Intrinsa
(Testosterone Transdermal System)

NDA 21-769

Indication

"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 difficulty."

Dosing regimen**:**

One patch (300 mcg/day) applied to abdomen twice weekly on a continuous basis. Patch should be replaced with a fresh patch every three to four days.

Review by the Division of Reproductive and Urologic Drug Products

November 3, 2004

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1 BACKGROUND

The proposed indication for the transdermal testosterone system is for the "treatment of hypoactive sexual desire disorder in surgically menopausal women receiving concomitant estrogen therapy."

1.1 DEFINITION OF FSD

Over the years, there has been uncertainty as to exactly what constitutes a female sexual disorder or dysfunction (FSD). The World Health Organization's *International Statistical Classification of Diseases and Related Problems* (ICD-10) suggests that sexual dysfunctions are "the various ways in which an individual is unable to participate in a sexual relationship as he or she would wish." The main categories of sexual dysfunction include lack of sexual desire, sexual aversion disorder, failure of genital response (arousal disorder), orgasmic dysfunction, dyspareunia, and excessive sexual drive. The DSM-IV suggests that sexual dysfunctions are "disturbances in sexual desire and in the psychophysiologic changes that characterize the sexual response cycle and cause marked distress and interpersonal difficulty." The dysfunctions include hypoactive sexual desire, sexual aversion, female arousal disorder, female orgasmic disorder, dyspareunia, and vaginismus.

In 1999, the new American Foundation of Urologic Disease (AFUD) FSD diagnostic and classification system was proposed. The AFUD definitions state that disorders must be associated with personal distress, and may be either acquired or lifelong (chronic). The many causes of FSD can be broadly categorized into the following: vascular, neurological, psychogenic, and hormonal-endocrine. The diagnosis of FSD, according to AFUD, requires the clinician to obtain a detailed patient history that defines the problem and identifies causative or confounding conditions and important psychosocial information. The presence of more than one dysfunction should be explored as considerable interdependence may exist. The 4 major components of FSD according to the AFUD classification are the following:

1. Sexual desire disorder [hypoactive sexual desire disorder, HSDD]
2. Sexual arousal disorder [FSAD]
3. Orgasmic disorder [FSOD]
4. Sexual pain disorder [no common acronym]

1.1.1 Hypoactive Sexual Desire Disorder

Hypoactive sexual desire disorder (HSDD), the proposed indication for Intrinsa, is the persistent or recurring deficiency (or absence) of sexual fantasies, thoughts and/or desire for, or receptivity to, sexual activity, which causes personal distress. The cause may be either physiological or psychological or a combination of both. Common physiological etiologies include hormone deficiencies, medications, and surgical interventions. Any disruption of the female hormonal milieu caused by these etiologies can result in decreased sexual desire. The lack of, or a decrease in, sexual desire may also be secondary to poor sexual arousal and response, or to pain associated with sexual activity. HSDD is sometimes a psychologically or emotionally based problem that can result from a variety of reasons, including a history of sexual abuse or trauma. For instance, depression and the treatment of depression are common problems in women with low sexual desire. Another factor may be difficulty with inability to attain or maintain sufficient sexual excitement, a condition known as female sexual arousal disorder (FSAD).

1.2 FDA GUIDANCE

In May 2000 the FDA distributed the first draft guidance for industry for the "Clinical Development of Drug Products for FSD" (see Appendix 1). Although the definition of FSD was continuing to evolve at that time (and still is evolving), emphasis was placed on clearly defining the component or components of FSD that would be targeted for developing therapies and the potential subgroups (e.g., age, premenopausal vs. menopausal; different hormonal therapy) that might respond differently to therapy. Relatively strict inclusion and exclusion criteria were encouraged. The guidance states that personal distress should be measured to ensure appropriate patient selection for trial participation but should not serve as the primary endpoint for establishing effectiveness.

FDA Guidance recommendations for the clinical development program and clinical trial design for FSD therapies included the following:

1. Instruments, questionnaires, scales that are used for diagnosis and endpoints should be developed, tested, and validated in women with FSD and should be able to differentiate between normal women and women with different components of FSD
2. Primary endpoints should be statistically significant and clinically meaningful over time and related to the components of FSD being studied
3. The primary endpoint should include change in the number of satisfactory sexual events over time [from baseline to end of treatment] compared to placebo
4. Sexual events or encounters include:
   a) satisfactory sexual intercourse
   b) sexual intercourse resulting in orgasm
   c) oral sex resulting in orgasm
   d) partner-initiated or self masturbation resulting in orgasm
5. Endpoints based on health-related quality of life (HRQL) claims should be linked to clinically meaningful objective endpoints
6. Two controlled Phase 3 trials of 6 months treatment duration should be conducted to support an NDA
7. Pre-treatment baseline assessment period of 4-8 weeks
8. Use of a daily diary to record all sexual activities

1.3 AGREEMENTS WITH APPLICANT

Table 1 below is a brief tabular summary of the major interactions between the Division and Procter and Gamble Pharmaceuticals, Inc. (P&GP). Instrument development and validation were completed for the 3 most important endpoints in the Phase 3 trials. Issues that were raised by the Division at the end-of-Phase 2 meeting, with the Phase 3 protocols, and at the pre-NDA meeting were addressed by the Applicant. The Applicant conducted their development program consistent with the Division's May 2000 draft guidance and subsequent advice from the Division. The following were key issues that were raised in discussions with the Applicant:

1. Conducting the Phase 3 trials primarily in the U.S., because of the concern for major cultural differences in female sexuality in non-U.S. countries.
2. Establishing and validating the diagnosis of HSDD separate from the other major components of FSD

3. The importance of establishing a minimally important clinical difference (MICD) to support the primary endpoint and to help define the responder analysis
4. Meeting the ICH guideline for long-term exposure; adding follow-up visits for safety after treatment ends
5. Need for a responder analysis as a secondary analysis to support the primary endpoint analysis
6. Handling missing data; the last observation carried forward (LOCF) method was changed to satisfy the Division
7. Need for additional assessments of androgenic effects, including virilization and voice changes

Table 1 Regulatory Activity

IND #59, 232 (Procter & Gamble Pharmaceuticals, Applicant)	
Date	**Topic**
16 Jul 99	Applicant Pre-IND meeting (IND #59,232)
8 Dec 99	Telecon re instrument validation and Phase 2 protocol
5 Dec 01	End-of Phase 2 (EOP2) meeting; fax to Applicant on 30 Nov 01
3 Apr 02	FDA response to Applicant follow-up to EOP2 meeting (letter)
5 Aug 02	FDA comments on Phase 3 protocols (letter)
11 Dec 02	FDA feedback on tradename and validation of diagnosis of HSDD (letter)
26 Jun 03	Pre-NDA meeting
21 Jun 04	NDA received

2 CLINICAL DEVELOPMENT

It has been reported in several national U.S. surveys that the proportion of menopausal women having low sexual desire (HSDD) ranges from 7-33%. Testosterone levels in populations of menopausal women with and without low libido have shown overlapping ranges of levels regardless of the libido status. Testosterone levels alone have not been shown to have a predictable value for diagnosing HSDD or characterizing the severity of the condition. As noted earlier, HSDD is diagnosed by a careful medical and psychosocial history, symptoms, and the associated distress.

2.1 TESTOSTERONE THERAPY FOR HSDD

In the 1980s and 1990s there were a few reports of small studies using intramuscular or subcutaneous testosterone to treat HSDD in menopausal women. Treatment resulting in increased sexual desire and sexual activity as measured by non-validated instruments for sexual function was often associated with supraphysiologic serum testosterone levels.

2.2 APPLICANT'S EARLY CLINICAL DEVELOPMENT PROGRAM

Because there was no approved therapy available for this indication, the Applicant embarked on a clinical program to develop a testosterone transdermal system (TTS) for the treatment of HSDD in surgically menopausal women. A transdermal delivery was selected for its ability to deliver a relatively steady dose of testosterone that is not affected by first pass effects of liver metabolism. The pharmacokinetics (PK) of testosterone from the transdermal system were evaluated in single

and multiple dose studies, in standard PK and population PK studies, for durations of 4 days to 12 months, at different application sites (abdomen or buttocks), over a range of testosterone doses. Overall, there were 3 bioavailability and 3 PK studies.

2.3 DOSE SELECTION

In Phase 2 studies, the Applicant investigated a range of doses. The 150 mcg/day dose was not effective, and the 450 mcg/day dose provided no clear benefit beyond that of the 300 mcg/day dose. Based on these observations, the Applicant selected a dose of 300 mcg/day for their Phase 3 clinical trials.

2.4 INSTRUMENT DEVELOPMENT AND VALIDATION

Following the FDA's Guidance on FSD, which states it is important to use validated instruments for assessing responses to FSD therapy in specific target populations, the Applicant developed three psychometric instruments for use in surgically menopausal women in the US, Canada, Europe and Australia. These instruments were designed to measure efficacy endpoints in women with HSDD in surgically and naturally menopausal women. Table lists these 3 instruments.

Table 2 Instruments Used to Measure Response to Treatment

Sexual Activity Log (SAL) Counts sexual activity, with and without intercourse, 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
Personal Distress Scale (PDS) Measures how a woman has felt about her lack of interest in sex over the previous 30 days. Endpoint: Distress

The FDA Draft Guidance stresses that the primary endpoint for assessing the effectiveness of therapies for FSD is the number of satisfactory sexual events. The number of satisfactory events, the primary endpoint of the Applicant's two major Phase 3 trials, was assessed using the Sexual Activity Log (SAL). The SAL is a record of sexual activity from the previous 7 days. The determination of "satisfaction" was made by the subject herself, rather than by her partner or a clinician. The completed weekly diary was collected every 4 weeks (from the preceding 4 weeks) throughout the 24-week trials.

The Profile of Female Sexual Function (PFSF) contains 37 questions that measure subjective aspects of HSDD in the 7 separate domains listed in the table. The number of questions per domain ranges from 9 for Desire to 3 for Arousal and Concerns. The Personal Distress Scale (PDS) contains 9 items in a single domain and measures personal distress associated with a patient's lack of interest in sex. Based on the subject's experience and feelings over the preceding 30 days, subjects filled out the PFSF and PDS at Weeks 0, 4, 8, 12, and 24 in the Phase 3 trials. The PFSF and PDS scores for each domain were then normalized so that they ranged from 0-100. Scores of 0, 20, 40, 60, 80, and 100 for each domain correspond, on average, to the following categories of response: "Never," "Seldom," "Sometimes," "Often," "Very Often," and "Always," respectively. A decrease in the PDS score indicates a decrease in a subject's distress.

Based on their validation study, the Applicant believes that the 3 instruments were shown to be valid, consistent, and reliable for the measurement of HSDD in both naturally and surgically menopausal women. Appendix 2 contains the PDS and the items from the Desire domain of the PFSF.

2.5 OVERVIEW OF CLINICAL TRIALS

The clinical program to evaluate the efficacy of TTS in the treatment of HSDD in surgically menopausal (SM) women consisted of seven trials (see Table 2), two of which evaluated multiple dose levels. The two Phase 2b and the two Phase 3 trials were similar in design and used the three instruments developed by the Applicant in surgically menopausal women. The two blinded, placebo-controlled Phase 3 studies (2001133 and 2001134) were the major studies submitted to support efficacy and safety. They each enrolled over 500 women. These studies were conducted utilizing the 300 microgram dose identified as the optimal dose in the earlier Phase 2b studies.

There were two special studies linked to the Phase 3 trials. A subset of 132 subjects (68 placebo and 64 active treatment) from the Phase 3 24-week studies was evaluated in a clinical relevance study (CMKUS030993) to determine whether they experienced meaningful benefits during study participation. The goal of this sub-study was to determine the minimally important clinical difference (MICD) for several parameters. The open label extension studies each included a blinded 13-week "withdrawal study" from weeks 52-65 to evaluate the persistence of treatment effect in a total of 205 women. All were positive responders on active treatment during weeks 24-52 (see Section 4.9).

Table 2 List of Controlled, Blinded Efficacy Studies

Study Phase/ #	**N @ Testosterone dose** (mcg/day)	**N @ Placebo dose**	**Estrogen Therapy**	**Comments**
II a T96006	N= 75 @ 150 N= 75 @ 300	N= 75	Oral CEE	12 wk @ each dose; crossover
II b 1999068	N= 107 @ 150 N= 110 @ 300 N= 111 @ 450	N= 119	Oral only	300 mcg/day was the lowest, safest effective dose
II b 1999092	N= 37 @ 300	N= 39	Transdermal only	Small European study
III 2001133	N= 283 @ 300	N= 279	Oral and transdermal	24-week pivotal
III 2001134	N= 266 @ 300	N= 266	Oral and transdermal	24-week pivotal
Sub-studies of 2001133 and 2001134				
CMK030993 Exit interview study	N= 64 @ 300	N= 68	Oral and transdermal	Meaningful Rx benefit (MICD)*
Withdrawal study	N= 102 @ 300	N= 103	Oral and transdermal	Persistence of Rx benefit- withdrawal
Total	N= 771@ 300**	N= 778		

*MICD = minimally important clinical difference or minimally meaningful clinical difference.

** N= 771 unique subjects using the TTS 300 mcg/day dose; does not include the 64 exit interview and 102 withdrawal subjects.

Safety of the testosterone transdermal system (TTS) was monitored in clinical trials for periods of 6 months (957 subjects) and 12 months (494 subjects) as described in the safety section of this review. After the completion of the two Phase 3 12-month trials, P&G has elected to conduct long-term safety surveillance (open-label) of subjects treated with TTS for up to an additional 3 years. This surveillance is currently on-going (321 women are enrolled beyond 12 months).

3 CLINICAL TRIAL DESIGN

3.1 DESCRIPTION OF PHASE 2 TRIAL PROTOCOLS

Study 1999068 was a randomized, double blind, placebo-controlled multicenter trial investigating the effects of three TTS doses on sexual outcome measures using the SAL and PFSF. The 447 subjects had all undergone a hysterectomy and oophorectomy and had low libido. The study consisted of a 8-week pre-treatment period followed by a 24-week efficacy period and a 28-week safety extension period. Routine laboratory and androgen/estrogen hormonal levels were followed from baseline through the 24 weeks.

Study 1999092 was a randomized, double blind, placebo-controlled multicenter trial investigating the effects of 300 mcg/day on sexual outcome measures using the SAL and PFSF. The 77 subjects had all undergone a hysterectomy and oophorectomy, had low libido, and were on transdermal estrogen therapy (ET). The study consisted of a 8-week pre-treatment period followed by a 24-week efficacy period. Subjects were stratified into 2 groups prior to randomization based on their dose of ET (≤0.05 mg, >0.05 mg). Routine laboratory and androgen/estrogen hormonal levels were followed from baseline through the 24 weeks.

