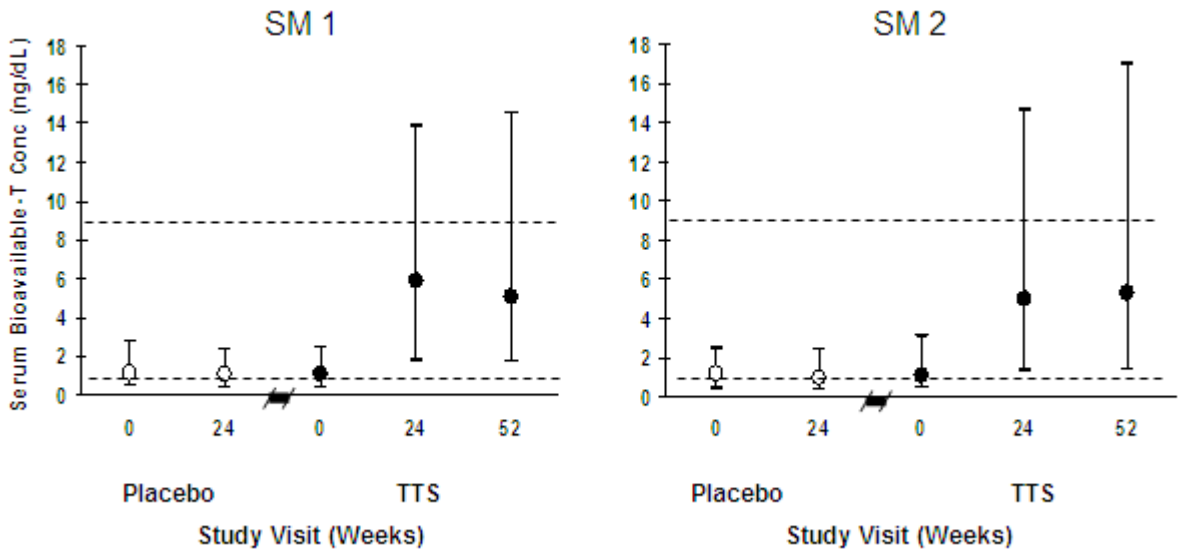
weeks were maintained through 52 weeks of treatment, indicating no continued accumulation of hormones over this period. Serum estradiol (Figure 50) and estrone (Figure 51) levels did not change with testosterone treatment. SHBG levels were influenced by route of estrogen administration (Figures 52 and 53) but were not influenced by testosterone dosing. Among patients receiving testosterone transdermal treatment, patients on oral concomitant estrogen had higher SHBG levels and lower free testosterone levels than patients on transdermal concomitant estrogen (Figure 53).

Figure 47
Serum free testosterone in the Phase III studies, by timepoint.



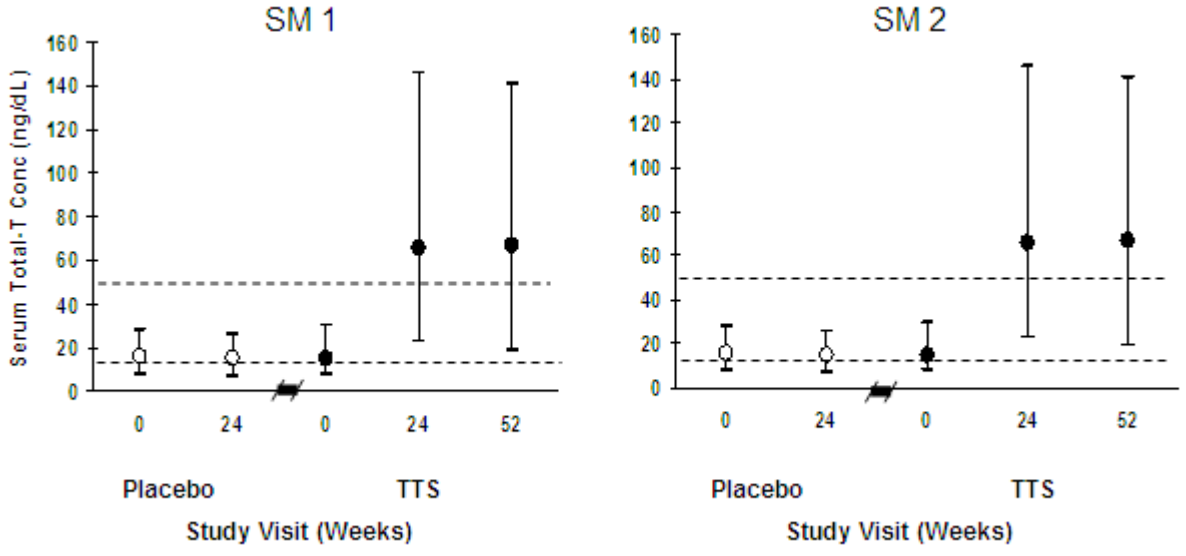
TTS=testosterone transdermal system. Whiskers represent the 10th and 90th percentile; dots represent the median. Dashed lines indicate the reference range for premenopausal women.

Figure 48
Serum bioavailable testosterone in the Phase III studies, by timepoint.



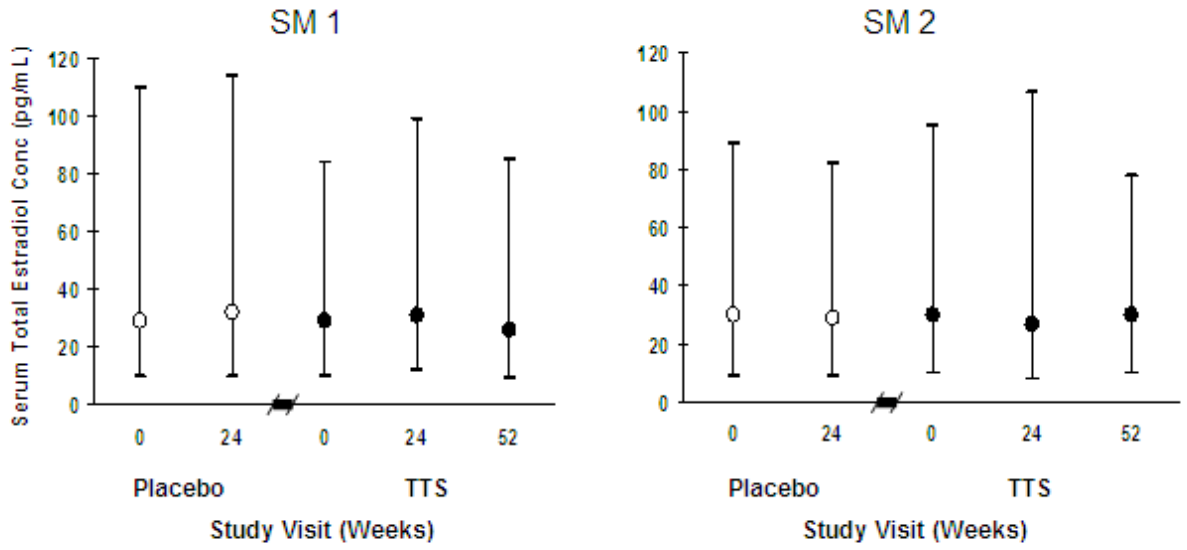
TTS=testosterone transdermal system. Whiskers represent the 10th and 90th percentile; dots represent the median. Dashed lines indicate the reference range for premenopausal women.

Figure 49
Serum total testosterone in the Phase III studies, by timepoint.



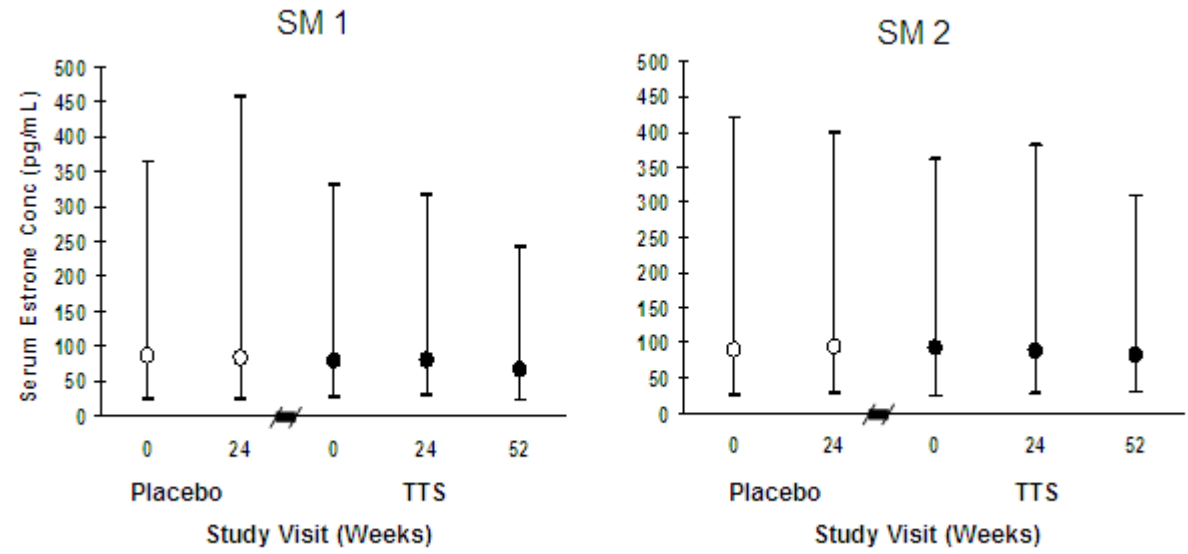
TTS=testosterone transdermal system. Whiskers represent the 10th and 90th percentile; dots represent the median. Dashed lines indicate the reference range for premenopausal women.

Figure 50
Serum total estradiol in the Phase III studies, by time point.



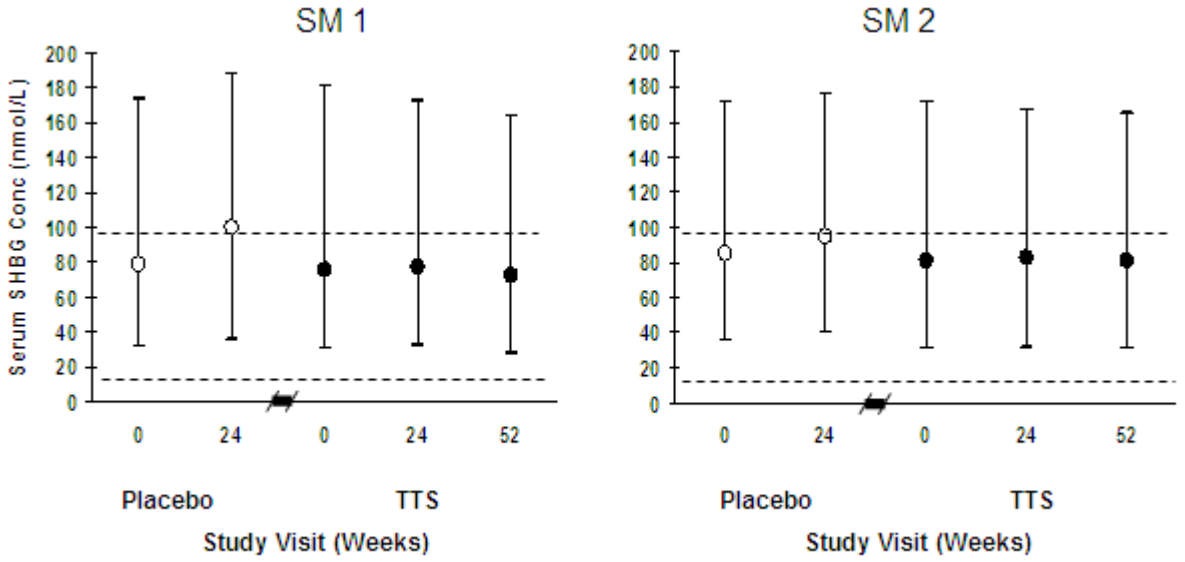
TTS=testosterone transdermal system. Whiskers represent the 10th and 90th percentile; dots represent the median.