3.2 DESCRIPTION OF PHASE 3 TRIAL PROTOCOLS

The two Phase 3 studies were nearly identical in design (clinical laboratory tests differed slightly between the studies). Each was a multicenter, multinational study conducted in SM women with HSDD. Each was based on a 24-week, randomized, double-blind (DB), placebo-controlled (PC), parallel-group design to assess efficacy and safety. Each was followed by a 28-week open label (OL) extension period to assess safety.

Subjects were stratified based on their use of oral or transdermal ET. Within each stratum, subjects were randomly assigned in a 1:1 ratio to receive 300 mcg/day TTS or a placebo patch. Subjects applied the investigational TTS to their abdomen twice weekly (each patch was worn for approximately 3-4 days). Upon completion of the 24-week DB efficacy and safety period of the study, subjects receiving placebo were switched to 300 mcg/day TTS, while the active cohort remained on active treatment. The subjects and study site personnel remained blinded to the initial randomized treatment throughout the open label portion of each study.

The primary objective of each study was to assess the efficacy of 300 mcg/day TTS in treating HSDD in SM women on concomitant oral or transdermal estrogen therapy. Efficacy was assessed by the change in the 4-week frequency of total satisfying sexual events (SSEs) from baseline to Week 24. Key secondary objectives were:

1. personal distress as measured by the PDS score
2. sexual desire as measured by the PFSF

The frequency of satisfactory sexual events was recorded on the SAL that was completed by subjects at home on a weekly basis and returned to the clinical sites at the next scheduled visit. The PFSF and PDS were completed at the clinical sites at baseline (Week 0) and Weeks 4, 8, 12,

and 24. Safety was evaluated by monitoring adverse events (AEs), routine clinical laboratory measurements, vital signs, and physical examinations. Skin appearance at the most recent abdominal patch application site was evaluated at each clinic visit for patch site symptoms of irritation. Objective assessments of androgenic effects on the skin (increases in hair growth at the lip and chin, facial depilation, and degree of facial acne vulgaris) were also evaluated in each study. Serum samples were analyzed in each study at baseline and Weeks 12 and 24 for determination of free, total, and bioavailable testosterone, SHBG, free and total estradiol, and estrone.

3.3 INCLUSION/EXCLUSION CRITERIA

3.3.1 Inclusion Criteria

Inclusion criteria were developed to ensure that subjects entering the study were surgically menopausal, satisfied major diagnostic criteria for acquired (not chronic) HSDD, and were in stable relationships in which partner factors would not preclude the possibility of demonstrating a treatment effect.

Women were screened for study participation according to the following inclusion criteria at Week -8 (Visit 1) unless otherwise specified. Eligible women must have:

1) been 20 to 70 years old and in generally good health based on medical history, physical examination, and laboratory evaluation;
2) undergone bilateral salpingo-oophorectomy and hysterectomy at least 6 months prior to screening and had no physical impediment to sexual function for at least 3 months prior to screening (documented evidence of surgery had to be provided). If the surgical report was not available, a history consistent with removal of both ovaries was to be obtained. Attempts to obtain the surgical report were documented;
3) been receiving a stable dose of ET for at least 3 months prior to screening with the intention of maintaining that regimen.
    - This treatment should have resulted in, on average, less than 3 moderate to severe hot flashes per day.
    - Acceptable therapies included approved oral estrogens and approved transdermal estrogen patch regimens.
    - Compounded estrogen preparations, selective estrogen receptor modulators (SERMs), or phytoestrogens preparations were not to be substituted for the ET requirement;
4) been, in her own judgment, in a stable monogamous sexual relationship that was perceived to be secure and communicative, for at least 1 year prior to study entry. The relationship was to be with the same partner who was sexually functional, both psychologically and physically, and expected to be physically present (i.e., available for sexual activity at some time during a 24-hour day) at least 50% of each month during the 8-week pretreatment and 24-week efficacy period of the study;

5) answered affirmatively to ALL five of the following questions:

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

6) if ≥ 40 years of age, had a clinically acceptable screening bilateral mammogram (no evidence of malignancy) as determined by the local radiologist (subjects could have submitted a mammogram done up to 2 months prior to screening). Subjects under 40 years of age at screening could have elected to have mammograms if they wished, but these were not required for study entry;

7) had a clinically acceptable Pap smear as read by a central cytology facility (no evidence of malignancy or squamous intraepithelial lesions) if the cervix was present. A Pap smear at study entry could have been performed on subjects without a cervix at the discretion of the investigator;

3.3.2 Exclusion Criteria

Exclusion criteria were developed to ensure that psychological or physical factors, other than low testosterone, that could cause hypoactive sexual desire were not present. Potential study subjects with medical conditions that might cause them to be at increased risk for adverse events (AEs) were also excluded, as were subjects taking drugs or nutritional supplements that were likely to affect sexual function.

Women were screened for study participation according to the following exclusion criteria at Week -8 (Visit 1) or as specified. Eligible women must not:

1) have had dyspareunia not alleviated by lubricants, any physical limitations, or sexual trauma since their oophorectomy that would have interfered with normal sexual function;

2) have been experiencing any chronic or acute life stress relating to any major life change, such as recent loss of income or the death of a close family member, that could have, in the opinion of the investigator, significantly interfered with sexual activity;

3) have had significant psychiatric disorder (including mild depressive disorder, as evidenced by a score of ≥ 14 on the Beck Depression Inventory-II [BDI-II]), or had a significant alcohol or drug dependency and/or been receiving pharmacologic treatment for such illness or disorder;

4) have had evidence of clinically significant organic disease on the history and/or physical examination that would have, in the opinion of the investigator, prevented the patient from completing the study, or otherwise affected the outcome of the study. Subjects could not have had any major illness, active gallbladder disease, gynecological or breast surgery, including excisional biopsies, within the last 6 months;

5) have used within the last 12 weeks any medications/preparations that could have affected sexual function or otherwise interfered with interpretation of study results.

6) have used tablet or powder forms of phytoestrogens for less than 12 weeks prior to Week -8 (Visit 1). No use or stable use of phytoestrogens for 12 weeks or longer was acceptable;

7) have used (averaging more than once a week) in the past 30 days the following preparations: dehydroepiandrosterone (DHEA), melatonin, or other drugs or supplements that could have, in the opinion of the investigator, affected sexual function;

8) have received marketed or investigational oral, sublingual, topical, transdermal, injectable, or vaginal androgen therapy at any time during the past 3 months, or investigational implantable androgen therapy at any time in the past 7 months;

9) have had current severe dermatological problems (e.g., severe or cystic acne) or had a known or suspected hypersensitivity or allergy to any adhesive or any of the constituents of the transdermal systems;

10) have had a history of breast cancer or estrogen-dependent neoplasia (e.g., endometrial cancer) or any gynecological cancer at any time before study entry or other cancer (except basal or squamous cell carcinoma) within the last 5 years;

11) have had diabetes, a history of cerebrovascular disease, thromboembolic disorders, myocardial infarction, or angina at any time before study entry or thrombophlebitis within the last 5 years;

12) have had a thyroid-stimulating hormone (TSH) value at screening above the upper limit of normal confirmed by a free T4 outside the normal laboratory range (subjects with an abnormal TSH, normal free T4, and no clinical signs or symptoms of thyroid disease, with or without replacement treatment, could have been admitted to the study);

13) have had, in the opinion of the investigator, clinically significant abnormal pretreatment laboratory parameters (a single repeat assay was allowed if an assay result was questionable) that would have materially impacted the patient's ability to participate in the study;

14) have had the following laboratory values:

- serum creatinine > 2.5 mg/dL
- serum total bilirubin ≥ 2 times the upper limit of normal
- alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 3 times the upper limit of normal; or

15) have previously participated in Study 1999068 or 1999092 or have participated in a clinical trial within 30 days or received an investigational medication within 30 days (women participating in observational studies, however, could have been included).

Division comment:

- **In the Phase 2 studies T96006 and 1999068, per protocol, all the women had documented low serum testosterone levels [free T <3.5 pg/mL; normal range is 0.9-7.3]. This free T criterion was dropped in the Phase 3 studies because the Applicant's Phase 2b experience indicated that almost no potential study subject had baseline T levels exceeding the level set. Baseline serum testosterone parameters were obtained, however, as were testosterone levels at Weeks 12 and 24 during the 2 controlled Phase 3 trials.**

3.4 SCHEDULE OF ASSESSMENTS

The Schedule of Visit Procedures for the Phase 3 clinical trials is listed in Table 3.

Table 3 Schedule of Visit Procedures: Phase 3 Trials

PROCEDURE	Screening Period		Efficacy Treatment Period						
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9
	Wk -8	Wk -4	Wk 0	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24
Informed Consent	X								
Eligibility Criteria	X	X	X						
Personal/Demographic Data	X								
Medical, Gynecological and Drug History	X	X	X						
Physical Examination (including breast and pelvic exam)		X							X
Bilateral Mammogram		X							
Vital signs (BP, heart rate, temperature), weight	X		X			X			X
Cholesterol, triglycerides, LDL, HDL, glucose, hemoglobin A1c, insulin, serum chemistry , liver function tests, hematology	X								X
Hormone measurements (Androgens, Estrogens and SHBG)		X				X			X
Hirsutism, Frequency of facial depilation, Acne score		X				X			X
Randomize to treatment			X						
Review of inventories with patients	X	X							
Collect completed SAL		X	X	X	X	X	X	X	X
Complete PFSF, PDS			X	X	X	X			X
Concomitant Medications				X	X	X	X	X	X
AE Adverse Events	X	X	X	X	X	X	X	X	X

3.5 ENDPOINTS & STATISTICAL ANALYSIS

3.5.1 Primary Endpoint

The primary efficacy endpoint was the change from baseline in the total frequency of satisfying sexual events at 24 weeks (sum of the 4 consecutive weekly frequencies on SAL questions 3 and 6 during Weeks 21-24). In this document, the frequency of satisfying sexual events is presented as the total count over a 4-week period.

3.5.2 Principal Secondary Endpoints

Secondary endpoints were the sexual desire domain score of the PFSF and the PDS Score (Distress) at 24 weeks. Each item within a domain has 6 possible answers ranging from all of the time to none of the time. Raw domain scores were computed by summing the scores for items within a domain and transforming the score to a 0 to 100 scale. (See Section 2.4.)

3.5.3 Primary Analysis

The primary analysis was based on the intent-to-treat (ITT) population.

The change from baseline in the total frequency of satisfying sexual activity, summed over Weeks 21-24, was regressed on treatment group, pooled center, baseline average 4 week frequency of satisfying sexual activity, age, and ET route in an ANCOVA analysis. Least squares estimates of the mean 4 week frequency of satisfying sexual activity for the 300 mcg/day testosterone arm and the placebo arm were computed, as were 95% confidence intervals and a p-value testing the null hypothesis of no treatment differences. Secondary models, including possible interactions (e.g., pooled center by treatment), were explored to evaluate consistency of treatment effects across other factors.

To account for subjects who did not complete the 24-week efficacy period of the study and therefore had missing SAL weekly frequencies for Weeks 21-24, a last observation carried forward (LOCF) approach was used. For each patient, the sexual activity corresponding to the last SAL and 3 preceding SALs was used in the analysis. For example, if the last SAL returned from a patient is the Week 23 SAL, then the frequency of sexual activity recorded for weeks 20-23 was used in the analysis. To account for missing weekly assessments within any four-week interval of follow-up, the average of non-missing assessments was imputed for the missing assessment.

The prospectively defined analyses of the primary endpoint were not the same in all studies. The Phase 2b studies used Poisson regression analysis, and the Phase 3 studies used ANCOVA and Wilcox-rank sums (WRS). The WRS was used in the Phase 3 studies to provide appropriate comparisons between 300 mcg/day TTS and placebo in cases where the ANCOVA assumptions were violated. Because a few influential outliers occurred in Study 2001134, WRS was conducted for cross-study comparisons, in addition to ANCOVA. All efficacy analyses are based on the change from baseline in the total satisfying sexual activity at Week 24, using the ITT population and a LOCF approach.

4 CLINICAL TRIAL OUTCOMES

4.1 ENROLLMENT

Phase 3 Study 2001133 enrolled 562 subjects in the U.S., Canada, and Australia (52 clinical sites). A total of 451 (80%) subjects completed the efficacy and safety period through Week 24. Of these subjects, 449 participated in the 28-week open label period and 380 (85%) completed through Week 52. Phase 3 Study 2001134 enrolled 533 subjects in the U.S., Canada, and Australia (51 clinical sites). A total of 418 (78%) subjects completed through Week 24. Of these subjects, 388 (93%) participated in the 28-week open label period and 261 (67%) of the 388 completed through Week 52 (see Table 4).

Table 4 Phase 3 Trial Enrollment and Completion

Study Week	Study 2001133		Study 2001134		Totals
Blinded Phase	N	%	N	%	
0 (Enrollment)	526	100%	533	100%	1,059
24 (Completion)	451	86%	418	78%	869 (82%)
Open Label Phase					
24 (Enrollment)	449	100%	388	100%	837
52 (Completion)	380	85%	261	67%	641 (77%)

4.2 DEMOGRAPHIC DATA - COMBINED TRIALS

Demographics were similar across between the placebo and TTS groups. In the 4 trials combined (Phase 2b and 3 studies, see Table 2) the following baseline demographic and anthropometric data were observed among the 1,401 subjects:

1. Age: mean 49 (7.5 SD); median 49; Min-Max 26-70
2. Age distribution: 10% were 30-39; 41% were 40-49, 41% were 50-59; 6% 60-64
3. Race: 89% Caucasian; 6% African American; 3% Hispanic
4. Geography: 89% U.S.; 3% Canada; 4% Europe; 4% Australia
5. Marital status: 87% married to partner; 13% not married
6. Duration of relationship with partner (years): mean 18.6 (11.35 SD); median 17; Min-Max 1-54
7. Baseline weight (kg): mean 73.1 (15.3 SD); median 71; Min-Max 40.6-153.6
8. Baseline height (cm): mean 163.8 (6.38); median 163; Min-Max 132-183
9. Body Mass Index: mean 27.2 (5.51); median 26; Min-Max 17-58
10. Estrogen therapy route: 77% oral; 23% transdermal
11. Age at hysterectomy: mean 39.6(7.9); median 40; Min-Max 17-66
12. Age at oophorectomy: mean 40.4 (7.8); median 41; Min-Max 17-66
13. Years since surgery: ~9 (7.2); median 7-8; Min-Max 0.5-42.5
14. Tobacco use: 53% never; 30% previously; 17% currently
15. Alcohol use: 22% never; 4% previously; 73% currently

Division comment:

- **The population in this study reflects the age group who has undergone hysterectomy in the U.S., but African American women are dramatically underrepresented in the study populations. Data from the MMWR Hysterectomy Surveillance – United States, 1994-1999 reported by Keshavarz H, et al, found that women aged 40-44 had the highest**

hysterectomy rate compared to other age groups – 52% of hysterectomies were performed in women <45 years of age. Fifty-five percent of women in the U. S. who had a hysterectomy had a bilateral oophorectomy. When age and race were examined together, the group with the highest rate of hysterectomy was African American women aged 40-44 years – 16.8 per 1,000, compared to 10.8 per 1000 in the same age group of white women.