Figure 51
Serum estrone in the Phase III studies, by time point.



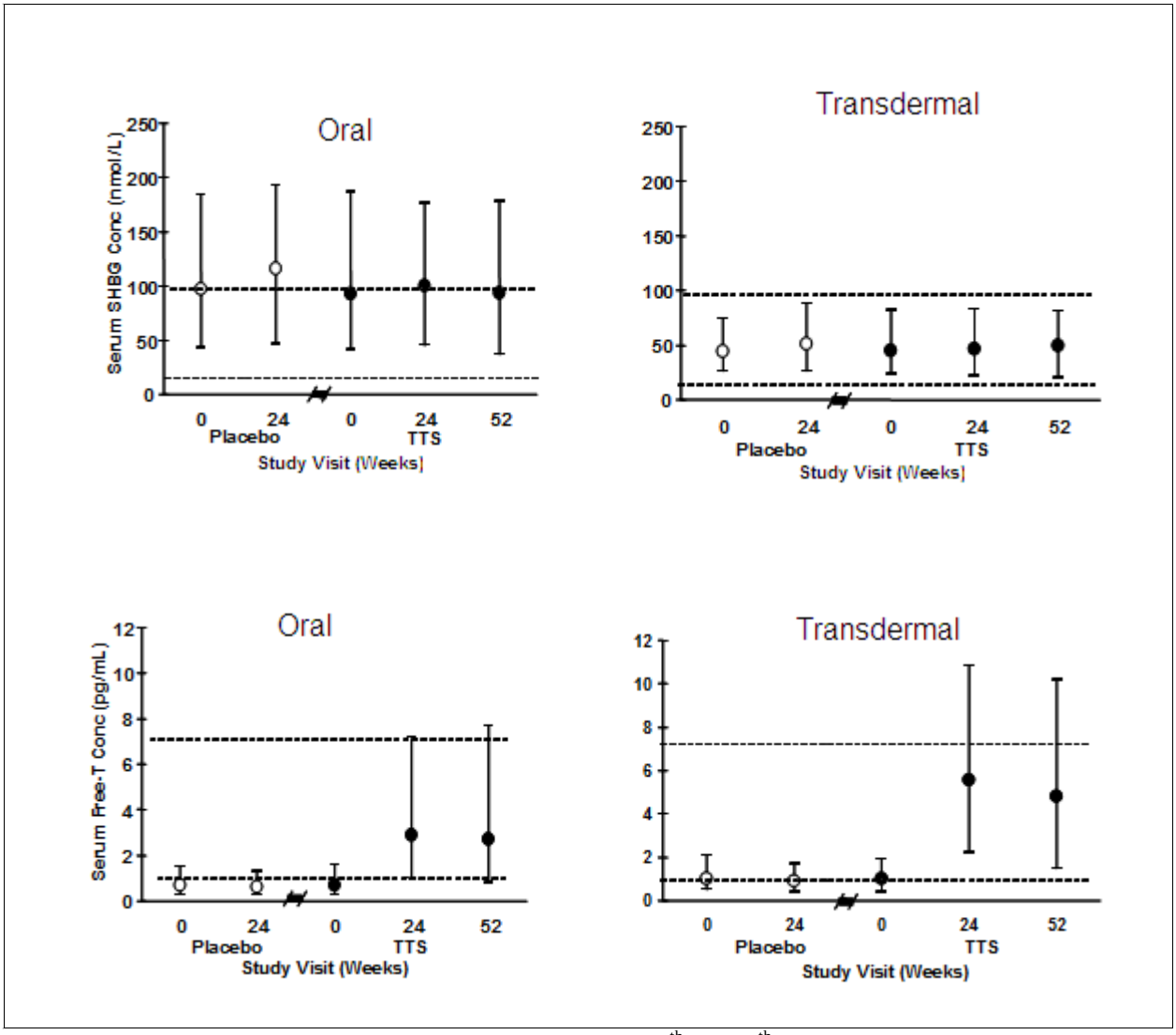
Testosterone transdermal system. Whiskers represent the 10th and 90th percentile; dots represent the median.

Figure 52
Serum SHBG in the Phase III studies, by timepoint.



TTS=testosterone transdermal system. Whiskers represent the 10th and 90th percentile; dots represent the median. Dashed lines indicate the reference range for premenopausal women.

Figure 53
Free testosterone and SHBG levels by treatment group and route of concomitant estrogen administration. Phase III Studies



TTP=testosterone transdermal patch. Whiskers represent the 10th and 90th percentile; dots represent the median. Dashed lines indicate the reference range for premenopausal women.

At the time of the safety update, hormone data were available from 92 patients (out of 96 patients expected to have hormone data when ongoing analyses are completed) who met the pharmacokinetic evaluability criteria and had approximately 78 weeks of exposure to TTS. The median concentrations of free and bioavailable testosterone and total DHT did not demonstrate significant changes over time ($p > 0.05$). The median concentrations of total testosterone demonstrated changes of borderline statistical significance over time ($p = 0.051$). Serum SHBG concentrations exhibited significant changes (reductions) over time but the changes in median concentrations between Week 52 and Week 78 were within 10% (Table 50).

Table 50
Serum Hormone Concentrations for Patients Receiving TTS by Total Exposure
Combined Studies SM 1 and SM 2
(PK Evaluable Patients)

	Baseline	12 Weeks	24 Weeks	52 Weeks	78 Weeks
Free testosterone (pg/ml)					
n	951	209	708	385	91
Median	0.70	4.00	3.30	3.50	4.60
Min	0.0	0.3	0.1	0.3	0.5
Max	18.7	61.8	107.7	63.1	25.1
P-value*					0.3626
Bioavailable testosterone (ng/dl)					
n	942	208	701	385	91
Median	1.070	5.875	5.280	5.680	6.570
Min	0.09	0.45	0.30	0.51	0.73
Max	38.08	104.70	204.77	129.05	52.04
P-value*					0.1128
SHBG (nmol/l)					
n	956	212	713	388	92
Median	85.5	81.0	81.0	74.0	68.5
Min	7	8	7	9	10
Max	416	295	446	478	305
P-value*					<0.0001

Data summarized in this table are for the subset of patients who had blood samples collected within 5 days of applying the last patch before scheduled study visit at timepoint.
SHBG = sex hormone binding globulin; TTS = 300 mcg/day testosterone transdermal system.
* Test of no effect over time in the log-transformed hormone concentration values across post-baseline visits for free testosterone and bioavailable testosterone, and across all visits for SHBG using repeated measures analysis of variance (ANOVA) model adjusted by study and time.

Hormone levels in the Phase III trials indicate that the 300 mcg/day testosterone transdermal system increased median serum free testosterone to within the normal range for premenopausal women, with no evidence of accumulation.

4.4 Relationships between Changes in Testosterone Levels and Efficacy

Analysis of the relationships between changes from baseline in serum free, bioavailable, and total testosterone concentrations and improvements in efficacy endpoints in the clinical studies demonstrated modest but statistically significant correlations between these parameters (Table 51). Studies were combined for analysis of hormone/endpoint relationships.

Table 51
Correlation of Change from Baseline and Hormone Levels at Week 24

Study Grouping	Endpoint	Total T	Free T	Bio T
Phase II Pooled	Total # of Satisfying	0.14	0.21 *	0.21 *
	Sexual Desire	0.25 *	0.28 *	0.22 *
	Personal Distress Scale (PDS)	-0.24 *	-0.25 *	-0.18
Phase III SM Pooled	Total # of Satisfying	0.16 *	0.17 *	0.17 *
	Sexual Desire	0.23 *	0.22 *	0.20 *
	Personal Distress Scale (PDS)	-0.18 *	-0.16 *	-0.17 *
NM - 1	Total # of Satisfying	0.23 *	0.21 *	0.18 *
	Sexual Desire	0.18 *	0.19 *	0.17 *
	Personal Distress Scale (PDS)	-0.16 *	-0.15 *	-0.16 *

Data summarized in this table are for the subset of patients who had blood samples collected within 5 days of applying the last
patch before the scheduled study visit and who met the evaluability criteria established for primary efficacy endpoint analysis.
Data shown are spearman correlation coefficients.
T = testosterone; Bio = bioavailable;
* Spearman correlation is statistically significant ($p < 0.05$).

4.5 Relationships between Changes in Testosterone Levels and Safety Endpoints

Androgenic adverse events that occurred during the Phase IIb and Phase III studies (combined) were further investigated by evaluating serum hormone levels (free testosterone, total testosterone and total DHT), in patients with these effects. There was no evidence of a relationship between the probability of having an androgenic adverse event (acne, hirsutism, alopecia, voice deepening, each considered separately) and the serum hormone level (free testosterone, total testosterone, or total DHT), with one exception. There was a statistically significant association between the probability of having hirsutism and the maximum serum free testosterone level (p=0.014) (Table 52). A statistically significant association was also observed between the changes in objective assessments of facial hair and free testosterone level. Hirsutism was more likely to occur with increasing maximum free testosterone level. (Maximum serum free testosterone refers to the highest value obtained for each patient while on treatment.) Although there was an association, a threshold maximum free testosterone level that acceptably predicted hirsutism could not be identified by statistical analysis. These analyses did not demonstrate a statistically significant association between either acne, alopecia, or voice deepening with free testosterone level.

Table 52
Incidence of Androgenic Adverse Events by Treatment Group and Quartiles (TTS Group) for Maximum Free T (pg/ml)
24-week Double-blind Period
Combined Studies (1999068, 1999092, SM 1, and SM 2)

		TTS (N=696)							
Patients	Placebo (N=703) n (%)	MaxFreeT Missing (N=118) n (%)	MaxFreeT <=2.6 (N=148) n (%)	MaxFreeT >2.6&<=4.2 (N=145) n (%)	MaxFreeT >4.2&<=6.8 (N=143) n (%)	MaxFreeT > 6.8 (N=142) n (%)	TTS (N=696) n (%)	p-value	C-Statistic
Acne	49 (7%)	9 (7.6%)	11 (7.4%)	8 (5.5%)	19 (13.3%)	16 (11.3%)	63 (9.1%)	0.1819	0.560
Alopecia	19 (2.7%)	5 (4.2%)	6 (4.1%)	6 (4.1%)	2 (1.4%)	5 (3.5%)	24 (3.4%)	0.2239	0.567
Hirsutism	35 (5%)	6 (5.1%)	5 (3.4%)	9 (6.2%)	15 (10.5%)	14 (9.9%)	49 (7%)	0.0142	0.612
Voice Deepening	12 (1.7%)	3 (2.5%)	2 (1.4%)	4 (2.8%)	3 (2.1%)	4 (2.8%)	16 (2.3%)	0.9472	0.511

Double-blind includes all combined studies (1999068, 1999092, SM 1, and SM 2) during Weeks 0-24.
TTS = 300 mcg/day testosterone transdermal system. MaxFreeT refers to the highest value of serum free testosterone obtained for each patient while on treatment.
Quartiles based on values for patients treated with TTS only.
p-value from the logistic regression to test the null hypothesis of no relationship between the probability of having an AE and the maximum hormone value.
C-statistic estimates the ability of maximum Free T to discriminate patients who had an AE from those who did not. A value of 0.5 indicates no discriminating ability. A value of $\geq$0.7 indicates acceptable discriminating ability.

The relationship between free testosterone level and androgenic adverse events was further evaluated by comparing the incidence of androgenic adverse events in patients with maximum serum free testosterone in the lowest 10^{th} percentile, the 10^{th} to 90^{th} percentile, or >the 90^{th} percentile. This analysis showed that the incidence of androgenic adverse events was not consistently higher in patients with the highest testosterone values compared with patients with lower levels (Table 53).