4.3 DISCONTINUATION (WITHDRAWAL) RATES

Studies combined: A total of 1401 subjects (704 in the placebo group; 697 in the 300 mcg/day TTS group) were enrolled in Studies 2001133 (Phase 3), 2001134 (Phase 3), 1999068 and 1999092 (both Phase 2). A similar percentage of subjects in the two treatment groups completed these studies through Week 24. A total of 309 (22%) subjects were discontinued during the 24-week double blind period. The most common reasons for discontinuation were AEs (8% each) and voluntary withdrawals (7% placebo, 9% TTS) (see Table 5). Discontinuation for adverse events will be discussed in more detail in Section 5.3.1.1 of this document.

Table 5 Subject Disposition: Combined Data from Four Double Blind Studies with 24 Weeks of Testosterone Exposure

Category	Placebo (N=704) n (%)	TTS (N=697) n (%)	Overall (N=1401) n (%)
Randomized To Treatment			
Completed	548 (78%)	544 (78%)	1092 (78%)
Discontinued	156 (22%)	153 (22%)	309 (22%)
Reason For Discontinuation			
Adverse Event	59 (8%)	57 (8%)	116 (8%)
Protocol Violation	7 (1%)	12 (2%)	19 (1%)
Voluntary Withdrawal	51 (7%)	62 (9%)	113 (8%)
Investigator Recommended	5 (1%)	1 (<1%)	6 (<1%)
Lost to Follow-Up	32 (5%)	21 (3%)	53 (4%)
Unable to Meet Protocol Criteria	2 (<1%)	0 (0%)	2 (<1%)

Individual studies: When compared among the individual studies, a similar percentage of subjects (within 1-2%) in each treatment group in each trial withdrew due to the 6 reasons listed above. The only exception was in Study 2001133 where a lower percentage of subjects on placebo (12/279= 4%) voluntarily withdrew (not due to an AE) as compared to the TTS subjects (26/283= 9%).

Discontinuation over time: No increases in the rate of patient withdrawals in the 4 combined studies were observed with increased duration of exposure to 300 mcg/day TTS when comparing each 4-week time period during the 24-week studies. The percentage of subjects who withdrew from each of the studies was similar between the two treatment groups for each 4-week period. For each 4-week period, the range was 3.1-5.5% for placebo and 3.0-4.3% for TTS. Similar results were observed when time to withdrawal was compared between the two individual Phase 3 studies.

4.4 EFFICACY OUTCOMES

4.4.1 Baseline Findings

Mean scores at baseline: The overall mean scores at baseline in the two phase 2 and two phase 3 studies for the SAL 4-week frequency of total satisfying sexual events (3.0), PFSF sexual desire (21.2), and personal distress (64.5) were consistent with mean scores from other studies with women who considered themselves to have few satisfying sexual activities, low sexual desire, and were distressed about their lack of sexual desire. Baseline disease severity as judged by the three main endpoints (satisfying sexual events, distress scores, and desire scores) was similar between the active and placebo treatment groups across the four studies.

Division comment:

- **Data collected by the Applicant early in the development program in 2000 during the time of the initial 3 instrument validation studies showed on average 3-4 total satisfying sexual episodes (SSEs) per 4 weeks in women with HSDD [N= 347] in Europe, the U.S. and Canada compared with "normal" age-matched controls [N= 260] who reported 10-12+ SSEs per 4 weeks. The sexual desire score associated with HSDD was 30 ± 5 (0-100 range) and with normal controls was 60 ± 5. The personal distress score (0-100 range) was 55 ± 5 in women with HSDD and 5 ± 2 in age-matched controls.**
- **It is of note that a PFSF sexual desire score of 21 corresponds, on average, to "seldom" having an interest in sexual activity, and that a PDS score of 65 corresponds, on average, to being "often" distressed about the lack of interest in sexual activity.**

Estrogen formulations used: Overall, 77% of the subjects in the combined studies were taking concomitant oral estrogen therapy (ET) and 23% were receiving concomitant transdermal ET. Subjects who participated in Studies 2001133 and 2001134 used either oral or transdermal ET. Subjects in Study 1999068 used concomitant oral ET, whereas subjects in Study 1999092 used concomitant transdermal ET only. Of the 1,075 subjects on oral ET, the percentage of subjects taking higher dose oral ET (defined by the Applicant as >0.625 mg Premarin or its equivalent) was 48% and those on higher dose transdermal ET (defined by the Applicant as >0.05 mg) was 54%. The remaining subjects were receiving lower dose oral or transdermal ET. In the oral estrogen therapy group, the percentage of subjects taking conjugated equine estrogen (63%) and non-conjugated equine estrogen (37%) was also similar between the two treatment groups in the 3 studies using oral ET. The next most commonly used form of concomitant ET was estradiol.

Division comment:

- **A significant percentage of subjects were using higher doses of estrogen. Current guidelines recommend use of the lowest effective dose of estrogen. It is unclear whether women in these studies were on the lowest effective dose of estrogen for them as individuals.**

4.5 PRIMARY EFFICACY OUTCOME (TOTAL SSES AT WEEK 24)

The primary endpoint was the change in SSEs (sum of the SAL Question 3 and 6 - satisfying sexual activity with or without intercourse).

A discussion and analysis of the efficacy results follows, with results from the 4 individual studies shown first, followed by Figures (bar graphs) of the individual and combined results shown together.

Division comment:

- **The Division statistician found the analysis plan to be acceptable.**

Table 6 Number of Satisfactory Sexual Events

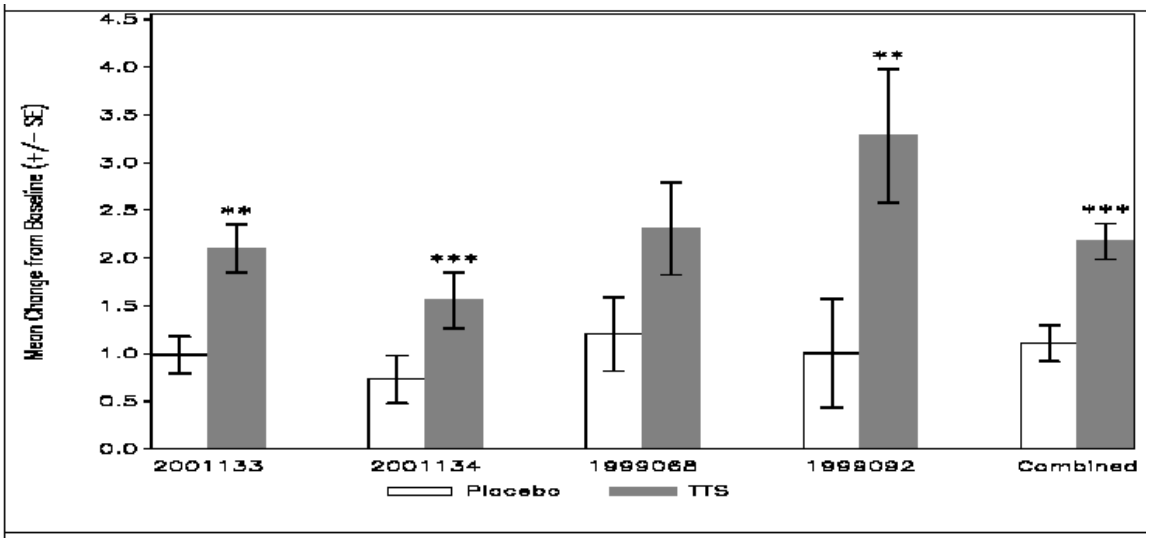
Study Number (Number of subjects)	Testosterone dose (mcg/day)	Baseline Mean[a]	Mean Change from Baseline at Week 24[a,b]	Efficacy Analysis Method	Results p-value
Frequency of Total Satisfying Sexual Episodes (SSEs)					
Phase 3 trials					
2001133 (N=562)	0 (placebo)	2.94	0.98	ANCOVA	p=0.0003
	300	2.82	2.13		
2001134 (N=532)	0 (placebo)	3.19	0.73	Wilcoxon Rank Sum[b]	p=0.0010
	300	3.04	1.56		
Phase 2 trials					
1999068* (N=229)	0 (placebo)	2.8	1.20	Poisson Regression	p=0.0493
	300	2.92	2.32		
1999092* (N=76)	0 (placebo)	3.20	1.12	Poisson Regression	p=0.0641
	300	2.08	3.08		

* Source: E-Table 4, ISE.
[a] The frequency of SSEs was based on data from the SAL from baseline and the last 4 recorded weeks.
[b] Mean change from baseline adjusted for age, estrogen therapy route, pooled centers, and baseline value.

To be evaluable for efficacy, a subject had to receive at least 8 weeks of blinded treatment. The table above shows the mean change from baseline in the SSEs for the last recorded 4-week period of time. In both Phase 3 studies (2001133 and 2001134), compared with placebo, subjects treated with 300 mcg/day TTS had an increase in the frequency of total SSEs.

Mean changes from baseline on 300 mcg/day TTS and placebo are shown in Figure 1.

Figure 1 Change from Baseline in 4-week Frequency of SSEs at Week 24



Data for individual studies shown corresponds to the mean change from baseline (±) 1 standard error (SE). Data for combined studies corresponds to mean change from baseline adjusted for study (±) 1 standard error. ** =p<0.01; ***=p<0.001 based on analysis of covariance (ANCOVA) model for combined studies and Wilcoxon Rank-Sum (WRS) test for individual studies.

Division comment:

- **The crucial question is the clinical significance of the change with active treatment yielding, on average, one more satisfying sexual event per 4 weeks compared to placebo.**

4.6 PRINCIPAL SECONDARY ENDPOINTS

The most important secondary endpoints were the decrease in the personal distress score of the PDS and the increase in the sexual desire domain of the PFSF.

Division comment:

- **Experts in the field consider that both an increase in sexual desire and a decrease in personal distress are necessary components of a clinically meaningful HSDD treatment.**

4.6.1 Change in Personal Distress

The PDS measures personal distress associated with subjects' low desire for, and lack of interest in, sex. The PDS instrument contains 9 items in a single domain. Subjects filled out the questionnaire based on their experiences and feelings over the preceding 30 days. (See Section 2.4.) A decrease in the PDS score indicates a decrease in a patient's distress.

Across the two Phase 3 trials, the baseline score for distress ranged from 62.57 to 66.38 for the placebo group and from 64.78 to 66.61 for the TTS group, which corresponds to an average answer of "often" being distressed for the 9 questions (see Table 7). The Least-Squares Means difference between the change in placebo and TTS scores was approximately 7.3.

Division comment:

- **The Applicant reports that women without HSDD have a score of 5 ± 2 on this scale.**

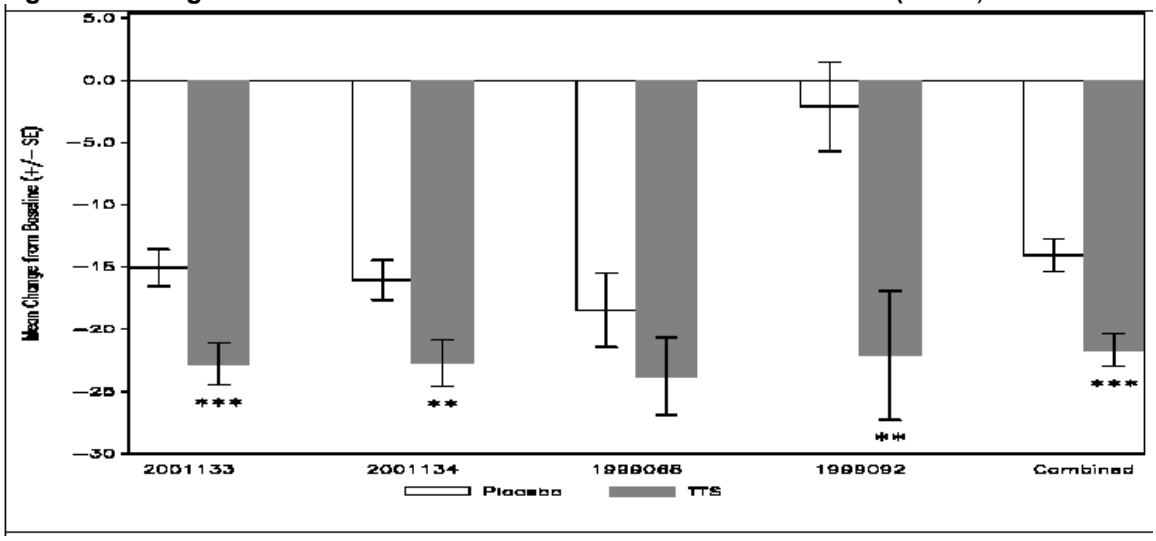
Table 7 Change in Personal Distress Scores

Study Number	Testosterone dose (mcg/day)	Baseline Mean[a]	Mean Change from Baseline at Week 24[a,b]	Efficacy Analysis Method	Results p-value
Personal Distress Score					
Phase 3 studies					
2001133	0	62.57	-16.31		
(N=562)	300	64.78	-23.55	ANCOVA	p=0.0006
2001134	0	66.38	-18.27		
(N=532)	300	66.61	-24.34	ANCOVA	p=0.0091
Phase 2 trials					
1999068*	0 (placebo)	64.71	-18.46		
(N=229)	300	65.39	-23.76	ANCOVA	p=0.1258
1999092*	0 (placebo)	56.73	-2.11		
(N=76)	300	57.14	-22.10	ANCOVA	p=0.0025

[a] Range for distress score is 0-100.
[b] Mean change from baseline adjusted for age, estrogen therapy route, pooled centers, and baseline value.

The changes from baseline in the PDS score at Week 24 for the four individual studies and the studies combined are shown in Figure 2.

Figure 2 Change from Baseline in Personal Distress Scale at Week 24 (LOCF)



Data for individual studies shown corresponds to the mean change from baseline (±) 1 standard error. Data for combined studies corresponds to mean change from baseline adjusted for study (±) 1 standard error. ** = p<0.01; *** = p<0.001 based on analysis of covariance (ANCOVA) model.

Division comment:

- **The difference in mean reduction in the distress scores in the TTS treated subjects compared to those in the placebo group correspond to less than an average change of one unit on the PDS questionnaire's response scale (range 1 to 6).**

4.6.2 Change in Sexual Desire

Change in desire was assessed using the Desire domain of the PFSF (see Section 2.4). Subjects were instructed that feelings could be either mental or physical and could occur in the absence of sexual activity. Their responses were to reference the past 30 days.

Division comment:

- **The Applicant reported that women without HSDD had a score of 60 ± 5 for this domain.**

Across the two phase 3 trials, the baseline score for sexual desire ranged from 20.82 to 23.37 for the placebo group and from 19.79 to 21.67 for the active treatment group. This generally corresponds with an average answer of "seldom" for the 9 items in the desire domain.

Table 8 Change in Sexual Desire Score

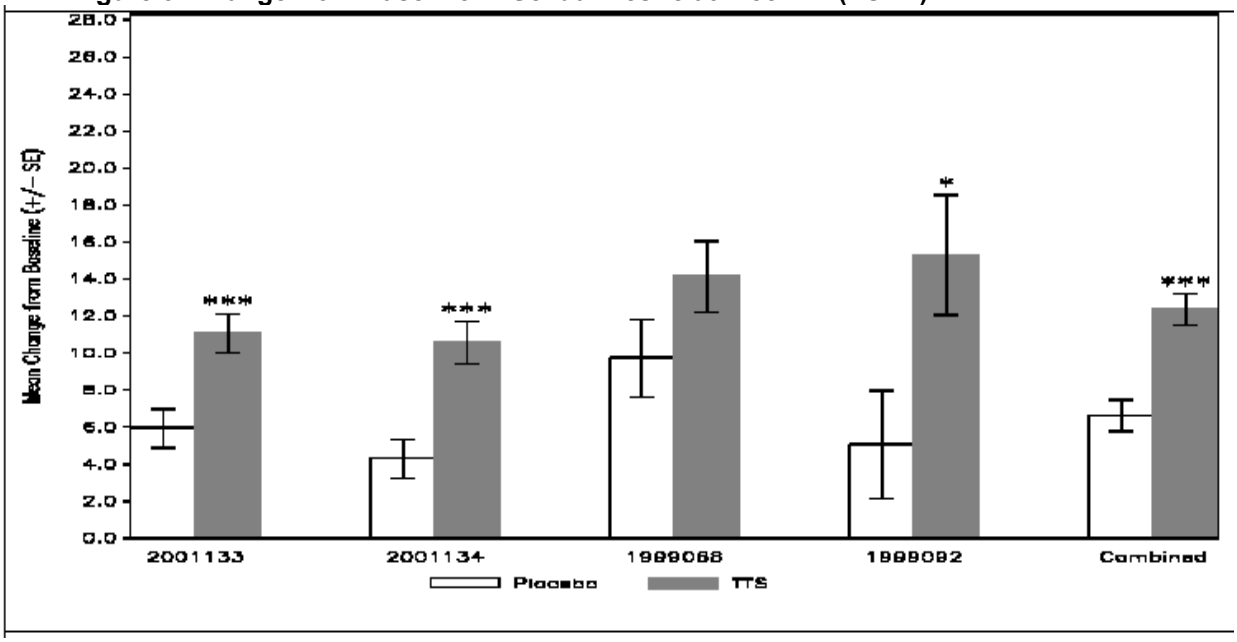
Study Number	Testosterone dose (mcg/day)	Baseline Mean[a]	Mean Change from Baseline at Week 24[a,b]	Efficacy Analysis Method	Results p-value
Phase 3 trials					
2001133	0 (placebo)	20.82	6.90	ANCOVA	p=0.0006
(N=562)	300	19.79	11.85		
2001134	0 (placebo)	23.37	6.21	ANCOVA	p=0.0006
(N=532)	300	21.67	11.38		
Phase 2 trials					
1999068*	0 (placebo)	20.14	8.38	ANCOVA	p=0.0498
(N=229)	300	20.94	13.67		
1999092*	0 (placebo)	19.89	5.98	ANCOVA	p=0.0214
(N=76)	300	23.12	16.43		

*Source: E-Table 5, ISE.

[a] Range for sexual desire score is 0-100.
[b] Mean change from baseline adjusted for age, estrogen therapy route, pooled centers, and baseline value.

The changes from baseline in the PFSF Desire domain score at Week 24 for the four individual studies and the studies combined are shown in Figure 3.

Figure 3 Change from Baseline in Sexual Desire at Week 24 (LOCF)



Data for individual studies corresponds to mean change from baseline (±) 1 standard error (SE).
Data for combined studies corresponds to mean change from baseline adjusted for study (±) 1 standard error.
* = p<0.05; *** = p<0.001 based on analysis of covariance (ANCOVA) model. LOCF= last observation carried forward.

Division comment:

- **The clinical significance of the increase with active treatment yielding, on average, an increase of only 5-6 points more than placebo on a scale of 100 is unknown.**

4.7 SUMMARY OF PHASE 3 EFFICACY FINDINGS

An overview of the results for the primary and two most important secondary efficacy endpoints for the two phase 3 clinical trials can be found in Table 9.

Table 9 Changes in Frequency of SSEs, and Sexual Desire and Personal Distress Scores

Endpoint Study Number	Testosterone dose (mcg/day)	Baseline Mean[a]	Mean Change from Baseline at Week 24[a,b]	Efficacy Analysis Method	Results p-value
Frequency of Total SSEs					
2001133	0	2.94	0.98	ANCOVA	p=0.0003
	300	2.82	2.13		
2001134	0	3.19	0.73	Wilcoxon Rank Sum[b]	p=0.0010
	300	3.04	1.56		
Sexual Desire Score [range 0 to 100]					
2001133	0	20.82	6.90	ANCOVA	p=0.0006
	300	19.79	11.85		
2001134	0	23.37	6.21	ANCOVA	p=0.0006
	300	21.67	11.38		
Personal Distress Score [range 0 to 100]					
2001133	0	62.57	-16.31		
	300	64.78	-23.55	ANCOVA	p=0.0006
2001134	0	66.38	-18.27		
	300	66.61	-24.34	ANCOVA	p=0.0006

[a] For frequency of total satisfying sexual 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. For frequency of total satisfying episodes in Study 2001134, 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.

4.8 SECONDARY ANALYSES OF PRIMARY AND PRINCIPAL SECONDARY ENDPOINTS

4.8.1 Responder Analyses

The Applicant conducted a responder analysis for the primary efficacy endpoint of SSEs and the secondary endpoint of change in the desire score. The definition of a response was based upon the Applicant's findings from Study CMK#US030993, which was designed to identify the minimally important clinical difference (MICD) (see Section 4.10).

4.8.1.1 Applicant-Defined Responder Analyses

Change in Satisfactory Sexual Events Based on the findings of Study CMK#US030993, the Applicant concluded that an increase of 1.1 events per four weeks was the minimally important clinical difference. The responder analysis based on this MICD value of > 1 SSE per four weeks is shown in Table 10 below. For each of the studies, a greater proportion of subjects in the TTS groups were identified as having a positive response to treatment. In the two phase 3 studies, the difference in response rate between TTS and placebo groups ranged from approximately 11 to 17%.

Table 10 Responder Analysis for Change in SSEs at Week 24

Study	Placebo Sample/responders (% responders)[A]	TTS Sample/responders (% responders)
2001133	273/95 (34.8%)	276/126 (45.7%)
2001134	255/64 (25.1%)	258/109 (42.2%)
1999068	112/43 (38.4%)	108/55 (50.9%)
1999092	37/10 (27.0%)	35/22 (62.9%)
Combined	**677/212 (31.3%)**	**677/312 (46.1%)**

The LOCF analysis at Week 24 was based on responses recorded on the last SAL evaluated.
The sample is the number of subjects with baseline and Week 24 (LOCF) responses.
[A] A responder is a patient with a change from baseline in their **total SSEs of > 1 episode.**

Change in Sexual Desire Based on the findings of Study CMK#US030993, the Applicant concluded that an increase of ≥ 8.9 points on a scale of 1 to 100 on the Desire domain of the PFSF was the minimally important clinical difference. The responder analysis based on this MICD value of ≥ 8.9 points is shown in Table 11 below. For each of the studies, a greater proportion of subjects in the TTS groups were identified as having a positive response to treatment. In the two phase 3 studies, the difference in response rate between TTS and placebo groups ranged from approximately 15 to 17%

Table 11 Responder Analysis for Change in Sexual Desire at Week 24

Study	Placebo Sample/responders (% responders)[A]	TTS Sample/responders (% responders)
200113	269/93 (34.6%)	269/138 (51.3%)
200134	257/87 (33.9%)	252/124 (49.2%)
1999068	101/40 (39.6%)	102/55 (53.9%)
1999092	35/15 (42.9%)	34/18 (52.9%)
Combined	**662/235 (35.5%)**	**657/335 (51.0%)**

The LOCF analysis at Week 24 was based on responses recorded on the last PFSF evaluated.
The sample is the number of subjects with baseline and Week 24 (LOCF) responses.
[A] A responder is a patient with a change from baseline in their **sexual desire score ≥ 8.89**.

4.8.1.2 FDA-Requested Responder Analysis

Distribution of Changes from Baseline in SSEs The Division requested a post hoc analysis showing the distribution of changes from baseline in SSEs in the placebo and TTS groups in the two Phase 3 trials. The results are shown in Table 12.

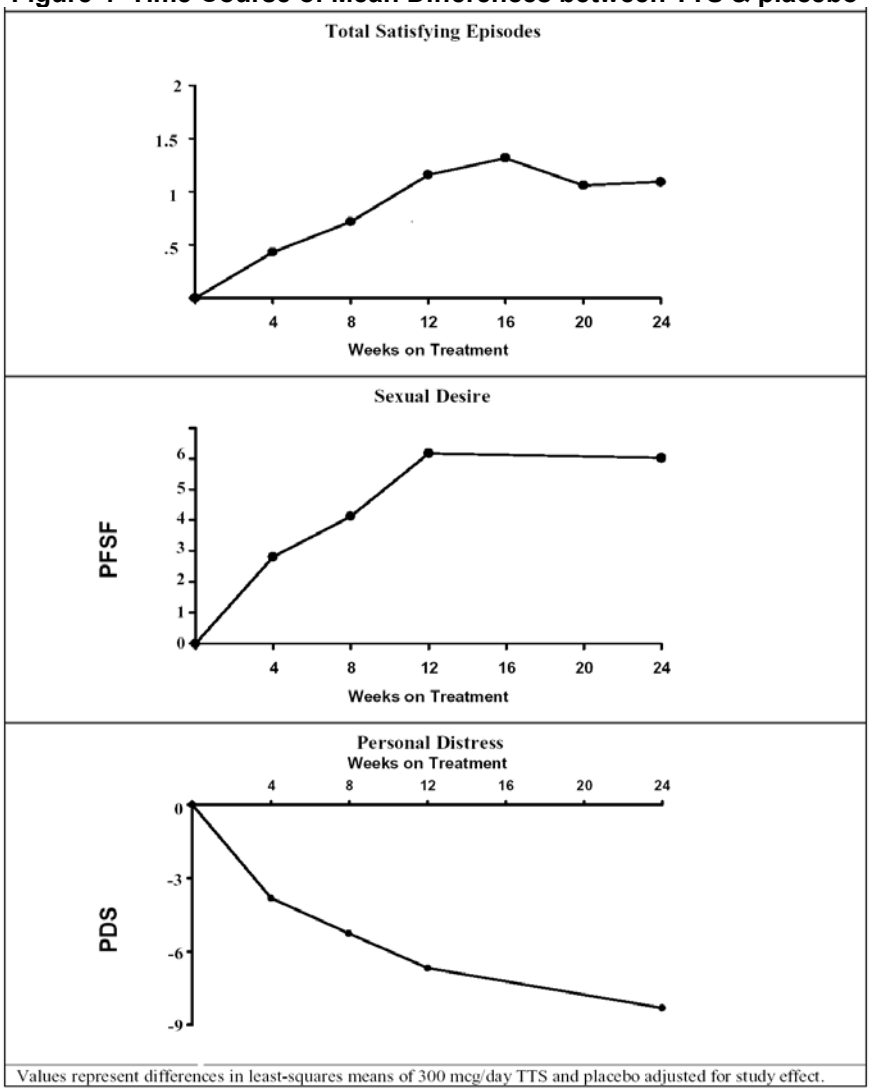
Table 12 Distribution of Changes from Baseline in SSEs

	Study 2001133		Study 2001134	
Change category (Increase in SSEs)	Placebo (N=273) n (%)	TTS (N=276) n (%)	Placebo (N=255) n (%)	TTS (N=258) n (%)
< 0 SSE	90 (33.0)	73 (26.4)	105 (41.2)	83 (32.2)
0 to <1.0	70 (25.6)	57 (20.7)	62 (24.3)	46 (17.8)
1 to <2.0	44 (16.1)	35 (12.7)	30 (11.8)	40 (15.5)
2 to <3.0	17 (6.2)	26 (9.4)	17 (6.7)	16 (6.2)
3 to <4.0	15 (5.5)	21 (7.6)	10 (3.9)	19 (7.4)
4 to <5.0	11 (4.0)	21 (7.6)	11 (4.3)	13 (5.0)
≥ 5	26 (9.5)	43 (15.6)	20 (7.8)	41 (15.9)
n (%) = number and percentage of women in category; N = sample size				

4.8.2 Onset of Treatment Effects:

Overall, maximal mean differences between placebo and TTS treated subjects for SSEs and sexual desire were observed by 12 weeks and were maintained to 24 weeks. Mean differences between placebo and TTS treated subjects in distress continued to decline over the 24-week treatment period. Figure 4 below combines findings from Studies 2001133 and 2001134.

Figure 4 Time Course of Mean Differences between TTS & placebo



4.9 PERSISTENCE OF TREATMENT EFFECT

The persistence of treatment effects was assessed during a 13-week double blind follow-up period (Weeks 53-65) of Studies 2001133 and 2001134. All subjects who completed both the 24 week double blind placebo-controlled phase and the subsequent 28 week open label TTS phase of the two phase 3 trials were offered the opportunity to participate in a study to evaluate persistence of treatment effect. Subjects who agreed to participate were asked a set of questions about their response to treatment during the previous 28-week open label period. The subset of subjects who responded positively to specific questions, including having experienced an increase in desire for sexual activity and an increase in satisfying sexual activity compared with before entering the study, were randomized in a 1:1 ratio to receive placebo or TTS in a double-blind manner for 13 weeks. Sex therapists conducted follow-up telephone interviews with these subjects between Weeks 63 and 65 to assess persistence of treatment effect. Of the 205 subjects enrolled, 199 (97%) completed interviews.