Table 53.
Incidence of Androgenic Adverse Events by Treatment Group and Percentiles for Maximum Free T (pg/ml)
24-week Double-blind Period
Combined Studies (1999068, 1999092, SM 1, and SM 2)

		TTS (N=696)				
		MaxFreeT	MaxFreeT	MaxFreeT	MaxFreeT	
		Missing	≤1.6	1.6 to 10.2	≥10.2	
	Placebo		(≤ 10th percentile)	(10-90th percentile)	(≥90th percentile)	
	(N=703)	(N=118)	(N=57)	(N=463)	(N=58)	TTS
Patients	n (%)	n (%)	n (%)	n (%)	n (%)	(N=696)
Acne	49 (7)	9 (7.6)	5 (8.8)	43 (9.3)	6 (10.3)	63 (9.1)
Alopecia	19 (2.7)	5 (4.2)	4 (7.0)	13 (2.8)	2 (3.5)	24 (3.4)
Hirsutism	35 (5)	6 (5.1)	3 (5.3)	37 (8.0)	3 (5.2)	49 (7)
Voice Deepening	12 (1.7)	3 (2.5)	1 (1.8)	12 (2.6)	0	16 (2.3)

TTS = 300 mcg/day testosterone transdermal system. . MaxFreeT refers to the highest value of serum free testosterone obtained for each patient while on treatment.
Quartiles based on values for patients treated with TTS only.

When changes from baseline in selected laboratory parameters (liver function tests, coagulation parameters, measurements of carbohydrate metabolism, hematology, lipids) in the 24-week double-blind period of the combined Phase IIb and Phase III studies (Studies 1999068, 1999092, SM 1, and SM 2) were examined for each treatment group using non-parametric analysis of covariance after adjustment for baseline, statistically significant differences between placebo and TTS were observed for only five parameters: prothrombin time (sec), total bilirubin (mg/dL), hematocrit (%), hemoglobin (g/dL), LDL-cholesterol (mg/dL). These parameters were further examined by looking at the changes from baseline in groups of testosterone-treated patients with maximum free testosterone levels in the lowest 10^{th} percentile, 10^{th} to 90^{th} percentile, and $\geq 90^{th}$ percentile (Table 54). This analysis showed that the mean change from baseline was not consistently higher in patients with the highest free testosterone values compared with patients with lower levels.

Table 54
Laboratory Parameters by Treatment Group and Percentiles for Maximum Free T (pg/ml)
24-week Double-blind Period
Combined Studies (1999068, 1999092, SM 1, and SM 2)*

		TTS (N=696)				
	Placebo (N=703)	MaxFreeT Missing (N=118)	MaxFreeT ≤1.6 (≤ 10th percentile) (N=57)	MaxFreeT 1.6 to 10.2 (10-90th percentile) (N=463)	MaxFreeT ≥10.2 (≥90th percentile) (N=58)	TTS (N=696)
Prothrombin time (sec) *	10.85 [-0.24] n=242	10.84 [-0.21] n=36	10.92 [-0.21] n=31	10.81 [-0.08] n=173	10.71 [-0.16] n=14	10.82 [-0.12] n=254
Bilirubin (mg/dL)	0.46 [-0.01] n=613	0.42 [-0.01] n=60	0.43 [0.05] n=53	0.46 [0.00] n=450	0.46 [0.05] n=56	0.46 [0.01] n=619
Hematocrit (%)	39.93 [0.13] n=587	39.99 [0.53] n=57	39.58 [0.63] n=52	39.94 [0.36] n=434	40.74 [0.67] n=55	39.99 [0.43] n=598
Hemoglobin (g/dL)	13.47 [0.02] n=591	13.38 [0.24] n=58	13.32 [0.21] n=52	13.46 [0.10] n=435	13.71 [0.26] n=55	13.46 [0.14] n=600
LDL cholesterol (mg/dL)	121.4 [-2.0] n=612	122.8 [1.5] n=60	128.7 [-4.0] n=53	122.6 [0.2] n=447	127.4 [-2.2] n=56	123.6 [-0.2] n=616

Values are means at baseline [mean change from baseline at 24 weeks].
.MaxFreeT refers to the highest value of serum free testosterone obtained for each patient while on treatment.
* Prothrombin time (sec) was based on the SM1 study only since the reference ranges were different in 1999068 and 1999092 (SM1 reference range [10-13] and Phase IIb reference range [9-11.5]). Note that it was not collected in SM2.
Values are means at baseline [mean change from baseline at 24 weeks/exit]. N=number of ITT patients. n=number of patients with laboratory values.

4.6 Population Pharmacokinetics

Population pharmacokinetic analysis was performed using serum total, free, and bioavailable testosterone concentrations collected in two Phase III studies, SM 1 and SM 2. A total of 549 patients received active drug in these studies and were eligible for this analysis. Blood samples were collected at Week -4 (baseline Visit 2) and during Weeks 24 and 52 in Study SM 1. An additional sample was collected at Week 12 in Study SM 2. Linear mixed-effect regression analysis was performed to explore relationships between serum free, total, bioavailable testosterone and various patient specific factors (covariates) listed below using Procedure Mixed within SAS software This included an analysis of the effect of enzyme inducers and/or inhibitors of CYP3A4 on serum free, total, and bioavailable testosterone concentrations. This enzyme system was selected because it is associated with the major pathways of testosterone metabolism.

Patients with HSDD who were enrolled in the Phase III studies were in otherwise good general health with few, if any, co-morbidities. Consequently, based on the known properties of testosterone, the theoretical potential for co-morbid conditions to impact testosterone concentrations was considered. Most of the focus has been on functional status of organs of elimination when considering potential disease impact on testosterone transdermal therapy. Testosterone is eliminated primarily through metabolic processes with only limited elimination as intact hormone in urine. Therefore, significant renal impairment is not expected to have a major impact on testosterone concentration in patients receiving testosterone. The liver is the major site of metabolism of testosterone. It is theoretically possible for clearance of testosterone to be reduced in patients with severe hepatic impairment. In addition, in patients with conditions associated with significant edema and increased interstitial fluid, or significant decrease in blood flow to skin (e.g., congestive heart failure), application of the testosterone transdermal system may lead to testosterone accumulation in tissues, increased variability of absorption, and decreased clearance.

The categorical covariates analyzed in the integrated analysis of the SM 1 and SM 2 studies include ethnic origin, smoking status, alcohol use, and concomitant medication. The continuous covariates analyzed in integrated analysis included age, body weight, renal function and SHBG concentration. Table 55 summarizes the population PK analysis covariates and results.

Table 55
Subpopulation Analyses
PK Data from Studies SM 1 and SM 2

Name of Covariates		Analysis Specification	Results
Studies	Two pivotal Phase 3 studies	Studies SM 1 and SM 2	Testosterone concentrations were consistent between the two pivotal Phase 3 studies.
Demographic Parameters	Age	Age range 28 to 70 years	Serum total, free, and bioavailable testosterone concentrations were not affected by age.
	Body Weight	Body wt range of 44 to 154 kg	A significant relationship was observed between total testosterone concentrations and body weight. As body weight increases, total testosterone concentration decreases. With a 3-fold increase in body weight, a 25% decrease in total testosterone is observed. However, there is no significant relationship between body weight and free testosterone.
	Ethnic Origin (Race)	Caucasian, African American, Hispanic, Indian (American), Asian (Oriental), and Other	Serum total, free, and bioavailable testosterone concentrations were not affected by ethnic origin.
	Alcohol Use	Tested as 2 groups (Alcohol user or non-user)	Serum total, free, and bioavailable testosterone concentrations were not affected by alcohol use.
	Smoking Status	Tested as 2 groups (Smoker or Non Smoker)	Serum total, free, and bioavailable testosterone concentrations were not affected by smoking status.
Concomitant Medication	Estrogen therapy	Tested as 3 groups (Oral Estrogen, Premarin Only, and Transdermal Estrogen)	Patients receiving transdermal estrogen therapy had higher (27%) free testosterone concentrations than those that took Premarin.

Table 55
Subpopulation Analyses
PK Data from Studies SM 1 and SM 2

Name of Covariates		Analysis Specification	Results
Concomitant medications (cont)	CYP Inducers and Inhibitors	Tested as patients taking inhibitors of CYP3A4, and inducers of enzymes versus the group that did not take these concomitant drugs	Although the available data are limited, serum total, free, and bioavailable testosterone concentrations did not appear to be altered when administered with inhibitors of CYP3A4. Due to the paucity of patients receiving CYP3A4 inducers (n = 3), the effect of CYP3A4 inducers on the pharmacokinetics of testosterone can not be evaluated in this study population.
Special Population	Renal Function	Tested using estimated creatinine clearance (using Cockroft - Gault equation) 49 to 277 mL/min	Serum total, free, and bioavailable testosterone concentrations were not affected by renal function
	Hepatic Function		Not tested because it was not possible to classify the patients into different groups based on the variables collected
SHBG Concentration			An inverse relationship between free and bioavailable testosterone concentrations with SHBG concentrations was observed due to the high extent of binding to this plasma protein and high extraction ratio.
Duration of Treatment		Week 12, Week 24, and Week 52	On average, testosterone concentrations tended to decrease only slightly over the course of the study. Decreases ranged from 15% to 25% depending on the analyte. There was no evidence of continuous accumulation of hormone concentrations.

In summary, results of this population pharmacokinetic analysis demonstrated that serum total, free, and bioavailable testosterone concentrations were not affected by alcohol use, smoking status, age, renal function, or race. Testosterone concentrations did not appear to be altered when administered with inhibitors of CYP3A4. A significant relationship was observed between total testosterone concentrations and body weight. There was no correlation, however, between free testosterone and body weight. Additionally, patients receiving transdermal estrogen therapy had higher (27%) free testosterone concentrations than those that took Premarin.

5. Conclusions and Risk/Benefit Analysis

HSDD is a recognized medical condition that causes impairment of sexual function and personal distress in women (American Psychiatric Association, 2000). Estimates suggest that 17% to 30% of the 10 million surgically menopausal women in the US may have the condition. Surgically menopausal women may be predisposed to develop this condition because of the loss of ovarian testosterone production following oophorectomy (Bachman et al., 2002). This condition causes substantial suffering for many women (Leiblum et al., 2003; Graziottin and Koochaki, 2003). Sexual dysfunction also substantially impairs partner relationships (Sarrel & Whitehead, 1985).

No medically accepted pharmacologic therapy is currently available for HSDD and, as a result, there is widespread use by women of testosterone products intended for men and contraindicated in women. This practice puts thousands of women at risk of because products approved for treatment of hypogonadism in men provide 10 to 20 times the doses appropriate treatment of HSDD in women.

Clinical trials demonstrate that the 300 mcg/day testosterone transdermal system is effective in treatment of HSDD in surgically menopausal women, as demonstrated by increases in frequency of satisfying sexual activity and in sexual desire, with a corresponding decrease in personal distress. The decrease in distress seen with 300 mcg/day testosterone transdermal system treatment is particularly important, as distress is one of the defining symptoms of the condition, and the relief of this distress is evidence that the benefits of treatment are clinically meaningful. The magnitude of the treatment benefits was also clinically meaningful, as established by a clinical relevance study that used anchoring methodology to define the minimum changes in endpoints that were meaningful to patients. Benefits of treatment were observed consistently across a number of efficacy measurements that address the broad spectrum of women's sexual function and feelings (activity, desire, distress, arousal, pleasure, orgasm, sexual self-image, responsiveness, and sexual concerns) and across various subpopulations. This consistent response across a variety of endpoints demonstrates that treatment with the 300 mcg/day testosterone transdermal system has beneficial effects on a broad spectrum of aspects of female sexuality that may be impaired in women with HSDD.

The safety and tolerability data from the Phase III studies for exposures for up to 52 to 78 weeks indicate that the product can be used in this population for this duration with a low risk of serious adverse effects. The most common adverse effects that were associated with treatment, acne, unwanted hair growth, and application site reactions, were mostly mild and did not cause discontinuation in most cases. These events are easily evaluated by both the patient and physician, and may be considered tolerability or cosmetic issues as opposed to medical risks. No irreversible, severe androgenic adverse events were seen in the trials.

The use of a transdermal delivery system for testosterone in this population provides distinct advantages. Transdermal delivery avoids first-pass hepatic metabolism, which may make transdermal testosterone less likely to produce adverse effects. In addition, serum testosterone levels will drop within hours of removal of the system, allowing easy control of patient exposure to testosterone in the event of an adverse reaction. Previous testosterone products tested in women, such as implants, have typically delivered much higher doses of testosterone than the dose delivered by the 300 mcg/day testosterone transdermal system. In the Phase III clinical

trials, long-term dosing of the 300 mcg/day transdermal system resulted in a median serum free testosterone level that was within the free testosterone reference range established in premenopausal women. No increase in estradiol levels or changes in adrenal hormones were noted during the clinical trials, which provides further reassurance concerning the safety of the product.

The population in the safety and efficacy trials was menopausal women on systemic concomitant estrogen or estrogen/progestin therapy for at least 6 months before beginning testosterone treatment. The product has not been tested in menopausal women who are not also receiving estrogen therapy. At the time that these studies were initiated, estrogen therapy was commonly used in postmenopausal women. Results of the Women's Health Initiative have led to a reassessment of the risks and benefits of estrogen (WHI Steering Committee, 2004). Although the use of this product in women not receiving systemic estrogen has not yet been evaluated, the sponsor is currently conducting such a study.

Overall, the risks associated with this dose for durations up to 52 to 78 weeks were low and acceptable to patients and the benefits are clinically meaningful for surgically menopausal patients with HSDD on concomitant estrogen. Because of the uncertainties associated with longer-term hormonal treatment, treatment with the testosterone transdermal system should be for a duration consistent with treatment goals and risks for the individual woman. Before beginning treatment, the physician should assess other possible causes of sexual dysfunction (e.g., relationship difficulties, other medical problems, medication side effects); these factors should also be considered and addressed when developing a treatment plan. The risk/benefit ratio indicates that a trial of 300 mcg/day testosterone transdermal system would be appropriate for surgically menopausal women with HSDD. Failure to respond should prompt reassessment, including review of the form of concomitant estrogen therapy. Women on oral estrogens have SHBG levels that vary more widely and are higher on average than women receiving transdermal estrogen. Because of the effects of SHBG on free testosterone levels, a change in route of administration of the concomitant estrogen from oral to transdermal may improve the response to treatment.

In order to maximize safe use of the product, the sponsor is obtaining expert input to develop materials to educate health care professionals on the HSDD condition, how to identify women with HSDD, and how to ensure appropriate use of the product. In addition, the sponsor has developed a Patient Information Leaflet (PIL) that has been tested quantitatively with patients to ensure that it effectively communicates the desired information. Copies of the PI and PIL, as well as a description of the proposed plan to ensure proper use, can be found as attachments to this document. In order to further understand the safety of long-term use, the sponsor is monitoring safety in pivotal trial patients who have elected to continue testosterone treatment for an additional 1 to 2 years. After approval, the sponsor will submit all spontaneous adverse events reports to the FDA. In addition, the sponsor proposes to complement these signal detection methods with a postmarketing pharmacoepidemiologic study that will use a large claims database to assess the incidence and risk of potential adverse health outcomes of interest. Further information about the plan to maximize safe use can be found in an attachment to this briefing document.

In summary, these clinical trials demonstrate that the 300 mcg/day testosterone transdermal system is effective and has a favorable safety profile when used for the treatment of HSDD in surgically menopausal women on concomitant estrogen therapy.

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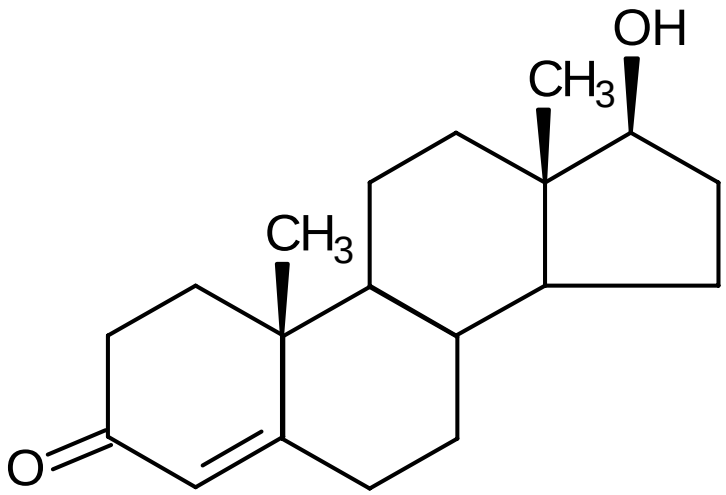
INTRINSA™ (TESTOSTERONE TRANSDERMAL PATCH)

CIII

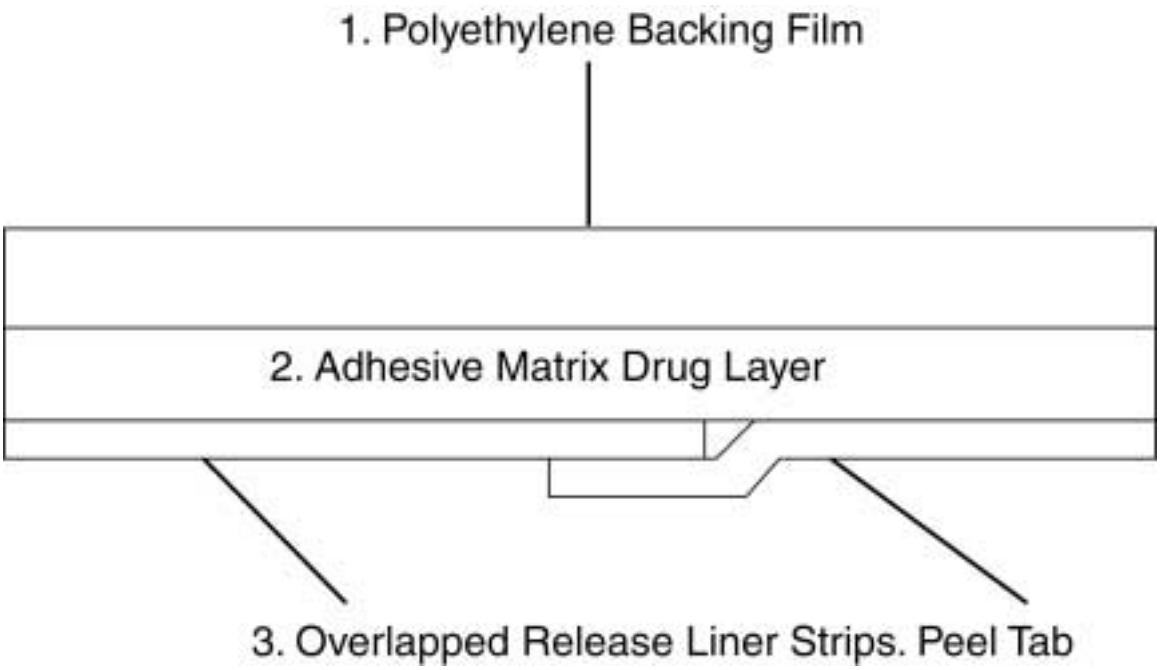
DESCRIPTION

Intrinsa (testosterone transdermal patch) provides nominal delivery of 300 mcg/day of testosterone over a 3- to 4-day interval when applied to intact abdominal skin. The patch contains 8.4 mg of testosterone USP and has a contact surface area of 28 cm^2. Testosterone is an endogenous hormone in both women and men. The testosterone USP used in this patch is a white or creamy white crystalline powder, chemically described as 17β-hydroxyandrost-4-en-3-one. It has an empirical formula of $C_{19}H_{28}O_2$, and a molecular weight of 288.43. The structural formula is:



Testosterone
$C_{19}H_{28}O_2$ M.W. 288.43

The Intrinsa patch consists of three layers. Proceeding from the visible surface toward the surface attached to the skin as shown in the cross sectional view below, the first layer is a translucent low-density polyethylene backing film. The second layer is the adhesive matrix drug layer that will be in contact with the skin and contains the active ingredient testosterone USP and the permeation enhancer sorbitan monooleate dissolved in an acrylic adhesive. The third layer contains two strips of overlapped siliconized polyester release liner that protect the adhesive layer during storage and are removed prior to application of the patch to the skin.



CLINICAL PHARMACOLOGY

Testosterone, the principal circulating androgen in women, is a steroid secreted by the ovaries and adrenal glands. In premenopausal women, the rate of production of testosterone is 100 to 400 mcg/day, of which half is contributed by the ovary as either testosterone or a precursor. In premenopausal women who undergo bilateral oophorectomy, serum testosterone concentration declines by approximately 50%. Serum levels of androgens also fall substantially as women age.

Androgens are active at multiple organ sites, including genital tissue, central nervous system, bone, breast, skin (hair growth and hair distribution), skeletal muscle, and adipose tissue. Decreases in serum testosterone levels have been associated with sexual function changes, including decreased libido (sexual desire), sexual receptivity and pleasure, a diminished sense of well being or dysphoric mood and persistent, unexplained fatigue. Vasomotor instability and decreased vaginal lubrication have also been associated with decreased testosterone levels and have been seen even in patients who have adequate serum estrogen levels. Other potential signs or symptoms of androgen insufficiency include bone loss and decreased muscle strength.

Pharmacokinetics:

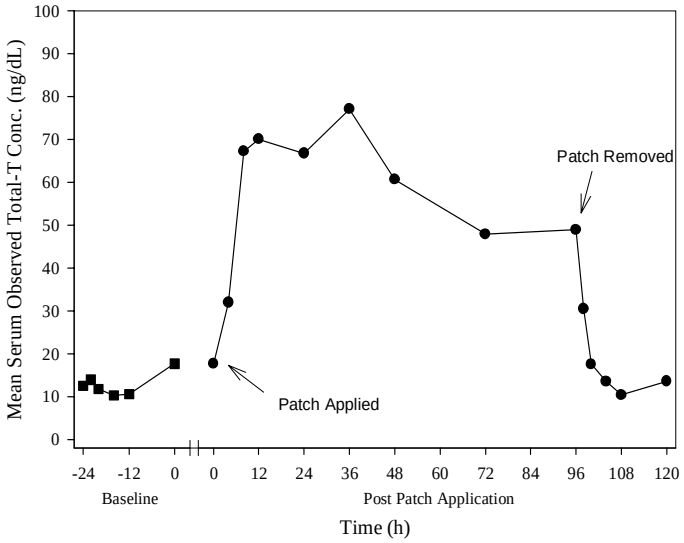
Absorption

Testosterone from Intrinsa (testosterone transdermal patch) is absorbed across intact skin by a passive diffusion process that is primarily controlled by permeation across the stratum corneum. The mean nominal testosterone dose delivered from the 28 cm^2 Intrinsa patch is approximately 300 mcg/day.

In a single-dose pharmacokinetic study in 12 surgically menopausal women receiving concurrent oral conjugated equine estrogens (CEE), the mean serum concentrations of total testosterone increased to a maximum value within 24 to 36 hours and remained within a relatively narrow range over the entire 4-day wear period. Testosterone has a short terminal exponential half-life

(approx. 2 hours), therefore, the serum concentrations return to near baseline values within 12 hours of removing the patch (Figure 1).

Figure 1
Mean total testosterone serum concentration-time profile following a single patch application



Application of Intrinsa on the buttocks resulted in approximately 12% and 20% lower serum concentrations of free and total testosterone, respectively, compared with abdominal application.

In a multiple-dose, randomized, crossover study conducted in 17 surgically menopausal women receiving stable doses of concomitant CEE (0.625 mg/day or higher), the pharmacokinetic parameters of testosterone exhibited dose-proportional increases over a dose range of 150 to 450 mcg/day. Serum concentrations of testosterone attain steady-state by the application of the second patch when applied in a twice-a-week regimen.

Serum hormone concentrations were measured in two safety and efficacy studies (INTIMATE SM 1 AND INTIMATE SM 2; see Clinical Studies) in which 549 patients received Intrinsa for up to 52 weeks while also receiving concomitant oral or transdermal estrogen. The serum concentrations of free and total testosterone increased significantly compared with baseline values in patients treated with Intrinsa.