The primary endpoint in this study was the sex therapists' assessment of a "noticeable decrease" in desire for sexual activity during the 13 week treatment period. A higher percentage of women

in the placebo group compared with TTS [62.7% vs. 43.3%] reported a "noticeable decrease" in desire for sexual activity during the 13 week study. In addition, a higher percentage of women in the placebo group compared to the TTS group [47.1% vs. 25.8%] reported experiencing a decrease in the frequency of SSEs. (See Table 13.)

Table 13 Persistence of Treatment Effect

Question	Placebo		TTS	
	n/N	%	n/N	%
Noticeable Decrease in Desire for Sexual Activity (Therapist)	64/102	62.7	42/97	43.3
Noticeable Decrease in Desire for Sexual Activity (Patient)	64/102	62.7	42/97	43.3
Noticeable Decrease in Overall Clinical Benefit (Therapist)	62/102	60.8	45/97	46.4
Noticeable Decrease in Overall Clinical Benefit (Patient)	64/102	62.7	40/97	41.2
Noticeable Decrease in Satisfying Sexual Activity (Patient)	48/102	47.1	25/97	25.8
Noticeable Decrease in Desire to Initiate Activity (Patient)	61/102	59.8	37/97	38.1
Noticeable Decrease in Anticipation of Sexual Activity (Patient)	55/102	53.9	32/97	33.0
N= number of subjects with interviews; n= number of subjects with noticeable decrease % = n/N, percentage of subjects with the finding				

Division comment:

- **The goal of the randomized discontinuation study was to assess the dependence of the apparent treatment effect upon continuation of active therapy. In order to assess this meaningfully, the same efficacy assessments should be employed as were used in the efficacy studies. Use of different assessment tools and endpoints by the Applicant makes interpretation of the results difficult.**

4.10 STUDY CMK#US030993 (MINIMALLY IMPORTANT CLINICAL DIFFERENCES)

A clinical relevance study was designed by the Applicant to investigate the subjects' perspective on the results of their study treatment during the blinded portion of studies 2001133 and 2001134. The primary objectives of the clinical relevance study were to determine whether subjects experienced benefits of study treatment that they considered meaningful, and to define the magnitude of changes in selected clinical endpoints that were associated with a meaningful treatment benefit as defined by the women themselves.

The study data came from a subset of women from the two Phase 3 efficacy studies. A series of 132 one-on-one patient interviews were conducted by one trained, experienced female interviewer using a structured interview guide that contained both open-ended and fixed-response (yes/no or scaled-response) questions. All interviews were conducted no later than 2 weeks after subjects completed or exited double blind treatment. The subjects, interviewer, study site personnel, and the Applicant representatives who observed interviews or analyzed clinical data all remained blinded to the treatment assignments (active or placebo). Baseline demographics and disease severity in this subset were representative of the entire group of women in the Phase 3 studies.

The primary assessment in the clinical relevance study was based on the subjects' answers (yes or no) to the following question, which was asked with reference to their 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?"

Subjects were dichotomized based on their answer to the above question. For each of the two groups, the mean and median changes from baseline in the three study endpoints (satisfying sexual activity [SSEs], personal distress, and sexual desire) were determined (see Table 14). Of the 54 subjects reporting a meaningful benefit, 39% had received placebo and 61% TTS treatment. Among placebo subjects, 31% reported they had a meaningful benefit; among TTS subjects, 52% reported a meaningful benefit.

Table 14 Changes from Baseline in TTS and Placebo Subjects Combined Based on the Subject's Assessment of Clinical Benefit

Parameter	Experienced meaningful benefit?	N (%) 132 (100%)	Change from baseline in 4-week frequency*			
			Mean	Median	Minimum	Maximum
SSEs	Yes	54 (41.2%)	4.4	2.26	-1.7	25.0
	No	77 (58.8%)	0.5	0.0	-5.9	16.3
Distress Score	Yes	54 (40.9%)	-36.5	-34.3	-100	28.6
	No	78 (59.1%)	-8.8	-8.57	-51.4	45.7
Desire Score	Yes	54 (40.9%)	21.0	16.7	-17.8	66.7
	No	78 (59.1%)	2.9	2.22	-33.3	44.4

*Interview population (N= 132): change from baseline in given parameter at Week 24
Mean baseline values for all subjects in the Phase 3 trials were: SSEs= 3.0; Distress score=65.1; Desire score = 21.4

For the 3 endpoints examined, there was a range of changes from baseline and there was overlap between subjects who reported a meaningful overall benefit and subjects who reported no meaningful overall benefit. However, all 3 endpoints in subjects who reported an overall meaningful benefit showed mean and median changes from baseline that were numerically greater than those in subjects who reported no meaningful benefit.

Patient responses in this study were used to define a minimally important clinical difference (MICD) from baseline in total satisfying activity (SSEs) and desire scores. Using Receiver Operating Characteristics (ROC) analysis, the MICDs were defined as the values that best dichotomized subjects on the basis of reported meaningful benefit. The MICDs determined by the Applicant were:

- an increase of > 1.0 in satisfying sexual events per 4 weeks
- an increase of ≥8.9 in sexual desire score
- a decrease of at least 20 points in distress score

These responder definitions were applied to the Phase 3 results to examine the differences between the percentages of responders on TTS treatment and placebo (see Section 4.8.1).

Division's comment:

- **Small differences in outcomes between active and placebo treatment groups may be statistically significant yet clinically unimportant. Making this distinction is particularly important, and often quite difficult, for outcomes based on health-related quality of life endpoints. The design and interpretation of studies to identify minimally important clinical difference (MICDs) can be difficult and fraught with problems. Experts in the development, validation, and interpretation of instruments to determine MICDs may not agree with:**

  - The appropriateness of the design of Study CMK#US030993,
  - The Applicant's interpretation of the study findings, and/or
  - The Applicant's values for the MICDs for the primary and principal secondary efficacy endpoints.

4.11 SUMMARY OF EFFICACY AND RELATED ISSUES

The clinical development program by the Applicant followed the May 2000 FDA Draft Guidance for industry for products being developed for a female sexual dysfunction indication. Two Phase 3 trials were conducted in a patient population of surgically menopausal women with HSDD. The primary endpoint was the change in the number of satisfactory sexual episodes (SSEs), and the two key secondary endpoints were the change in sexual desire and personal distress scores. Three instruments were developed to record and measure the efficacy endpoints.

Changes in the primary and secondary endpoints are summarized in Table 15.

Table 15 Changes in Frequency of SSEs, and Sexual Desire and Personal Distress Scores

Endpoint Study Number	Testosterone dose (mcg/day)	Baseline Mean[a]	Mean Change from Baseline at Week 24[a,b]	Efficacy Analysis Method	Results p-value
Frequency of Total SSEs					
2001133	0	2.94	0.98	ANCOVA	p=0.0003
	300	2.82	2.13		
2001134	0	3.19	0.73	Wilcoxon Rank Sum[b]	p=0.0010
	300	3.04	1.56		
Sexual Desire Score [range 0 to 100]					
2001133	0	20.82	6.90	ANCOVA	p=0.0006
	300	19.79	11.85		
2001134	0	23.37	6.21	ANCOVA	p=0.0006
	300	21.67	11.38		
Personal Distress Score [range 0 to 100]					
2001133	0	62.57	-16.31		
	300	64.78	-23.55	ANCOVA	p=0.0006
2001134	0	66.38	-18.27		
	300	66.61	-24.34	ANCOVA	p=0.0006

[a] For frequency of total satisfying sexual 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. For frequency of total satisfying episodes in Study 2001134, 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.

Division comment:

- **Although all these differences were statistically significant, it is unknown whether they are clinically meaningful.**

5 SAFETY

5.1 OVERVIEW OF SAFETY CONCERNS WITH TESTOSTERONE

In the aftermath of the Women's Health Initiative (WHI) studies[1,2] of the risks and benefits of estrogen and combined estrogen and progestin therapy in postmenopausal women, use of hormone therapy in this population is subject to heightened scrutiny. The fact that the results of these relatively long-term, randomized, double-blind, placebo-controlled trials were at variance with data provided by a number of observational studies suggests that short-term or uncontrolled studies may not provide adequate estimates of the risks of hormonal therapy in postmenopausal women.

The proposed indication, for use in surgically menopausal women receiving concomitant estrogen therapy, raises two important issues that should be considered:

1. Women who take this product will be on estrogen, the duration and safety of which must be examined in light of the WHI estrogen-only study in women status post hysterectomy.
2. Another hormone, testosterone, will be added to estrogen. In the second WHI study, the addition of progesterone to estrogen increased the risk of breast cancer and cardiovascular effects. It is unknown whether the addition of a different hormone, testosterone, might have similar or unanticipated adverse effects.

The literature provides little information about the safety of exposing postmenopausal women to testosterone at doses that produce plasma concentrations that are within or slightly above the range of those normally observed in reproductive aged women. What data are available often concern formulations or dose levels that differ from that achieved by the TTS patch. Nonetheless, potential concerns that have been raised in the literature include:

- Cardiovascular safety – potentially mediated by testosterone's effects on
    - lipids
    - vascular tone
    - plasma viscosity
    - coagulation
    - polycythemia
    - insulin resistance
- Androgenic effects in women
    - acne
    - hirsutism
    - alopecia
    - voice deepening
    - clitoromegaly
- Hepatotoxicity
- Effects on mood and behavior
- Endometrial hyperplasia and cancer
- Breast cancer

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[1] The Women's Health Initiative Steering Committee, Effects of Conjugated Equine Estrogen in Postmenopausal Women with Hysterectomy, JAMA, 291: 1701-12, 2004

[2] Writing Group for the Women's Health Initiative Investigators, Risks and Benefits of Estrogen plus Progestin in Healthy Menopausal Women, JAMA, 288: 321-33, 2002

The safety database for subjects using TTS was examined for evidence of these effects in women treated with testosterone and estrogen therapy.

5.2 OVERVIEW OF SAFETY DATABASE

5.2.1 Studies Included

Integrated safety data from two phase 2 studies (Studies 1999068 and 1999092, hereinafter referred to as 068 and 092, respectively) and two pivotal phase 3 trials (Studies 2001133 and 2001134, hereinafter referred to as 133 and 134, respectively) were reviewed. All four of these studies were 24-week, randomized, double-blind, parallel-group, placebo-controlled trials evaluating the safety and efficacy of a testosterone transdermal delivery system (TTS) in surgically menopausal women with HSDD. Study 068 compared patches that delivered doses of 0 (placebo), 150, 300 or 450 mcg/day when applied twice weekly. Studies 092, 133 and 134 utilized a TTS which administered a daily dose of 300 mcg when applied twice weekly.

Three of the studies continued on as safety extensions: Study 068 as a double-blind, placebo-controlled trial for an additional 28 weeks, and Studies 133 and 134 as open-label active treatment extensions for an additional 28 weeks. Following completion of the first year of these studies, limited additional open-label safety surveillance data have been obtained from subjects from Studies 133 and 134 who continued to use the TTS for an additional 26 weeks beyond the first year, in what is planned to be a two year safety extension. Thus, the primary data available for safety review include:

- A 24 week placebo-controlled phase, which enrolled 1399 subjects (696 on TTS) in four studies
- A 28 week open label phase, which enrolled 837 subjects (all on TTS) from the two phase 3 studies (of these, 418 had been on placebo in the double blind phase and 419 had been on active treatment)
- An ongoing open label safety extension phase (for which data from weeks 52-78 is currently available), which enrolled 321 subjects (all on TTS) from the two phase 3 studies (of these, 167 previously had been treated with TTS for 28 weeks and 154 previously had been treated with TTS for 52 weeks)

An additional special safety study was also reviewed. Study 2003082 was a 24-week, randomized, double-blind, placebo-controlled trial which evaluated effects of the 300 mcg TTS on mammographic breast density and breast epithelial proliferation in naturally menopausal women also taking combined estrogen/progestogens hormone products.

5.2.2 Demographics of Safety Population

Demographic information for subjects from the integrated safety population comprising Studies 068, 092, 133 and 134 are presented in Table 16. Demographic data for the subjects from Studies 133 and 134 who continued into the open label and extension phases indicate that they were representative of the safety population as a whole.

Table 16 Demographic Data for Integrated Safety Population

Parameter	Placebo (N=703)	TTS (N=696)	Overall (N=1399)
Age (years)			
n	703	696	1399
Mean (SD)	49.1 (7.42)	49 (7.59)	49 (7.5)
Median	50	49	49
Min-Max	26-70	28-70	26-70
Age Category			
20-29	6 (1%)	2 (<1%)	8 (1%)
30-39	60 (9%)	74 (11%)	134 (10%)
40-49	276 (39%)	292 (42%)	568 (41%)
50-59	308 (44%)	265 (38%)	573 (41%)
60-64	43 (6%)	47 (7%)	90 (6%)
65+	10 (1%)	16 (2%)	26 (2%)
Race/Ethnicity			
Indian (American)	2 (<1%)	2 (<1%)	4 (<1%)
Asian (Oriental)	2 (<1%)	1 (<1%)	3 (<1%)
Black	48 (7%)	36 (5%)	84 (6%)
Caucasian	625 (89%)	624 (90%)	1249 (89%)
Hispanic	19 (3%)	24 (3%)	43 (3%)
Multi-Racial	1 (<1%)	3 (<1%)	4 (<1%)
Portuguese	1 (<1%)	0 (0%)	1 (<1%)
Unknown	5 (1%)	6 (1%)	11 (1%)
Geography			
United States	627 (89%)	622 (89%)	1249 (89%)
Canada	21 (3%)	22 (3%)	43 (3%)
Australia	28 (4%)	26 (4%)	54 (4%)
Europe	27 (4%)	26 (4%)	53 (4%)
Marital Status			
Married to Partner	616 (88%)	602 (86%)	1218 (87%)
Not Married to Partner	87 (12%)	94 (14%)	181 (13%)
Baseline Weight (kg)			
n	703	695	1398
Mean (SD)	73.7 (15.78)	72.5 (14.79)	73.1 (15.3)
Median	71	70	71
Min-Max	40.6-140	44.1-153.6	40.6-153.6
Baseline Height (cm)			
n	702	694	1396
Mean (SD)	163.8 (6.23)	163.7 (6.54)	163.8 (6.38)
Median	163	164	163
Min-Max	142.2-182.9	132.1-182.8	132.1-182.9

Source: E-Table 3, eff-sum.pdf, p 118-9

5.2.3 Safety Outcomes Evaluated

The four studies provided data on the following safety parameters:

- Adverse events – deaths, serious adverse events, withdrawals due to adverse events, common adverse events
- Androgenic effects – acne, hirsutism, alopecia, voice deepening, clitoromegaly
- Application site reactions (ASRs)
- Impact on estrogen-related effects – hot flushes, breast tenderness
- Laboratory values – serum chemistry, including lipid, renal and hepatic panels, carbohydrate metabolism, hematology and coagulation profile

- Vital signs and weight

Subsets of subjects in Studies 068 and 092 also provided data on the effects of testosterone on total body composition, bone mineral density and markers of bone turnover, platelet aggregation, and vascular reactivity and impedance of blood flow as measured by the vascular pulsatility index. A study in naturally menopausal women provided data on mammographic breast density and breast epithelial proliferation.