Table 1
Serum Concentrations of Testosterone and SHBG in Patients Receiving Intrinsa in Clinical Safety and Efficacy Studies

Hormone	Baseline	Week 24	Week 52	Reference range for reproductive adult females
Free testosterone (pg/mL)	0.92 (0.03)	4.36 (0.16)	4.44 (0.31)	0.9 - 7.3
Total testosterone (ng/dL)	17.6 (0.4)	79.7 (2.7)	74.8 (3.6)	12 - 50
SHBG (nmol/L)	91.7 (2.5)	93.9 (2.8)	90.0 (3.6)	13 - 98

Values are mean (SE). SHBG=sex hormone binding globulin

There was no evidence of continuous accumulation of testosterone over 52 weeks of treatment. Unlike orally administered androgens that have been reported to decrease serum sex hormone binding globulin (SHBG) concentration, Intrinsa did not influence serum SHBG concentration. Serum concentrations of estrogens (estradiol and estrone) and adrenal hormones (androstenedione and DHEA-S) were not affected by Intrinsa dosing.

Distribution

In women, circulating testosterone is primarily bound in the serum to SHBG (65% to 80%) and to albumin (20% to 30%), leaving only about 0.5 to 2% as free fraction. The affinity of binding to serum SHBG is relatively high and the SHBG-bound fraction is regarded as not contributing to biological activity. Binding to albumin is of relatively low affinity and is reversible. The albumin-bound fraction and the unbound fraction are collectively termed “bioavailable” testosterone. The amount of SHBG and albumin in serum and the total testosterone concentration determine the distribution of free and bioavailable testosterone. Serum concentration of SHBG is influenced by the route of administration of concomitant estrogen therapy, e.g., higher values of SHBG are associated with oral estrogen therapy.

Metabolism

Testosterone is metabolized to various 17-ketosteroids through two different pathways. Inactivation of testosterone occurs primarily in the liver. The active metabolites of testosterone are estradiol and dihydrotestosterone (DHT). Testosterone is metabolized to DHT by steroid 5(alpha)-reductase. DHT binds with greater affinity to SHBG than does testosterone. DHT concentrations increased in parallel with testosterone concentrations during Intrinsa treatment. There were no significant differences in serum estradiol and estrone levels in patients treated with Intrinsa for up to 52 weeks compared to baseline.

Elimination
About 90% of a dose of testosterone given intramuscularly is excreted in the urine as glucuronide and sulfate conjugates of testosterone and its metabolites; about 6% of a dose is excreted in the feces, mostly in the unconjugated form.

Special Populations:
Pediatric
No pharmacokinetic studies have been conducted in patients less than 18 years of age.

Geriatric
No formal pharmacokinetic studies have been conducted in patients aged 65 or older. In safety and efficacy studies, serum testosterone concentrations of patients receiving Intrinsa were not affected by age over the range of 20 to 70 years.

Race and Ethnicity
In safety and efficacy studies, serum free and total testosterone concentrations in African Americans (6% of the study population) and Hispanics (3% of the study population) were similar to concentrations in the overall population.

Renal Insufficiency
No formal pharmacokinetic studies have been conducted in patients with renal insufficiency.

Hepatic Impairment
No formal pharmacokinetic studies have been conducted in patients with hepatic impairment.

CLINICAL STUDIES
The efficacy and safety of Intrinsa (testosterone transdermal patch), 300 mcg/day, were evaluated in two randomized, multinational, double-blind, placebo-controlled, parallel-group, clinical studies for 6 months. The double-blind period was followed by a 6-month, open-label period during which all patients received Intrinsa. These studies (INTIMATE SM 1, n=562; INTIMATE SM 2, n=533) enrolled surgically menopausal women (history of bilateral oophorectomy and hysterectomy) with hypoactive sexual desire disorder (HSDD), 20 to 70 years of age, who were receiving either oral or transdermal estrogen therapy. Approximately 80% of patients completed the double-blind trial period. Ninety-five percent of these patients elected to continue treatment in the 6-month, open-label, safety period.

HSDD is the persistent or recurrent deficiency or absence of sexual thoughts, fantasies and/or desire for or receptivity for sexual activity, which causes personal distress or interpersonal difficulties. Low sexual desire may be associated with low sexual activity, sexual arousal problems, and orgasm difficulties.

Both studies used three validated instruments to assess efficacy: the Sexual Activity Log (SAL) to quantify sexual activity; the Profile of Female Sexual Function (PFSF) to assess desire, arousal, sexual pleasure, orgasm, sexual responsiveness, sexual self-image, and sexual concerns; and the Personal Distress Scale (PDS) to assess distress associated with lack of sexual desire.

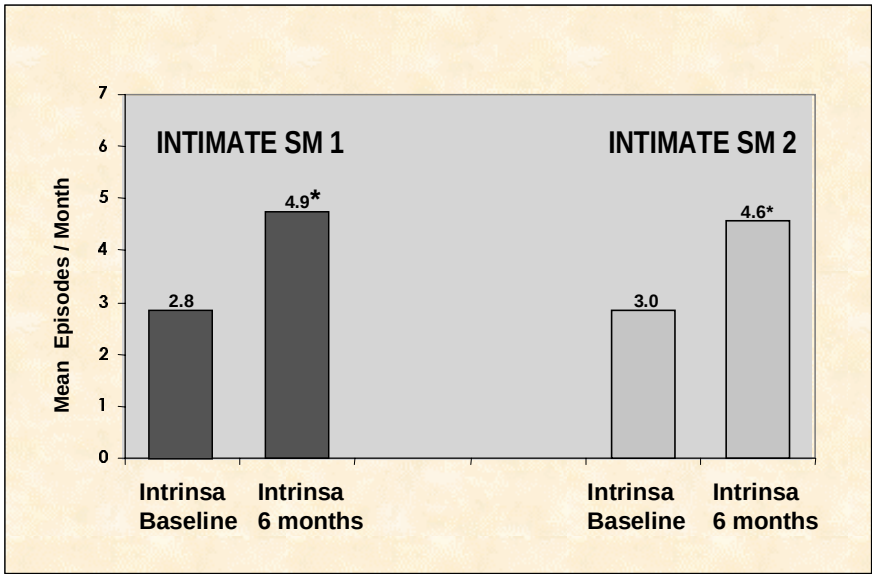
Patients treated with Intrinsa for 6 months experienced consistent and statistically significant increases from baseline and compared to placebo in the frequency of total satisfying sexual activity and sexual desire, and decreased distress associated with low sexual desire (Figures 2-4 and Table 2). Statistically significant improvements from baseline and compared with placebo in all other domains measured by the PFSF (sexual arousal, sexual pleasure, sexual responsiveness, sexual self-image, improved sexual concerns, and subjective assessments of orgasm) were also seen with Intrinsa treatment. Changes in the efficacy endpoints were consistent across both studies.

Table 2
Intrinsa Efficacy Endpoints (SAL, PFSF, PDS)

		INTIMATE SM 1			**INTIMATE SM 2**		
	Treatment	Baseline Mean	% Change From Baseline	p-value ^	Baseline Mean	% Change From Baseline	p-value ^
Sexual Activity Log *							
Total Satisfying Sexual Activity	TTP	2.82	74		3.04	51	
	Placebo	2.94	33	0.0003	3.19	23	0.001
Total Sexual Activity	TTP	4.98	26		5.54	14	
	Placebo	4.94	9	0.0036	5.53	3	0.0132
Total Orgasm	TTP	2.73	80		2.69	68	
	Placebo	2.65	37	0.0002	2.87	23	0.0005
PFSF Domain *							
Sexual Desire	TTP	19.79	56		21.67	49	
	Placebo	20.82	29	0.0006	23.37	18	0.0006
Sexual Arousal	TTP	26.91	81		27.2	74	
	Placebo	26.89	43	< 0.0001	28.96	37	0.0015
Orgasm	TTP	36.7	43		37.23	35	
	Placebo	35.45	23	0.0001	35.22	16	0.002
Sexual Pleasure	TTP	33.09	29		31.98	29	
	Placebo	34.21	8	0.0006	33.37	5	0.0002
Sexual Concerns	TTP	37.35	57		34.31	65	
(inverse scale)	Placebo	38.38	34	0.0003	38.49	31	0.0016
Sexual Responsiveness	TTP	44.11	30		44.4	28	
	Placebo	43.31	16	< 0.0001	48.23	9	0.0004
Sexual Self Image	TTP	32.81	29		34.11	26	
	Placebo	33.72	15	0.0232	35.09	12	0.0299
Personal Distress Scale **							
	TTP	64.78	-65		66.61	-68	
	Placebo	62.57	-40	0.0006	66.38	-48	0.0091

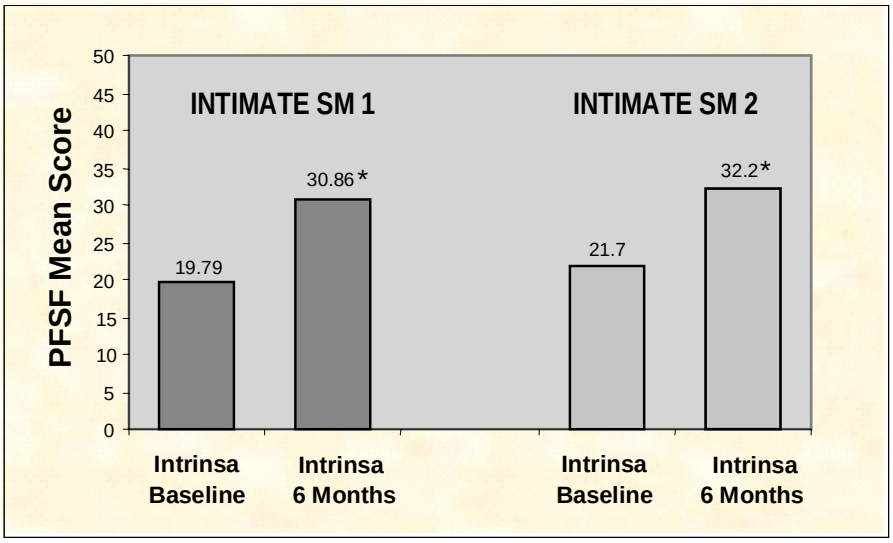
^ p values based on primary statistical analyses of testosterone transdermal patch compared to placebo
* % change from baseline is mean change divided by baseline mean
** % change from baseline is mean change divided by (100 minus baseline mean)