5.3 FINDINGS FROM CLINICAL TRIALS

5.3.1 Safety Findings –Testosterone vs. Placebo

5.3.1.1 Adverse Events

Deaths

There was a single death, in a placebo subject in Study 134 during the double blind phase of the study. Death was due to a basal ganglia hemorrhage, which followed a transverse sinus thrombosis that occurred five weeks after enrollment. The thrombosis was treated with enoxaparin, heparin and warfarin, and the patient died suddenly five days later. The transverse sinus thrombosis was judged possibly related to study drug and the basal ganglia hemorrhage was judged doubtfully related.

Serious Adverse Events

The rate of serious adverse events (SAEs) was 2.2% in the TTS group and 2.1% in the placebo group. The most commonly reported SAEs in the TTS group were application site reactions (1.3%) and nasopharyngitis and headache (each 0.9%), and in the placebo group, application site reactions, headache, migraine and back pain (each 0.6%).

Withdrawals due to Adverse Events

Eight percent of subjects in each group withdrew due to adverse events (AEs) in the double blind phase. The most common AEs associated with withdrawal were application site reactions (ASRs) in both groups and hirsutism in the TTS group. AEs in the overall categories of nervous system and psychiatric disorders were also responsible for a number of withdrawals in each group, each accounting for withdrawal of 1-2% of the enrollees. Nervous system disorders resulting in withdrawals included such MedDRA terms as headache, dysphonia, dizziness and transient ischemic attack, and occurred in 14 TTS and 8 placebo subjects. Psychiatric disorders that resulted in withdrawal included such MedDRA terms as anxiety, agitation, aggression and depression, and occurred in 12 TTS and 13 placebo subjects.

Common Adverse Events

Overall, AEs occurred in 76.1% of TTS subjects and 75.8% of placebo subjects. Events occurring at >2% frequency and with a numerically greater incidence in the TTS group are listed in Table 17. Events that occurred most commonly in the TTS group during the double blind phase were acne, upper respiratory infections, hirsutism and headaches. The TTS subjects had a higher proportion of overall AEs reported by the Applicant to be possibly or probably drug-related (26.8% vs. 23.4%), primarily due to greater occurrence of androgenic AEs. AEs that were considered by the Applicant prior to unblinding to be potentially drug-related and that occurred at >2% frequency and with a numerically greater incidence in the TTS group are listed in Table 18.

Table 17 Studies 068, 092, 133 & 134: Most Common Adverse Events (≥ 2%) During Double Blind Phase

Adverse Event	Placebo		TTS	
	N	%	N	%
Total N	703		696	
N with at least one AE	533	75.8	530	76.1
Acne NOS	46	6.5	61	8.8
URI NOS	51	7.3	57	8.2
Hirsutism	35	5.0	49	7.0
Headache	44	6.3	48	6.9
Influenza	20	2.8	20	2.9
UTI NOS	19	2.7	20	2.9
Alopecia	15	2.1	20	2.9
Gastrointestinal & abdominal pains (HLT)	9	1.3	19	2.7
Cough	15	2.1	16	2.3
Migraine NOS	12	1.7	16	2.3
Gastroenteritis viral NOS	13	1.8	15	2.2
Flushing	13	1.8	15	2.2
Hypertension NOS	9	1.3	14	2.0
Influenza-like illness	8	1.1	14	2.0

Note: HLT = Higher Level MedDRA Term, subsuming subheadings; NOS = Not otherwise specified
Source: Based on Table 7, *safety-sum.pdf, pp 75-124*

Table 18 Studies 068, 092, 133 & 134: Adverse Events Considered Possibly or Probably Drug-Related in Double Blind Phase

Adverse Event	Placebo		TTS	
	N	%	N	%
Total N	703		696	
Acne NOS	41	5.8	55	7.9
Hirsutism	33	4.7	49	7.0
Alopecia	14	2.0	17	2.4

Note: HLT = Higher Level MedDRA Term, subsuming subheadings; NOS = Not otherwise specified
ASRs are excluded from this listing.
Source: Based on Table 7, *safety-sum.pdf, pp 75-124*

Among cardiovascular, thrombotic and cancer-related events of interest, there were no MIs in either group during the double blind phase, although one placebo subject reported coronary artery disease as an AE and two TTS subjects reported angina as AEs. There was a cerebral hemorrhage and transverse sinus thrombosis in a placebo subject (the one death in the trial) and a transient ischemic attack (TIA) in a single TTS subject. There was a single DVT in a TTS subject, who had a past history of DVT and Factor V Leiden. There was a single case of breast cancer in the placebo group.

5.3.1.2 Androgenic Effects

In addition to assessing AE reports of androgenic effects, systematic ascertainment was made of several individual androgenic effects. At baseline, and Weeks 12, 24, 36 and 52, assessments at the lip and chin for increased hair were made, with scoring done according to the facial portion of the Lorenzo Pictorial Rating Scale (rated from 0-4), and assessment of facial acne was assessed on a 0-3 scale developed by Palatsi et al. Subjects were also asked at these visits about frequency of depilation. In addition, subjects were queried about voice changes or changes in scalp hair at Weeks 4, 24 and 52.

Hirsutism, acne and alopecia were the primary manifestations of androgenic effects noted in the trial subjects. Other events of concern include voice deepening (dysphonia or hoarseness), clitoromegaly and potential psychiatric effects (increased aggression, agitation or irritability).

The frequency of androgenic AEs during the double blind phase was higher in the TTS group (17.7%) than the placebo group (14.4%), primarily due to higher rates of acne and hirsutism (see Table 19). TTS subjects were also more likely to experience multiple androgenic AEs and to withdraw due to these AEs.

Table 19 Studies 068, 092, 133 & 134: Androgenic AEs in Double Blind Phase

Parameter	Placebo (N=703)		TTS (N=696)	
Number of adverse events (AEs)	123		163	
Mean number of AEs/patient	0.2		0.2	
Mean number of AEs/patients with AEs	1.2		1.3	
Patients[a]				
With Any AEs	101	(14.4%)	123	(17.7%)
Acne	49	(7.0%)	63	(9.1%)
Alopecia	19	(2.7%)	24	(3.4%)
Hirsutism	35	(5.0%)	49	(7.0%)
Voice Deepening	12	(1.7%)	16	(2.3%)
With One Type of AE	88	(87.1%)	98	(79.7%)
Acne Only	41	(40.6%)	48	(39.0%)
Alopecia Only	14	(13.9%)	10	(8.1%)
Hirsutism Only	28	(27.7%)	33	(26.8%)
Voice Deepening Only	5	(5.0%)	7	(5.7%)
With Two Types of AEs	12	(11.9%)	23	(18.7%)
Acne and Alopecia	1	(1.0%)	5	(4.1%)
Acne and Hirsutism	3	(3.0%)	7	(5.7%)
Acne and Voice Deepening	3	(3.0%)	1	(0.8%)
Alopecia and Hirsutism	2	(2.0%)	4	(3.3%)
Hirsutism and Voice Deepening	1	(1.0%)	3	(2.4%)
Alopecia and Voice Deepening	2	(2.0%)	3	(2.4%)
With Three Types of AEs	1	(1.0%)	0	(0.0%)
Acne, Alopecia and Hirsutism	0	(0.0%)	0	(0.0%)
Acne, Hirsutism and Voice Deepening	1	(1.0%)	0	(0.0%)
Alopecia, Hirsutism and Voice Deepening	0	(0.0%)	0	(0.0%)
With Four Types of AEs	0	(0.0%)	2	(1.6%)
Who Withdrew due to AEs	4	(0.6%)	11	(1.6%)

Source: S-Table 6, safety-sum.pdf, p 23

A single TTS subject reported clitoromegaly during the double blind phase; this was confirmed on physical examination, and resolved a month following study discontinuation. Her free testosterone level was 2.2 pg/ml (normal range 0.9 – 7.3 pg/ml).

Psychiatric AEs of interest as possible androgenic effects were specified by the Applicant as agitation, aggression or irritability. Frequency of these events were assessed based on these MedDRA terms, either from spontaneous subject reports or from AEs detected by investigators or other site personnel, and they occurred in 2% of subjects in each group. The rate of aggression was also identical, 0.9%, in each group.

Acne

AEs relating to acne were reported by 9.1% of TTS subjects and by 7.0% of placebo subjects in the double blind phase.

On the objective assessment of acne using the Palatsi acne scale, the TTS subjects showed greater frequency of increased acne scores, although the inter-group differences were not statistically significant. At Week 24, 3.3% of TTS subjects experienced increases of one or more points on the four-point Palatisi acne scale, as opposed to 2.4% of placebo subjects.

Alopecia

Alopecia was reported as an AE in 3.4% of TTS subjects and 2.7% of placebo subjects, and withdrawal rates were similar.

Hirsutism

Hirsutism was reported as an AE in 7.0% of TTS subjects and 5.0% of placebo subjects.

On the objective assessment, the Lorenzo scale, the rating of chin hirsutism increased from baseline in 6.1% of TTS subjects and 3.7% of placebo subjects by Week 24, and upper lip hirsutism increased in 6.6% of TTS subjects and 5.6% of placebo subjects by Week 24. Facial depilation frequency increased in 13.2% of both TTS and placebo subjects by the end of the double blind phase.

Voice Deepening

Voice deepening (defined as dysphonia or hoarseness) was reported as an adverse event in 2.3% of TTS subjects and 1.7% of placebo subjects in the double blind phase. Two TTS subjects withdrew due to this AE. One of these subjects rated her hoarseness severe, and it reportedly resolved two months after discontinuation of testosterone.

5.3.1.3 Application Site Reactions

Data on application site reactions were pooled only over the two phase 3 trials, as the severity criteria differed between the phase 2 and phase 3 studies, and because the Study 068 subjects wore two patches simultaneously to protect the blind. Rates were similar between the phase 2 and phase 3 studies. Fewer than 5% of phase 2 subjects discontinued participation due to application site reactions. Application site reactions occurring during the double blind phase were slightly higher in the placebo group (34.1% vs. 30.4%). Two subjects in each group were reported as possible cases of sensitization, but no confirmatory testing was performed. Three of these four subjects withdrew from the study.

5.3.1.4 Impact on Estrogen-Related Effects

Effects of possible interaction between testosterone and the estrogen therapy also administered to subjects were evaluated by assessing the occurrence of hot flushes and breast tenderness. The rate of hot flushes was numerically slightly greater in the TTS group (2.7% vs. 2.4%), and slightly more TTS subjects experienced severe hot flushes in the double blind phase (three vs. one placebo subject).

In the phase 2 studies, breast pain and tenderness was captured both by spontaneous adverse event reports and by directed questioning about breast tenderness at baseline and post-treatment. In the phase 3 studies, only spontaneous reports were used to count these events. Over the four studies, 4.2% of TTS subjects had breast pain AEs as compared to 4.8% of placebo subjects. Distributions of severity were similar between the two groups.

5.3.1.5 Laboratory Values

The laboratory data were pooled separately for phase 2 and for phase 3 studies, as different clinical labs were used to run the tests in the two phases. Only data from the phase 3 studies are reported below; the results in the phase 2 studies were generally consistent with those obtained in the phase 3 studies. Limits for markedly abnormal laboratory values are found in Appendix 3.

Lipid Profile

Changes from baseline in lipid profile during the double blind phase were small and not likely to be of clinical significance (Table 20). The TTS group had a smaller mean increase in HDL at Week 24 than did the placebo group (mean change 0.4 vs. 1.6 mg/dl in placebo). The frequency of markedly abnormal values was low, and similar between groups (see **Table** 21).

Table 20 Studies 133 & 134: Changes in Lipid Profile in Double Blind Phase

Laboratory Test	Placebo (N=545)					TTS (N=549)			
Visit	n	Mean (SD)	Median	Min - Max	p-value	n	Mean (SD)	Median	Min - Max
Total Cholesterol (mg/dL)									
Baseline [a]	479	216.2 (35.2)	214.0	110 - 342	_	488	217.7 (39.1)	213.0	109 - 404
Week 24	423	-2.5 (25.2)	-2.0	-161 - 95	_	424	-3.8 (26.6)	-2.0	-109 - 63
Week 24/Exit [b]	479	-2.4 (26.1)	-1.0	-161 - 95	_	488	-3.1 (27.1)	-1.0	-109 - 122
HDL-Cholesterol (mg/dL)									
Baseline [a]	479	64.3 (17.0)	62.0	13 - 124	_	488	62.2 (16.8)	60.5	30 - 156
Week 24	423	1.6 (9.0)	1.0	-25 - 38	_	424	0.4 (9.2)	0.0	-24 - 60
Week 24/Exit [b]	479	1.4 (9.2)	1.0	-34 - 38	_	488	0.6 (9.1)	0.0	-24 - 60
LDL-Cholesterol (mg/dL)									
Baseline [a]	479	122.5 (31.6)	119.0	48 - 278	_	488	125.1 (35.1)	122.0	46 - 311
Week 24	423	-2.5 (22.0)	-1.0	-119 - 80	_	424	-1.6 (23.1)	0.0	-114 - 57
Week 24/Exit [b]	479	-2.4 (22.3)	-1.0	-119 - 80	_	488	-1.1 (23.5)	0.0	-114 - 73
Triglycerides (mg/dL)									
Baseline [a]	479	149.0 (77.3)	132.0	25 - 549	_	488	155.5 (86.6)	135.5	39 - 623
Week 24	423	-9.4 (56.7)	-8.0	-245 - 176	_	424	-15.3 (58.5)	-9.0	-341 - 162
Week 24/Exit [b]	479	-8.6 (61.5)	-9.0	-245 - 446	_	488	-15.0 (58.8)	-11.0	-341 - 193

Source: S-Table 14, *safety-sum.pdf, p 46*

Table 21 Studies 133 & 134: Proportion of Subjects with Markedly Abnormal Values on Lipid Profiles in Double Blind Phase

Laboratory Test	Placebo N=545		TTS N=549	
	# abnl/ # with data	%	# abnl/ # with data	%
Total Cholesterol	1/479	0.21	1/488	0.20
HDL	0/479	0	0/488	0
LDL	7/479	1.46	5/488	1.02
Triglycerides	14/479	2.92	12/488	2.46

Source: Appendix 5.9, Table 4, *2001133.pdf, p 11154* and Appendix 5.9, Table 4, *2001134.pdf, p 10113*

Hepatic Profile

Changes in hepatic function during the double blind phase are displayed in Table 22. A single placebo subject had a markedly abnormal AST (baseline of 28 U/L rose to 126 at Week 24). A single TTS subject had a markedly abnormal ALT (baseline of 9 U/L rose to 191 at Week 24).