Figure 2
Increase in Total Satisfying Sexual Activity



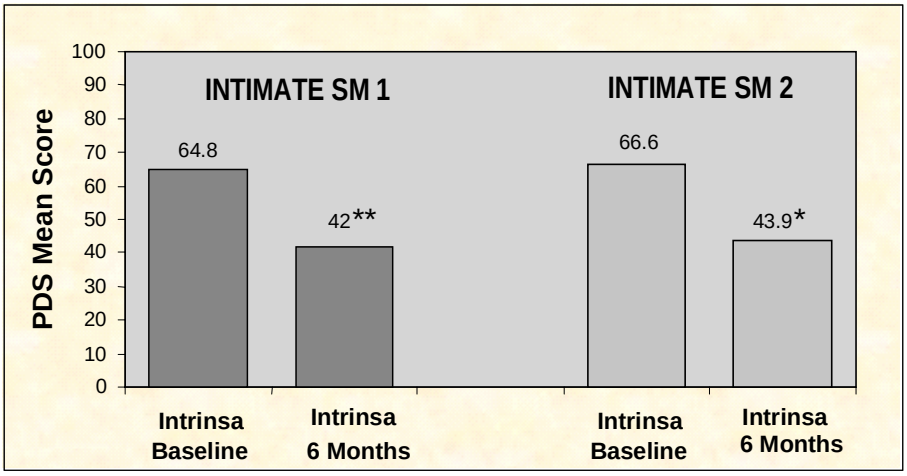
* P ≤ 0.001 vs. placebo

Figure 3
Increase in Sexual Desire



* P ≤ 0.001 vs. placebo

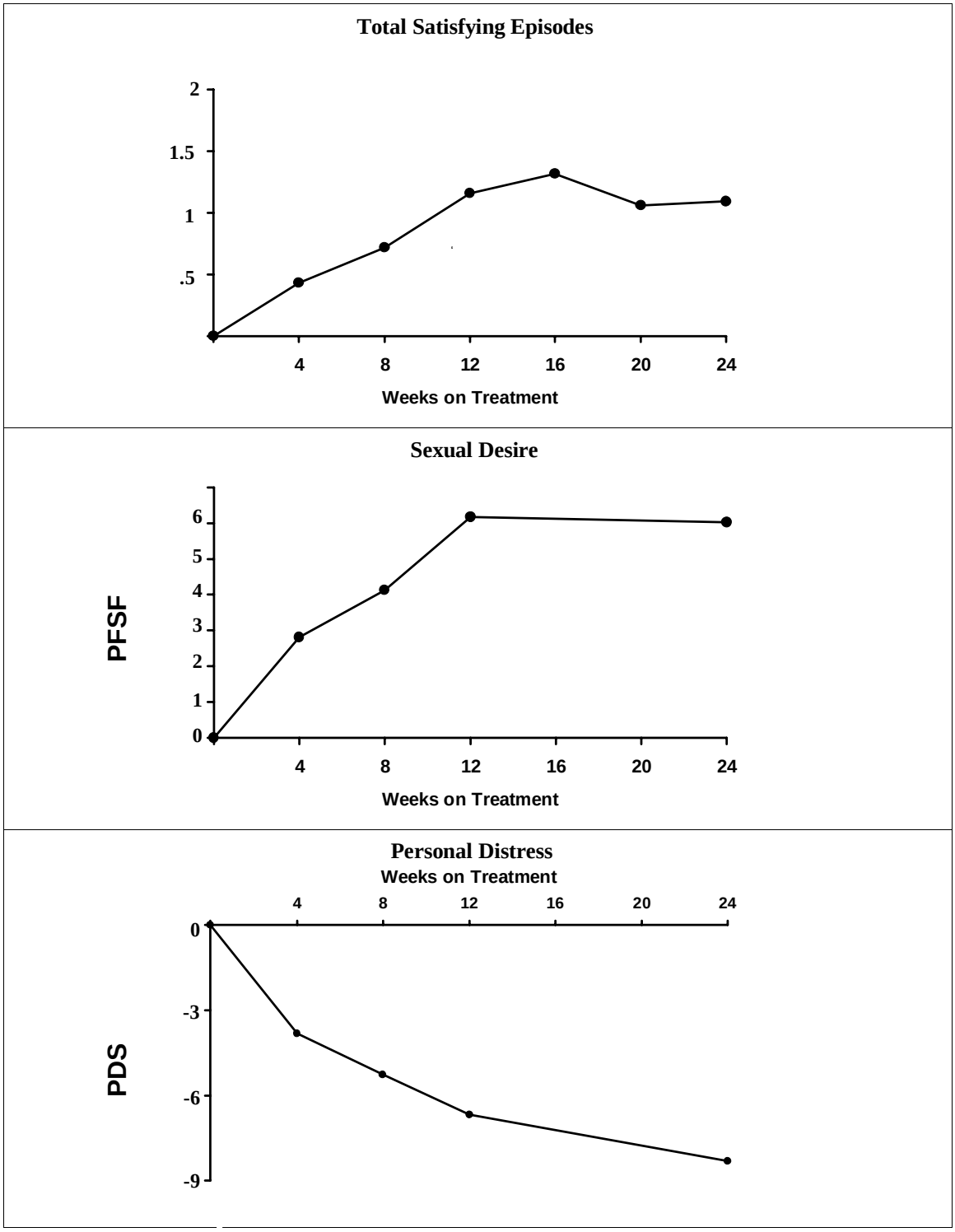
Figure 4
Decrease in Personal Distress



* P ≤ 0.01 vs placebo
** P ≤ 0.001 vs placebo

Improvements in Total Satisfying Episodes and Sexual Desire were seen as early as 4 weeks with maximal effects seen by about 12 weeks and maintained for the remainder of the 24 week efficacy period. Decreases in distress were also seen by 4 weeks and continued to decline for the remainder of the 24 week efficacy period (Figure 5).

Figure 5
Time Course of Intrinsa Treatment Effects
Mean Differences, TTP vs Placebo
Combined Studies, INTIMATE SM 1 and 2
(Intent-to-treat Patients)



The clinical relevance of the treatment benefit was established in a follow-up study in which a subset of patients from both trials (n=133) was interviewed at study exit by a trained interviewer. Both the patient and interviewer were blinded to the patient's treatment group assignment. As part of this interview, each patient was asked whether she had experienced a meaningful benefit from the patch. A statistically significantly higher percentage of women who received Intrinsa reported experiencing a clinically meaningful benefit compared with women who received placebo. These patient reports and the statistically significant decline in distress seen with Intrinsa therapy demonstrate that the increases in total satisfying sexual activity and sexual desire are relevant improvements.

Subgroup analyses of the combined studies support the effectiveness of Intrinsa in a variety of countries, across a range of demographic and reproductive characteristics, disease severity, types and routes of estrogen therapy, and baseline hormone concentrations. A generally consistent treatment effect across subpopulations is apparent in both total satisfying episodes and sexual desire, with degree of response dependent on the route of concomitant estrogen, i.e., transdermal estrogen > oral estrogen, and type of concomitant oral estrogen, i.e., non-CEE > CEE (conjugated equine estrogen). The difference in response is due in part to SHBG levels which are lower in patients on transdermal estrogen.

A placebo-controlled, dose-ranging trial evaluated 3 dose levels of the patch (150, 300 and 450 mcg/day) in 447 women receiving concomitant oral estrogen. This study demonstrated that the 150 mcg/day dose was not effective and the 450 mcg/day dose was well tolerated but did not show any benefits in efficacy over the 300 mcg/day dose.

INDICATIONS AND USAGE

Intrinsa is indicated for the treatment of hypoactive sexual desire disorder in surgically menopausal women receiving concomitant estrogen therapy.

Hypoactive sexual desire disorder (HSDD) is the persistent or recurrent deficiency or absence of sexual thoughts, fantasies and/or desire for or receptivity for sexual activity, which causes personal distress or interpersonal difficulties. Low sexual desire may be associated with low sexual activity, sexual arousal problems or orgasm difficulties.

CONTRAINDICATIONS

Testosterone should not be used in women who:

1. Are pregnant or may become pregnant. Testosterone may cause fetal harm when administered to a pregnant woman (see Carcinogenesis section). If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.
2. Are breast-feeding.
3. Have known or suspected cancer of the breast or estrogen-dependent neoplasia.

Intrinsa (testosterone transdermal patch) should not be used in patients with known hypersensitivity to the ingredients of the patch (see Description).

WARNINGS

Edema (with or without congestive heart failure) may be a serious complication from high doses of testosterone or other anabolic steroids in patients with preexisting cardiac, renal, or hepatic disease. These effects have not been studied with Intrinsa.

PRECAUTIONS

General:

Physicians should instruct patients to report possible side effects of androgens. Androgenic side effects (e.g., acne, changes in hair growth or hair loss) should be evaluated by the physician as appropriate. Some rare signs of virilization, such as voice deepening or clitoromegaly, may be irreversible and discontinuation of treatment should be considered.

Severe skin erythema, local edema, and blistering may occur with hypersensitivity to the patch. Use of the patch should be discontinued if this occurs.

Information for Patients:

Advise patients to carefully read the patient information leaflet.

Laboratory Tests:

No additional laboratory monitoring beyond that required for the individual patient's routine health care is recommended.

Drug Interactions:

No formal drug interaction studies have been performed with Intrinsa (testosterone transdermal patch).

Drugs that cause liver enzyme induction (e.g., barbiturates, carbamazepine, rifampicin, phenylbutazone, meprobamate and hydantoins) or inhibition of cytochrome P450 3A4 (e.g., ketoconazole, macrolide antibiotics) may cause changes in serum androgen concentrations by affecting testosterone metabolism.

Administration of injected testosterone cypionate has been reported to increase clearance of propranolol via enzyme induction in the majority of men tested. These effects have not been studied with Intrinsa.

When testosterone is given simultaneously with anticoagulants, the anticoagulant effect may increase. Patients receiving oral anticoagulants require close monitoring, especially when testosterone therapy is started or stopped.

In diabetic patients the metabolic effects of testosterone may decrease blood glucose and therefore insulin requirements.

Drug/Laboratory Test Interactions:

Androgens may decrease levels of thyroxin-binding globulin, resulting in decreased total T4 serum levels and increased resin uptake of T3 and T4. Free thyroid hormone levels remain unchanged, however, and there is no clinical evidence of thyroid dysfunction.

Carcinogenesis, Mutagenesis, Impairment of Fertility:

Animal Data: Testosterone has been tested by subcutaneous injection and implantation in mice and rats. In mice, the implants induced cervical-uterine tumors, which metastasized in some cases. High doses of testosterone, sufficient to increase serum testosterone levels by a factor of 100, have been reported to increase mammary tumor incidence in the Noble rat tumor model, but other studies (of limited scope) have failed to demonstrate a mammary response in either rats or mice. There is evidence that injection of testosterone into female mice of certain strains may increase their susceptibility to hepatoma. Testosterone is also known to increase the number of tumors and decrease the degree of differentiation of chemically induced carcinomas in the liver of rats.

Testosterone has a masculinizing effect on female rat fetuses when dosed subcutaneously at 0.5 or 1 mg/day (as the propionate ester) to pregnant rats during organogenesis. No fetal effects were seen with a dose of 0.1 mg (0.25 mg/kg), which is at least 40 times the clinical dose delivered by Intrinsa.

Pregnancy:

Pregnancy category X: See Contraindications. Intrinsa is not indicated for use in women who are or may become pregnant.

Nursing Women:

See Contraindications. Because of the potential for adverse outcomes in nursing infants, Intrinsa must not be used by nursing women.

Pediatric Use:

Safety and efficacy in patients less than 18 years old have not been established.

Geriatric Use:

Clinical studies of Intrinsa did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

ADVERSE REACTIONS

Overview:

More than 1500 menopausal women have received Intrinsa (testosterone transdermal patch) in clinical trials, including 549 surgically menopausal women enrolled in the INTIMATE SM trials (see Clinical Studies). In these trials, Intrinsa was well tolerated for up to 12 months of therapy based on evaluation of adverse events and laboratory evaluations, including lipid profiles, coagulation parameters, indicators of carbohydrate metabolism and serum chemistries. The safety profile in the final 6 months of treatment was similar to that in the first 6 months. The majority of adverse events were mild and did not cause patients to discontinue therapy. The overall discontinuation rate due to adverse events was low and not significantly different between treatment groups (7.5% in the placebo group and 8.4% in the Intrinsa group during the 6-month, placebo-controlled period). The most common adverse events in the Phase III clinical studies regardless of treatment group were application site reactions, upper respiratory infections, and headaches.

Discussion:

The adverse reaction information from clinical trials provides a basis for identifying the adverse events that appear to be related to drug use. Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may only approximate the rates observed in practice.

The safety of Intrinsa, 300 mcg/day was evaluated in two randomized, multinational, double-blind, placebo-controlled, parallel-group, clinical studies for 6 months; the double-blind period was followed by a 6-month, open-label period during which all patients received Intrinsa. These studies (INTIMATE SM 1, n=562; INTIMATE SM 2, n=533) enrolled surgically menopausal women with hypoactive sexual desire disorder (HSDD), 20 to 70 years of age, who were receiving either oral or transdermal estrogen therapy. Approximately 80% of patients completed the double-blind trial period. Ninety-five percent of these patients elected to continue treatment in the 6-month, open-label, safety period. The population was 90% Caucasian, 6.7% Black, 3.0% Hispanic and 0.3% of other races. The adverse events reported by $\geq$ 2% of patients receiving Intrinsa and at a higher incidence than in the placebo group are listed in Table 3.