Table 22 Studies 133 & 134: Changes in Hepatic Function in Double Blind Phase

Laboratory Test	Placebo (N=545)					TTS (N=549)			
Visit	n	Mean (SD)	Median	Min - Max	p-value	n	Mean (SD)	Median	Min - Max
Alkaline Phosphatase (U/L)									
Baseline [a]	479	80.0 (23.7)	78.0	25 - 171	_	488	78.9 (22.6)	77.0	20 - 183
Week 24	423	-1.0 (11.6)	-1.0	-71 - 68	_	424	-1.2 (16.1)	-2.0	-49 - 205
Week 24/Exit [b]	479	-0.9 (11.8)	-1.0	-71 - 68	_	488	-0.8 (15.6)	-1.0	-49 - 205
Alanine Aminotransferase (SGPT) (U/L)									
Baseline [a]	479	21.9 (10.4)	19.0	8 - 83	_	488	20.9 (9.8)	18.0	7 - 83
Week 24	423	0.2 (8.7)	0.0	-39 - 56	_	424	0.5 (12.3)	0.0	-58 - 182
Week 24/Exit [b]	479	0.2 (8.7)	0.0	-39 - 56	_	488	0.6 (11.7)	0.0	-58 - 182
Aspartate Aminotransferase (SGOT) (U/L)									
Baseline [a]	479	22.3 (7.5)	21.0	9 - 68	_	488	21.6 (6.2)	20.0	9 - 71
Week 24	423	0.2 (7.9)	0.0	-40 - 98	_	424	0.8 (7.2)	0.0	-26 - 82
Week 24/Exit [b]	479	0.3 (7.6)	0.0	-40 - 98	_	488	0.7 (7.0)	0.0	-26 - 82
Total Bilirubin (mg/dL)									
Baseline [a]	479	0.44 (0.21)	0.40	0.1 - 1.8	_	488	0.44 (0.23)	0.40	0.1 - 1.8
Week 24	423	-0.01 (0.16)	0.00	-0.8 - 0.5	_	424	0.01 (0.17)	0.00	-0.6 - 0.9
Week 24/Exit [b]	479	-0.01 (0.16)	0.00	-0.8 - 0.5	_	488	0.01 (0.17)	0.00	-0.6 - 0.9

Source: S-Table 16, safety-sum.pdf, p 50

Carbohydrate Metabolism

Changes in carbohydrate metabolism during the double blind phase are displayed in Table 23, with the frequency of markedly abnormal values in each group shown in Table 24.

Table 23 Studies 133 & 134: Changes in Carbohydrate Metabolism Markers during Double Blind Phase

Laboratory Test	Placebo (N=545)					TTS (N=549)			
Visit	n	Mean (SD)	Median	Min - Max	p-value	n	Mean (SD)	Median	Min - Max
Glucose (mg/dL)									
Baseline [a]	480	86.5 (8.6)	86.0	56 - 137	_	486	85.9 (8.5)	85.0	59 - 131
Week 24	423	-1.2 (8.3)	-1.0	-34 - 27	_	423	-0.4 (8.8)	-1.0	-42 - 60
Week 24/Exit [b]	480	-1.0 (8.6)	-1.0	-34 - 33	_	486	-0.5 (9.0)	-1.0	-42 - 60
Hemoglobin A1C (%)									
Baseline [a]	475	5.31 (0.37)	5.30	4.1 - 6.9	_	486	5.32 (0.36)	5.30	3.9 - 7.5
Week 24	419	0.03 (0.24)	0.00	-0.9 - 1.0	_	420	0.03 (0.24)	0.00	-0.7 - 1.0
Week 24/Exit [b]	475	0.03 (0.25)	0.00	-0.9 - 1.6	_	486	0.03 (0.24)	0.00	-0.7 - 1.0
Insulin (uIU/mL)									
Baseline [a]	469	8.8 (12.3)	7.0	1 - 237	_	481	7.9 (6.7)	6.0	2 - 68
Week 24	413	0.5 (6.1)	0.0	-47 - 36	_	420	1.4 (10.1)	0.0	-56 - 150
Week 24/Exit [b]	469	0.8 (10.0)	0.0	-130 - 86	_	481	1.6 (9.7)	1.0	-56 - 150

Source: S-Table 18, safety-sum.pdf, p 53

Table 24 Studies 133 & 134: Proportion of Subjects with Markedly Abnormal Values on Carbohydrate Metabolism Markers in Double Blind Phase

Laboratory Test	Placebo N=545		TTS N=549	
	# abnl/ # with data	%	# abnl/ # with data	%
Glucose	0/480	0	0/486	0
Hemoglobin A1c	0/475	0	0/486	0
Insulin	16/469	3.41	13/481	2.70

Source: Appendix 5.9, Table 13, *2001133.pdf, p 11167* and Appendix 5.9, Table 13, *2001134.pdf, p 9868*

Hematology

Changes from baseline in hemoglobin during the double blind phase are displayed in Table 25. The TTS group had a greater rise in hemoglobin relative to placebo that was reported to be statistically significant. A single placebo subject and two TTS subjects had markedly abnormal values on white blood cell count.

Table 25 Studies 133 & 134: Changes in Hemoglobin in Double Blind Phase

Laboratory Test	Placebo (N=545)					TTS (N=549)			
Visit	n	Mean (SD)	Median	Min - Max	p-value	n	Mean (SD)	Median	Min - Max
Hemoglobin (g/dL)									
Baseline [a]	462	13.52 (0.89)	13.60	9.2 - 16.0	_	475	13.49 (1.00)	13.40	9.7 - 16.5
Week 24	410	0.03 (0.65)	0.00	-2.0 - 3.7	_	411	0.14 (0.76)	0.10	-3.5 - 4.1
Week 24/Exit [b]	462	0.05 (0.66)	0.00	-2.0 - 3.7	_	475	0.15 (0.74)	0.10	-3.5 - 4.1

Source: S-Table 20, safety-sum.pdf, p 56

Coagulation Parameters

Coagulation parameters were only measured in Study 133. The changes in coagulation parameters during the double blind phase are displayed in Table 26. The frequency of markedly abnormal values in each group during the double blind phase is shown in Table 27. The two TTS subjects with prolonged prothrombin times were both being treated for prior thromboses, one with warfarin.

Table 26 Study 133: Changes in Coagulation Parameters in Double Blind Phase

Laboratory Test	Placebo (N=277)				TTS (N=283)			
Visit	n	Mean (SD)	Median	Min - Max	n	Mean (SD)	Median	Min - Max
Activated Partial Thromboplastin Time (sec)								
Baseline a	243	29.16 (3.79)	29.10	19.2 - 39.2	256	29.42 (4.15)	29.00	20.0 - 53.9
Week 24	218	-0.38 (3.44)	-0.50	-11.7 - 11.0	217	-0.38 (3.73)	-0.50	-12.1 - 15.4
Week 24/Exit b	243	-0.46 (3.60)	-0.50	-12.7 - 11.0	256	-0.42 (3.83)	-0.50	-21.3 - 15.4
ATIII								
Baseline a	241	104.0 (12.4)	105.0	59 - 140	254	105.0 (11.1)	105.0	58 - 139
Week 24	216	1.9 (14.1)	1.0	-65 - 57	215	1.2 (13.1)	2.0	-75 - 45
Week 24/Exit b	241	1.8 (13.9)	1.0	-65 - 57	254	1.4 (12.6)	2.0	-75 - 45
Fibrinogen (mg/dL)								
Baseline a	241	381.3 (95.9)	372.0	139 - 666	255	386.9 (85.5)	382.0	138 - 700
Week 24	216	10.3 (90.5)	10.0	-302 - 282	216	9.1 (79.6)	10.0	-213 - 311
Week 24/Exit b	241	11.4 (90.1)	10.0	-302 - 282	255	9.7 (79.2)	11.0	-213 - 311
Prothrombin Time (sec)								
Baseline a	242	10.85 (0.71)	10.80	9.0 - 16.4	254	10.82 (0.61)	10.80	9.1 - 13.8
Week 24	217	-0.23 (1.05)	-0.20	-5.8 - 10.2	215	-0.10 (0.88)	-0.20	-2.5 - 5.6
Week 24/Exit b	242	-0.24 (1.01)	-0.20	-5.8 - 10.2	254	-0.12 (0.85)	-0.20	-3.3 - 5.6

Source: Appendix 5.9, Table 2, *2001133.pdf, p 11152*

Table 27 Study 133: Proportion of Subjects with Markedly Abnormal Values on Coagulation Parameters in Double Blind Phase

Laboratory Test	Placebo (N=279) n/m (%)	TTS (N=283) n/m (%)
Activated Partial Thromboplastin Time (sec)	2/243 (0.8%)	3/256 (1.2%)
Fibrinogen (mg/dL)	0/241 (0.0%)	5/255 (2.0%)
Prothrombin Time (sec)	1/242 (0.4%)	2/254 (0.8%)

Source: Appendix 5.9, Table 19, *2001133.pdf, p 1*

5.3.1.6 Vital signs and Weight

There were no clinically relevant mean or median changes in systolic or diastolic blood pressure nor differences between TTS and placebo groups in the double blind phase. The mean (SD) and median changes from baseline in systolic blood pressure were -0.9 (13.3) and 0 mm Hg in the placebo group, and 0.2 (12.4) and 0 mm Hg in the TTS group. For diastolic blood pressure, the mean (SD) and median changes from baseline were -0.7 (9.0) and 0 mm Hg in the placebo group, and -0.3 (8.9) and 0 mm Hg in the TTS group. Shift tables were not provided.

The median weight change from baseline in the double blind phase was greater in the TTS group at Week 24 and at all preceding weight assessment periods. By the end of the double blind phase, TTS subjects had gained a mean of 0.38 kg (median 0.35 kg) as compared to placebo subjects, who had lost a mean of 0.25 kg (median change of 0).

5.3.2 Safety Findings with Increasing Duration of Testosterone Exposure (Open Label and Extension Phases)

5.3.2.1 Adverse Events

Deaths

There were no deaths in any TTS-exposed subjects, followed up to 18 months of exposure.

Serious Adverse Events

In the 6 month open label phase, the rate of (SAEs) was 1.7%, regardless of whether the subjects had received 28 or 52 weeks of testosterone. In the extension phase, which followed the open label phase, the overall rate of SAEs was 1.9%, but was higher in the group with a total of 12 months testosterone exposure (3%) than the group with a total of 18 months of testosterone exposure (0.6%). SAEs of concern in the open label phase were cholecystitis/cholelithiasis (3 subjects, one of whom was in the placebo->TTS group), pancreatitis (2 subjects, one of whom was in the placebo->TTS group) and metastatic breast cancer (in a placebo->TTS subject) and chest pain/dyspnea (in a TTS->TTS subject). Reported SAEs of concern in the extension phase were irregular heart rate, hypertension, chest pain, and ductal carcinoma in situ, each of which occurred in a single placebo->TTS->TTS subject.

Division comment:

- **Although in the extension phase, the group with shorter testosterone exposure (12 months) appears to have a five-fold greater rate of SAEs (3.0 vs. 0.6%), this difference was not tested for statistical significance, and it is unlikely that this rate is affected by the initial randomization to placebo one year prior to this phase of the study. Overall, the SAE rate in subjects remaining on testosterone for 12-18 months is about 2%, which is equivalent to the SAE rates seen in testosterone-exposed subjects in the double blind and open label phases.**
- **A placebo->TTS->TTS subject from Study 133, who was diagnosed with lobular breast cancer in the extension phase, was not reported by the Applicant as an SAE.**

- **The incidence of SAEs must be viewed in light of the fact that all subjects were taking estrogen as well as testosterone.**

Withdrawals due to Adverse Events

Withdrawal due to adverse events occurred in 60 (7.2%) of the 837 subjects participating in the open label phase of Studies 133 and 134, and in 17 (5.3%) of the 321 subjects in the extension phase up to 78 weeks. An additional four subjects withdrew due to AEs after completing 78 weeks of the study. The most common AEs resulting in withdrawal were hirsutism, application site reactions, weight increase, acne and alopecia in the open label phase and acne and alopecia in the extension phase.

Division comments:

- **Acne and alopecia continued to result in AE-related withdrawals through 78 weeks of testosterone exposure and hirsutism continued to be a frequent cause of AE-related withdrawals through the first year of treatment with testosterone.**
- **Subjects who continued into the extension phase tended to have AEs leading to withdrawal that differed from those noted in the double blind and open label phases. It is possible that the AEs that commonly led to withdrawal during the first year of the trials may also have limited the further participation of subjects in the extension phase. Events occurring uniquely in the extension phase and leading to withdrawal are concerning in aggregate, as they include palpitations, chest pain, fatigue, increased heart rate, dizziness, dyspnea and hypertension, all of which could reflect cardiovascular effects.**

Common Adverse Events

Overall AEs occurred in 57.1% of subjects in the open label phase and 52.6% of subjects in the extension phase. AEs that occurred with incidence of at least 2% in the open label phase are displayed in Table 28.

Table 28 Studies 133 & 134: Most Common Adverse Events (Incidence ≥ 2%) During Open Label Phase

	Placebo ->TTS N=418			TTS->TTS N=419		
	# AEs*	%*	Incidence Rate**	# AEs*	%*	Incidence Rate**
Adverse Event						
Hirsutism	66	15.8	0.151	72	17.2	0.171
Acne NOS	27	6.5	0.062	33	7.9	0.077
ASRs	23	5.5	0.055	24	5.7	0.049
Alopecia	8	1.9	0.018	14	3.3	0.033
Weight increased	4	1.0	0.009	11	2.6	0.026
URI tract sign & symptoms (HLT)	11	2.6	0.025	10	2.4	0.020
Headache	7	1.7	0.016	12	2.9	0.025
Musculoskeletal & connective tissue signs & symptoms NEC (HLT)	10	2.4	0.023	12	2.9	0.024
Sinusitis NOS	8	1.9	0.018	13	3.1	0.023
Arthralgia	10	2.4	0.023	7	1.7	0.017
Breast disorders NEC (HLT)	7	1.7	0.016	9	2.1	0.021
UTI (HLT)	9	2.2	0.021	5	1.2	0.007
Limb injuries NEC (HLT)	2	0.5	0.005	9	2.1	0.021

Note: HLT = Higher Level MedDRA Term, subsuming subheadings; NOS = not otherwise specified; NEC = not elsewhere classified

* AEs counts and the % AEs are based on the total # of AEs occurring between Weeks 25-52, regardless of whether the subject had ever previously reported that AE.