Table 3
Adverse Events at >2% Incidence and Higher in Intrinsa than Placebo

Adverse Events	Placebo (N=545) n (%)	Intrinsa (N=549) n (%)
Upper respiratory tract infection	46 (8.4%)	50 (9.1%)
Headaches	35 (6.4%)	43 (7.8%)
Hair growth	32 (5.9%)	40 (7.3%)
Acnes	28 (5.1%)	37 (6.7%)
Alopecias	16 (2.9%)	23 (4.2%)
Anxiety symptoms	13 (2.4%)	15 (2.7%)
Voice deepening	12 (2.2%)	15 (2.7%)
Migraine headaches	8 (1.5%)	15 (2.7%)
Gastrointestinal and abdominal pains (excl. oral and throat)	4 (0.7%)	14 (2.6%)
Nausea and vomiting symptoms	8 (1.5%)	12 (2.2%)
Influenza like illness	8 (1.5%)	12 (2.2%)
Gastroenteritis viral	9 (1.7%)	11 (2.0%)
Weight increased	8 (1.5%)	11 (2.0%)
Disturbances in initiating and maintaining sleep	8 (1.5%)	11 (2.0%)
Hypertension	8 (1.5%)	11 (2.0%)

More than ninety percent of acne, unwanted hair growth, voice deepening and alopecia reports were mild. Nine (1.6%) patients in the Intrinsa group and 3 (0.6%) patients in the placebo group withdrew from the studies because of these events.

There were no apparent differences in the safety profiles of patients on oral or transdermal concomitant estrogen. Patients above or below 50 years of age showed similar adverse event profiles.

Application site reactions were reported as moderate in 77 patients (7.0%) and severe in 9 patients (0.8%). Thirty-seven (3.4%) of patients discontinued treatment due to application site reactions.

A total of 837 study patients completing the 6-month, placebo-controlled period of the studies received open-label Intrinsa treatment for a further 6 months for collection of additional safety data. The safety profile as measured by adverse events and laboratory evaluations did not change with an additional 6 months of Intrinsa use. Intrinsa was well tolerated for up to 12 months of therapy.

DRUG ABUSE AND DEPENDENCE

Intrinsa (testosterone transdermal patch) contains testosterone, which is a Schedule III controlled substance under the Controlled Substances Act. Oral consumption of Intrinsa is not likely to result in clinically significant serum testosterone concentrations due to extensive first-pass metabolism.

OVERDOSAGE

The mode of administration of Intrinsa (testosterone transdermal patch) makes overdose unlikely. Removal of the patch results in a rapid decrease in serum testosterone levels (see PK section). There were no reports of symptomatic overdose in the Intrinsa clinical program.

DOSAGE AND ADMINISTRATION

Intrinsa (testosterone transdermal patch) 300 mcg/day should be applied twice weekly on a continuous basis. The patch should be replaced with a fresh patch every 3 to 4 days. The adhesive side of the patch should be applied to a clean, dry area of skin on the lower abdomen below the waist. Patches should not be applied to the breasts. A skin site with minimal wrinkling and without tight clothing is recommended. The site should not be oily, damaged, or irritated. The sites of application should be rotated with an interval of at least 7 days between applications to a particular site.

The patch should be applied immediately after opening the pouch and removing both parts of the protective release liner. The patch should be pressed firmly in place for about 10 seconds, making sure there is good contact with the skin, especially around the edges. If an area of the patch lifts, apply pressure to that area. If the patch detaches prematurely, it may be reapplied. If the same patch cannot be reapplied, a new patch should be applied to another location. In either case, the original treatment schedule should be maintained.

The safety of Intrinsa has been evaluated in studies of 1-year duration. Surveillance of patients who have decided to continue treatment with Intrinsa beyond 1 year is ongoing. Treatment with Intrinsa should be for a duration consistent with treatment goals and risks for the individual woman.

HOW SUPPLIED

Intrinsa (testosterone transdermal patch) – each 28 cm^2 patch contains 8.4 mg of testosterone USP for nominal delivery of 300 mcg of testosterone per day**.** Each patch surface is stamped with "PG T001".

Individual carton of 8 patches NDC 0149-0543-01

Store at 25ºC (77ºF) excursions permitted to 15-30º C (59-86ºF). Do not store unpouched. Apply immediately upon removal from the pouch.

Mfg. by: Watson Laboratories, Inc.
A Subsidiary of Watson Pharmaceuticals, Inc.
Corona, CA 92880

Dist. by: Procter & Gamble Pharmaceuticals, Inc., TM Owner
Cincinnati, OH 45202

U.S. Patent Nos. 5,122,383; 5,164,190; 5,460,820;
5,212,199; 5,227,169; 5,780,050; and 6,583,129

CAUTION

Federal law prohibits dispensing without prescription.

Federal law prohibits the transfer of this drug to any person other than the patient for whom it was prescribed.

INTRINSA™ (TESTOSTERONE TRANSDERMAL PATCH)

C III

INFORMATION FOR YOU – RX ONLY

Available Only With a Prescription. 300 Micrograms Testosterone per Day

Please read this entire leaflet carefully before using Intrinsa. This guide was prepared specifically to help you better understand the use of Intrinsa, as well as the response you may expect when you use it. It will cover the benefits and risks of treatment with Intrinsa. The following information should not take the place of your doctor's advice. Talk to your medical professional if you have any questions or concerns about this medication.

What is Intrinsa?

The Intrinsa™ (*testosterone transdermal patch*) patch that your medical professional has prescribed for you constantly releases small amounts of testosterone (pronounced: tes'-tos-ter-own) that is absorbed through your skin. The testosterone in Intrinsa is the same hormone produced in your body. Intrinsa is for the treatment of low sexual desire causing distress or concern.

The medical term for low sexual desire that causes distress or concern is Hypoactive Sexual Desire Disorder, also known as HSDD. If you have HSDD, you are not alone. An estimated 1.2 million surgically menopausal women in the United States suffer from HSDD.

In clinical studies, women with HSDD who used Intrinsa had satisfying sexual activity more often. They also reported improved sexual desire and decreased concern about their low sexual desire. Women using Intrinsa had improvements in sexual arousal, sexual pleasure, sexual responsiveness, sexual self-image, and orgasm.

Why is Testosterone Important?

Testosterone is a hormone that both men and women have, although women usually have much less than men. The ovaries make about half the testosterone in a woman's body. When your ovaries are removed, your body makes less testosterone than it did before surgery. Providing testosterone to women with low desire through the Intrinsa patch has been shown to increase desire for, responsiveness to, and pleasure during sexual activity.

Who is Intrinsa For?

Intrinsa is intended for use by a woman who:

- has had a complete hysterectomy (uterus and both ovaries removed) AND
- is experiencing low sexual desire that is causing her distress or concern AND
- has been prescribed estrogen therapy.

Who Should Not Take Intrinsa?

Intrinsa should not be used by:

- **Women who may become pregnant.**

- **Women who are pregnant**. If you think you may be pregnant, do not use Intrinsa. Using Intrinsa while you are pregnant may cause harm to your unborn child.

- **Women who are breastfeeding**. Intrinsa should not be used while you are breastfeeding because the drug may cause harm to your nursing child.

- **Women who have or think they may have estrogen-dependent cancers (breast, uterine, ovarian); or women who had these cancers in the past.**

- **Women who are allergic to the ingredients in Intrinsa.** The active ingredient is testosterone. The inactive ingredients are sorbitan monooleate, which helps testosterone be absorbed through your skin, and an acrylic adhesive that makes the patch stick to your skin.

If any of the above apply to you, remove the patch immediately and tell your medical professional.

Tell your doctor if:
- **you are taking other medications;**
- **you have any serious medical conditions, such as heart, liver or kidney disease.**

How Should I Use Intrinsa?

You will need to wear the Intrinsa patch every day for it to work. Use Intrinsa for as long as your doctor says you should.

1. You will need to change your patch two times each week, every three to four days. Determine the schedule for twice-a-week application that works best for you.
- Decide which two days you will change your patch. For example, Monday and Thursday, or Sunday and Wednesday.
- Be consistent.
- If you forget to change your patch on the correct date, apply a new one as soon as you remember. You should then continue on your regular schedule.

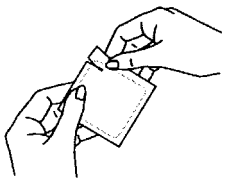
2. Apply Intrinsa to only your lower abdomen, below your waist.

- Avoid the waistline, because clothing may cause the patch to rub off.
- Do not apply Intrinsa to the breasts.
- When changing your patch based on your twice-a-week schedule, apply your new patch to a different place each time. For at least one week after removing a patch, do not place a new patch in the same location on your abdomen.
- If you apply the patch to any part of your body other than your abdomen, you will not receive full benefit of the patch.

3. Make sure the skin at the application site is:

- clean and dry (free of lotions, moisturizers, and powders);
- as smooth as possible (no major creases or skin folds);
- not cut or irritated (free of rashes or other skin problems);
- not rubbed by clothing.

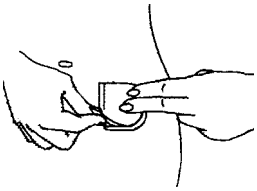
4. Apply Intrinsa.



- Tear open the pouch at the notches. **Do not use scissors**, as you may accidentally cut the patch.
- Remove the patch.
- Apply the patch immediately after removing it from the pouch.

- While holding the patch, remove half of the liner that covers the sticky part of the patch.
- **Avoid touching the sticky side of the patch with your fingers**.

- Apply the sticky side of the patch to the selected area of the abdomen.
- Press the sticky side of the patch firmly into place and smooth it.
- Fold back the patch and carefully remove the other half of the liner.



- Press the entire patch firmly against your skin. Use your fingers to make sure the edges of the patch stick to the skin.

You may shower or swim while wearing the patch. If a patch begins to come off, you may be able to make it stick again by pressing on it firmly. If it will not stick, discard it and apply a new patch to a different area. Then, continue to change the patch on the days you normally do.

5. How to dispose of the patch

- Following removal, the old patch should be folded in half so that the sticky side is folded together, then thrown away so that it cannot be touched or swallowed by a child or pet.
- Adhesive residue may remain on your skin after removing the patch. Gently washing the application site with warm water and a mild soap may help remove the adhesive. Any remaining residue can be removed with an adhesive removal wipe that you can get through your pharmacist.

What if I am Already Using an Estrogen Patch?

- The Intrinsa patch can be used at the same time as an estrogen patch.
- Do not place one patch on top of the other. You will only gain benefit from Intrinsa if the patch is directly in contact with your skin.

How Fast Can I Expect Intrinsa to Work?

Unlike some other medications, Intrinsa needs to be used continuously over a period of time in order to work. The Intrinsa patch will need to be worn on the abdomen daily and changed twice a week to be effective.

On average, women in clinical studies using Intrinsa experienced improvements in total satisfying sexual activity and sexual desire as early as the first month of treatment. They experienced the highest levels of improvement by the end of the first 3 months. These benefits were maintained through the end of the 6-month trials. Your individual response may vary. It may take longer than a month for you to notice an improvement.

What are Possible Side Effects Related to Intrinsa?

The majority of side effects reported were mild and did not cause patients to discontinue taking Intrinsa. As with many other patch products, the most common side effect with Intrinsa was rash, irritation or redness of the skin where the patch was applied.

Some side effects associated with testosterone were seen in Intrinsa clinical trials. In two studies of 1,094 women, approximately half received Intrinsa and the other half received a placebo patch (a patch with no drug in it). This table gives the percentage of women in each group that experienced these side effects:

	Placebo (545 women)	Intrinsa (549 women)
Increase in facial hair	5.9%	7.3%
Increase in acne	5.1%	6.7%
Thinning of scalp hair	2.9%	4.2%

Most women did not find these effects bothersome enough to stop treatment. Discuss these or any other side effects with your doctor.

If you develop any of the following serious, but rare, side effects, stop using Intrinsa and tell your doctor immediately:

- **deepening of your voice;**
- **an increase in size of your clitoris (part of the female genitals).**

How should Intrinsa be stored?

Do not store above room temperature (store between 68-77°F). Do not store the patch outside of the pouch. Patches should not be refrigerated.

Keep this and all drugs out of the reach of children.

Other Information

Do not use Intrinsa for conditions for which it was not prescribed. Do not give Intrinsa to other people, even if they have the same symptoms you have. It may harm them if their doctor has not determined that Intrinsa is right for them.

Overdosing of Intrinsa is unlikely when used as directed. Once the patch is removed, testosterone is rapidly eliminated by the body.

This leaflet summarizes the most important information about Intrinsa. If you would like more information, talk to your medical professional. You can ask your doctor or pharmacist for additional information about Intrinsa.

For more information about Intrinsa, please visit www.intrinsa.com.

Plan to Maximize Safe Use of Intrinsa

To maximize patients' safe use experience with Intrinsa, P&GP has taken a multi-faceted approach:

1. Educational materials, in various forms, will be available at launch designed for clinicians covering:

    a. Prevalence and clinical implications of HSDD
    b. Correct identification of post-menopausal patients with HSDD (and rule out inappropriate patients for treatment)
    c. Appropriate use of Intrinsa, including the indicated population, key safety information and the importance of the Patient Information Leaflet

2. Three different approaches will be employed to detect potential new safety signals:

    a. Monitoring of pivotal trial patients who have elected to continue on TTS for up to three years.
    b. Submission of spontaneous adverse event reports to the FDA semi-annually.
    c. Conduct of a pharmacoepidemiologic study of Intrinsa patients using a claims database to assess the incidence and risk of adverse health outcomes of interest.

Brief summaries of the individual approaches are summarized below.

Development of labeling for healthcare professionals and patients that will support safe use of Intrinsa

In addition to standard professional labeling (package insert), P&GP has developed and submitted a Patient Information Leaflet (PIL) in the NDA. The PIL will provide useful drug information for patients that will maximize safe use and optimize patient benefits. The PIL was developed according to the eight criteria for useful patient information proposed by the Keystone Center's 1996 Action. Menopausal women were asked to rate the PIL based on the following Keystone criteria: 1. Drug names, indication for use; 2. Contraindications, what to do; 3. How to use, monitor, and get most benefit for drug; 4. Precautions, how to avoid harm; 5. Serious or frequent adverse reactions, what to do; 6. General information, encouragement to ask questions; 7. Comprehensible (6-8th grade), legible.

The Intrinsa PIL was initially tested qualitatively to identify potential problem areas. This was followed by quantitative testing in 150 menopausal women. Patients scored high on the final PIL testing with regard to the Keystone criteria (average comprehension across all criteria - 88%) demonstrating a high degree of understanding. Additionally, patients felt encouraged to ask questions and rated the PIL high (89%) with regard to comprehensibility and legibility of information.

Development of educational materials for healthcare professionals subsequent to the approval of Intrinsa

1. Materials Developed by Procter & Gamble Pharmaceuticals (P&GP)

Materials being developed are intended to address three objectives:

a) Help clinicians diagnose HSDD in their surgically menopausal patients and identify patients for whom testosterone therapy is indicated.

P&GP is working with external experts to develop these diagnostic aids. The external experts are:

- Sandra R. Leiblum, PhD, Professor of Psychiatry, University of Medicine and Dentistry of New Jersey
- Raymond C. Rosen, PhD, Professor of Psychiatry and Medicine, University of Medicine and Dentistry of New Jersey
- Leonard R. Derogatis, PhD, Associate Professor of Psychiatry and Behavioral Sciences, School of Medicine, Johns Hopkins University
- Sheryl Kingsberg, PhD, Associate Professor of Reproductive Biology, Case Western Reserve University
- Glenn Braunstein, MD, Chair, Department of Medicine, Division of Endocrinology, Cedars Sinai Medical Center

Specific aids may include a pocket-sized card with questions to diagnose HSDD in surgically menopausal women, a PFSF/PDS short form, a review article, and an in-office poster intended for patients.

Key elements:
A 4 question PFSF diagnostic aid consistent with the DSM-IV definition for HSDD and similar to that used in our clinical program;
Other causes of HSDD that should be ruled out (such as depression);
Factors that could hinder the success of Intrinsa (such as vaginal dryness)

b) Educate clinicians about the appropriate use of Intrinsa

The tools will include a branded website and an e-detail that will reinforce the relevant PI information in an educational manner. The e-detail will deliver an interactive educational message directly to physicians, who agree to this form of communication, at a place and time that suits them, using electronic, internet-orientated technology. Both the website and e-detail will contain a questionnaire/survey to evaluate understanding of the materials. The e-detail will include a medically relevant incentive (e.g. voucher for patients for 1 month of drug) for physicians to complete the educational program.

Key elements:
Indicated population (surgically menopausal women with HSDD receiving estrogen);
Important safety information including contraindications, precautions, warnings, and identification of adverse events;
Importance of the PIL

c) *Educate clinicians across the US about the prevalence and clinical implications of female sexual dysfunction including HSDD*

The tools include a disease awareness website (www.fsdeducation.com) and a disease awareness slide kit.

Key elements:
Understanding the female sexual response;
Menopause related changes in female sexual function including HSDD;
Multifactorial etiology and prevalence in menopausal women;
Impact on menopausal women and their partners;
Diagnostic challenges for physicians including current status of physician-patient conversations on sexuality and initiating discussions with patients

2. CME Programs Supported by Unrestricted Grants

P&GP has provided unrestricted grants to several organizations to develop programs that provide continuing medical education on HSDD in post-menopausal women. As HSDD and the broader category of FSD are emerging disease areas, P&GP will continue supporting CME programs beyond 2005 for Gynecologists, Family Practice physicians and expanding to include Nurse Practitioners and Physicians Assistants in the interest of educating all health care practitioners.

The primary CME providers are summarized below:

The University of Medicine and Dentistry of New Jersey (UMDNJ)
Planned activities-to-date include live events in 20 metropolitan cities educating approximately 1250 Gynecologists between November 2004 and April 2005, and a website (timing late 2004) in conjunction with Baylor College of Medicine for CME education. The general learning objective for the live events is:

Educate participants on the assessment, diagnosis, and treatment of HSDD in postmenopausal women.

The Annenberg Center for Health Sciences
Planned activities include a video-driven audio-teleconference (V-DAT), which will air 10 times between October 12 and December 14, 2004, educating approximately 2000 Gynecologists, and a CD-ROM of patient – physician vignettes to assist physicians new to the area of female sexuality to properly screen the patients presenting with libido issues. The CD-ROM teaches which patients likely have HSDD due to androgen deficiency and which likely

need psychological or couples counseling. Learning objectives for the VDAT events are as follows:

Learning Objectives
At the conclusion of this activity, participants should be better able to:

- *Understand women's sexual cycle and the key factors impacting their sexual response*
- *Identify the prevalence, etiologies, and consequences of HSDD*
- *Recognize changes in sexual function and activity that occur in aging and menopausal women*
- *Utilize tools and techniques to effectively communicate with patients and partners about FSD and HSDD, facilitating accurate diagnosis and treatment.*
- *Select appropriate treatment approaches for patients with HSDD based on need and the relative merits and drawbacks of these approaches.*

Discovery Institute of Medical Education
Conducted a consensus panel (October 18, 2004) on the emerging approaches to care for HSDD among postmenopausal women. Consensus outcomes will be released in Spring 2005 in a CME supplement. The general learning objectives for this event were:

- *Provide a practical guide to clinicians who provide care to postmenopausal women and therefore have a high likelihood of encountering HSDD in their practices*
- *Provide practical tools, such as questions to use when initiating a dialogue with patients about sexual function, a guide to accurately diagnosing HSDD, and a stepwise algorithm for treating HSDD among menopausal women*

Independent Educational Grant
The Association of Reproductive Health Professionals (ARHP) and the National Women's Health Resource Center (NWHRC) plan to sponsor a three-year program (July 2004 - 2007) featuring sexuality education for surgically and naturally menopausal women. This project, supported through an independent educational grant from P&GP, will focus on both clinician and patient education on the topic. The goals of this project are:

- *Increase the level of meaningful, effective communication about sexuality between health care providers and their menopausal patients*
- *Increase the level of meaningful, effective communication about sexuality between menopausal women and their partners*
- *Educate menopausal women and health care providers about issues related to female sexual function.*

Conduct of standard postmarketing surveillance and reporting

Adverse events spontaneously reported to P&GP will be submitted to the FDA within 15 days for serious and unexpected adverse events, and semi-annually for the first 3 years post-approval and annually thereafter for all other events.

Extension of the Phase III trials to provide safety data for up to 3 years of TTS exposure

In the combined surgical and natural menopausal Intrinsa pivotal trials of 6 and 12 months' duration (N=2,689), approximately 2,110 patients received TTS (1345 patients with 6 months TTS exposure and 500 patients with 12 months TTS exposure). While twelve months' exposure has generally been sufficient for regulatory agency approval of new chemical entities administered long-term, P&GP decided to amend the pivotal trials for an additional two years' TTS exposure. A large proportion of patients (70%) continued on TTS in extension studies for year 2 and 3. Based on current enrollment, we expect to have greater than 200 patients reach the two year time point (with a total of 18-24 months' TTS exposure). In addition to continual collection of adverse events, patients return to the study sites at 6-month intervals for evaluation of vital signs, hematology labs, serum chemistry labs (including cholesterol, triglycerides, LDL, HDL, fasting glucose, and liver function), hormones (free, total and bioavailable T, SHBG and total DHT). At 12-month intervals patients undergo physical exams and mammograms.

Conduct of a pharmacoepidemiologic study of Intrinsa users to evaluate safety outcomes in an observational setting.

P&GP is committed to evaluating the long-term safety of TTS in the postmarketing phase. We propose to conduct a pharmacoepidemiologic study that systematically monitors patients in a large, administrative claims database for the purpose of signal detection. This observational research complements clinical trial research in that it can evaluate large numbers of exposed patients for longer periods in a "real world" setting. We also plan to establish an external epidemiology advisory group to provide guidance on study methodology and interpretation of results. As stated in the FDA draft Pharmacovigilance Guidance, "postmarketing safety data collection and risk assessment based on observational data are critical for evaluating and characterizing a product's risk profile and for making informed decisions on risk minimization." An overview of this pharmacoepidemiologic study follows.

Pharmacoepidemiologic Study Overview

We propose a thorough evaluation of TTS patients in the Ingenix Lab/Rx Database™ (Ingenix®) to assess the incidence and risk of potential adverse health outcomes of interest. Ingenix® covers over 20 million lives and includes longitudinal data representing health care services from professional, treatment facility, and outpatient pharmacy claims, as well as laboratory results for more than 80% of the covered lives. The database covers a wide geographic area of the U.S., with members residing primarily in the South (43%), as well as in the Midwest (35%), West (13%), and Northeast (9%). To determine whether there would be a sufficient number of patients exposed to TTS in this database, we examined surgically menopausal (SM) women and formulary considerations. In a recent 18-month period, there were 106,695 SM women 20-70 years of age, of which 10,530 (9.9%) filled at least one prescription for a testosterone product. Thus, Ingenix® contains a substantial number of SM patients receiving testosterone treatment. Current data from Ingenix® shows that 98.5% of all patients in United HealthCare (parent company of Ingenix®) plans have erectile dysfunction benefit coverage. Further, internal research indicates that plans which currently provide reimbursement for Viagra or other PDE5 agents will also provide coverage for TTS. Therefore, we anticipate substantial formulary coverage for TTS within the database.

In the proposed study, we plan to track all patients enrolled who are exposed to TTS, and establish criteria for appropriate control selection as a basis for comparison of safety endpoints of interest, such as cardiovascular disease and breast cancer. Both cohorts will be followed for a period of five years with analyses performed for the purposes of signal detection. If a safety signal emerges, we will make a concerted effort to contract with Ingenix® to validate these outcomes of interest by abstracting essential data elements from the medical records. In the data analysis phase, TTS use will be defined based on prescription patterns. The initial evaluation will be conducted after sufficient patient exposure to TTS is recorded in the Ingenix® database. We anticipate this would occur approximately 18 months after product launch if at least 10% of SM women receive one of more prescriptions for TTS during this initial period. Subsequent analyses will be conducted at regular intervals. Discussions with the Division will occur to obtain input to the postmarketing pharmacovigilance and pharmacoepidemiologic assessment plan.