**The incidence rate represents those AEs occurring for the first time between Weeks 25-52 divided by the number of 28 patient-week units of exposure time at risk during this period. Subjects who had previously reported that AE as occurring during a period of testosterone exposure were not considered at risk during the extension phase.

Source: Based on Table 11, *safety-sum.pdf, pp 130-81*

Rates of AEs occurring with at least 2% incidence in subjects in the extension study to 78 weeks are presented in Table 29.

Table 29 Studies 133 & 134: Most Common Adverse Events (≥ 2% Incidence Rate) During Extension Phase

	# AEs*	%*	# Incident AEs**	Incidence Rate**
Adverse Event				
Hirsutism	18	5.6	13	0.05
Alopecia	12	3.7	12	0.04
URIs	12	3.7	11	0.04
ASRs	12	3.7	8	0.03
Headaches	9	2.8	9	0.03
Nasopharyngitis	8	2.5	7	0.02
Bronchitis	7	2.2	7	0.02
Arthralgia	7	2.2	6	0.02
Acne	7	2.2	5	0.02
Hot flush	6	1.9	6	0.02
Pain & discomfort NEC	6	1.9	6	0.02
Influenza	6	1.9	4	0.01
UTIs	6	1.9	4	0.01
Anxiety	5	1.6	5	0.02
Hypertension	5	1.6	5	0.02
Gastrointestinal and abdominal pain	4	1.2	3	0.01

Note: HLT = Higher Level MedDRA Term, subsuming subheadings; NOS = not otherwise specified; NEC = not elsewhere classified
* AEs counts and the % AEs are based on the total # of AEs occurring between Weeks 53-78, regardless of whether the subject had ever previously reported that AE.
Source: Table 7, *2001133-134addendum.pdf, pp 19-22*

Among cardiovascular, thrombotic and cancer-related events of interest, there were no MIs, strokes or TIAs, DVTs or pulmonary emboli during the open label or extension phases. There was a single case of metastatic breast cancer in the placebo->TTS group. In the extension phase, there was one case of breast cancer and one case of breast cancer in situ in the placebo->TTS->TTS group.

5.3.2.2 Androgenic Effects

About 30% of subjects in the open label phase experienced androgenic AEs. This rate was higher than that seen in the TTS-treated subjects in the double blind phase, primarily because of a higher rate of hirsutism in the open label portion of the studies. Withdrawals due to these AEs were also higher in the open label phase. Androgenic AE rates, severity, and rate of withdrawal due to these AEs were slightly higher in the subjects who had 12 months exposure to testosterone as compared to those exposed for only 6 months.

Division comment:

- **The number of subjects with androgenic AEs in the open label phase may be overestimated. The Applicant did not provide a summary comparable to those done for the double blind or extension phases; therefore, the reviewer summed the**

occurrence of the individual androgenic events, which would overestimate subjects who experienced androgenic AEs in two or more categories.

In the extension phase, androgenic AEs were reported in 12% of subjects; these rates were similar to those seen in the TTS subjects in the double blind phase.

Subgroup analyses of rates of androgenic adverse events by route of estrogen therapy, age and race were conducted in the extension study, and no subpopulations of increased risk were identified.

A case of clitoromegaly in a TTS->TTS subject began about five months after starting testosterone, but was not reported until the open label period. The finding was confirmed on physical exam at the Week 52 visit. The subject continued into the extension phase with the event ongoing. Her maximum free testosterone level was 6.8 pg/ml. There were no new reports of clitoromegaly reported in the extension study.

The psychiatric events of interest as potential androgenic effects (agitation, anxiety and irritability) occurred in 1.7% of subjects in the open label phase, with an additional 0.7% experiencing aggression.

Acne

In the open label phase, 7.2% of subjects reported acne as an AE, with a higher frequency in the group with 12 months exposure to testosterone (7.9%) as compared to the group with 6 months exposure (6.5%). Fewer than 4% of subjects exposed for up to a year to testosterone experienced worsening of acne as rated on the Palatsi scale as compared to the last assessment before starting testosterone, and the rate was equal whether the exposure was for 12 or 18 months.

In the extension phase, 2.2% of subjects reported acne as an AE, with a higher frequency in the group with 12 months exposure to testosterone (3.0%) as compared to the group with 18 months exposure (1.3%). Again, fewer than 4% of subjects exposed for up to 78 weeks to testosterone experienced worsening of acne as rated on the Palatsi scale as compared to the last assessment before starting testosterone, and the rate was equal whether the exposure was for 12 or 18 months.

Division comment:

- **Worsening of acne on the Palatsi scale used in the objective assessment does not appear to increase with increasing duration of testosterone exposure. Over the three phases of the studies, approximately 3-4% of testosterone-exposed subjects experienced worsening of acne compared to their baseline rating. This is corroborated by the observation that the frequency of acne as an AE does not appear to increase with increasing duration of testosterone treatment.**

Alopecia

In the open label phase, 4.2% of subjects reported alopecia as an AE. The subjects with 12 months exposure to testosterone had higher rates of this AE, more frequent withdrawal due to this AE, and greater proportions of more severe alopecia than those exposed for only 6 months.

Alopecia was reported as an AE in 4.7% of subjects in the extension phase. The 5.8% rate in subjects on testosterone from Weeks 0-78 was greater than the 3.4% rate seen in subjects exposed to testosterone during Weeks 0-24, the 5.0% rate in subjects exposed during Weeks 0-52, and the 3.6% rate seen in subjects in the extension study who used testosterone only from Weeks 25-78. All of the cases in the TTS->TTS->TTS (18 month exposure) group were new onset cases, in subjects who had not previously experienced alopecia. Four subjects in this group withdrew due to alopecia, vs. none in the placebo->TTS->TTS group.

Division comment:

- **Alopecia appears to increase in frequency with increasing duration of testosterone exposure. The majority of the cases occurring in the later phases of the study represented new incident cases, rather than recurrent or ongoing cases. While this AE was never rated by the investigator as severe, it was responsible for subject withdrawal in all three phases of the studies.**

Hirsutism

In the open label phase, 16.5% of subjects overall reported hirsutism as an AE. This rate was numerically higher than that seen in placebo subjects or than that of testosterone-exposed subjects in either the double blind or the extension phase of the studies, as was the rate of withdrawal due to hirsutism. Rates were slightly higher in subjects with longer (12 months) exposure to testosterone, and their frequency of withdrawal due to this AE was more than double that of subjects with shorter (6 months) exposure to testosterone. Of subjects completing a year of the trials, chin hirsutism increased from baseline in 8.3% of subjects, and upper lip hirsutism increased in 10.6%. The frequency of depilation increased from baseline in 17.3% of subjects in the open label phase. On all three measures, the proportion of subjects with no change or a decrease from baseline was similar between those with 6 months and those with 12 months of testosterone exposure.

Overall, 5.6% of subjects in the extension phase reported hirsutism as an AE, with a greater frequency in subjects with 18 months exposure to testosterone than those with 12 months exposure. On the Lorenzo scale, the rating of chin hirsutism increased from baseline in 9% of subjects in the extension study, with no difference between those exposed to testosterone for 54 weeks and those exposed for 78 weeks. Upper lip hirsutism increased from baseline in 10% of each group in the extension study. Frequency of depilation increased in 19% of those exposed to testosterone for 54 weeks and in 26% of those exposed for 78 weeks.

Division comment:

- **With longer duration of testosterone exposure, hirsutism does not seem to be reported more frequently as an AE, nor is it rated as more apparent on the Lorenzo scale. However, the increased frequency of depilation suggests that women are in fact experiencing greater facial hair growth with longer testosterone exposure.**

Voice Deepening

In the open label phase, 2.6% of subjects overall experienced voice deepening, 2.4% of those receiving 6 months of testosterone, and 2.9% of those receiving 12 months exposure.

Voice deepening was reported as an AE in 1.6% of subjects in the extension phase; the rate was higher in subjects with 12 months exposure to testosterone (2.4%) than those with 18 months exposure (0.6%) .

Division comment:

- **Voice deepening does not appear to occur more frequently with longer exposure to testosterone, but remains similar to the rate seen in placebo subjects.**

5.3.2.3 Application Site Reactions

Application site reactions occurred in 5.6% of subjects in the open label phase and 3.7% of subjects in the extension study. Rates were similar regardless of whether subjects had initially been on placebo or TTS. There were no reported cases of sensitization.

5.3.2.4 Impact on Estrogen-Related Effects

Rates of hot flushes were low in the open label (1.3%) and extension phases (1.9%), and there were no consistent patterns regarding severity of hot flushes with increasing duration of exposure to testosterone.

In the open label and extension phases, rates of breast pain and tenderness were lower than in the double blind phase (1.8% and 1.2% respectively). Severity was greater during the open label phase in those subjects with longer testosterone exposure, although this pattern did not continue in the extension phase, where all events were mild.

5.3.2.5 Laboratory Values

Lipid Profile

In the open label phase, changes in lab values at Week 52 were small, but numerically more favorable in the TTS->TTS group (Table 30). Markedly abnormal values developed in a small percentage of subjects in both groups (range 0 to 4.4%) during the open label phase; abnormal LDL and triglyceride levels were numerically more common in subjects with longer exposure to testosterone (see Table 31).

Table 30 Studies 133 & 134: Changes in Lipid Profile in Open Label Phase

Laboratory Test	Placebo->TTS (N=418)				TTS->TTS (N=419)			
Visit	n	Mean (SD)	Median	Min - Max	n	Mean (SD)	Median	Min - Max
Total Cholesterol (mg/dL)								
Baseline [a]	371	213.8 (33.9)	211.0	120 - 299	357	216.4 (38.3)	212.0	109 - 404
Week 52	323	6.0 (25.3)	5.0	-121 - 94	311	5.1 (27.8)	7.0	-114 - 73
Week 52/Exit [b]	371	6.0 (25.4)	5.0	-121 - 94	357	3.6 (28.6)	6.0	-114 - 73
HDL-Cholesterol (mg/dL)								
Baseline [a]	371	66.4 (16.8)	65.0	32 - 124	357	61.9 (16.5)	61.0	30 - 156
Week 52	323	-0.1 (7.7)	0.0	-21 - 24	311	2.2 (9.6)	2.0	-33 - 41
Week 52/Exit [b]	371	0.0 (7.6)	0.0	-21 - 24	357	2.0 (9.3)	2.0	-33 - 41
LDL-Cholesterol (mg/dL)								
Baseline [a]	371	119.5 (30.8)	118.0	39 - 214	357	124.2 (34.1)	121.0	46 - 311
Week 52	323	5.8 (22.9)	6.0	-114 - 79	311	5.0 (23.7)	5.0	-105 - 75
Week 52/Exit [b]	371	5.6 (23.4)	6.0	-114 - 90	357	3.2 (24.8)	4.0	-105 - 75
Triglycerides (mg/dL)								
Baseline [a]	371	139.9 (71.7)	124.0	30 - 518	357	154.2 (82.7)	136.0	39 - 601
Week 52	323	2.3 (61.8)	-2.0	-159 - 426	311	-11.3 (66.1)	-7.0	-428 - 254
Week 52/Exit [b]	371	3.1 (60.2)	-1.0	-161 - 426	357	-9.7 (65.1)	-6.0	-428 - 254

Source: Table 50, safety-sum.pdf, pp 280-81

Table 31 Studies 133 & 134: Proportion of Subjects with Markedly Abnormal Values on Lipid Profiles in Open Label Phase

Laboratory Test	Placebo->TTS N=388		TTS->TTS N=419	
	# abnl/ # with data	%	# abnl/ # with data	%
Total Cholesterol	2/376	0.53	0/360	0
HDL	0/376	0	0/360	0
LDL	10/376	2.66	10/360	2.78
Triglycerides	15/376	3.99	16/360	4.44

Source: Appendix 5.9, Table 25, *2001133.pdf, p 11184* and Appendix 5.9, Table 20, *2001134.pdf, p 9880*

Lipid values reported in subjects who remained in the study extension to Week 78 are shown in Table 32 and proportions of subjects with markedly abnormal values at Week 78 are displayed in Table 33. There was a numerically greater decrease in triglycerides in those subjects with shorter testosterone exposure. The occurrence of markedly abnormal values was similar, regardless of the duration of exposure to testosterone.

Table 32 Studies 133 & 134: Changes in Lipid Profile in Extension Phase

Laboratory Test / Visit	Plc->TTS->TTS (N=167)				TTS->TTS->TTS (N=154)			
	n	Mean (SD)	Median	Min - Max	n	Mean (SD)	Median	Min - Max
Total Cholesterol (mg/dL)								
Week 52[a]	135	218.3 (37.4)	215.0	117 - 343	130	222.3 (37.0)	221.5	146 - 332
Week 78	120	-3.8 (27.7)	-1.5	-84 - 66	121	-1.5 (23.5)	-1.0	-96 - 81
Week 78/Exit[b]	135	-3.7 (26.9)	-2.0	-84 - 66	130	-2.8 (24.6)	-2.0	-96 - 81
HDL-Cholesterol (mg/dL)								
Week 52[a]	129	66.4 (18.1)	66.0	27 - 131	127	65.2 (16.2)	64.0	36 - 130
Week 78	114	0.0 (9.0)	0.0	-25 - 35	119	1.3 (8.0)	1.0	-22 - 19
Week 78/Exit[b]	129	0.1 (8.9)	0.0	-25 - 35	127	1.2 (8.0)	1.0	-22 - 19
LDL-Cholesterol (mg/dL)								
Week 52[a]	129	124.3 (33.9)	121.0	56 - 254	127	129.5 (33.3)	127.0	39 - 228
Week 78	114	-2.9 (23.1)	-2.0	-71 - 45	119	-2.9 (21.3)	-2.0	-83 - 57
Week 78/Exit[b]	129	-2.7 (22.9)	-1.0	-71 - 45	127	-3.4 (21.0)	-2.0	-83 - 57
Triglycerides (mg/dL)								
Week 52[a]	135	140.9 (95.7)	122.0	34 - 817	130	139.9 (81.3)	120.0	31 - 507
Week 78	120	-6.8 (57.8)	-2.0	-291 - 201	121	0.4 (47.2)	1.0	-149 - 149
Week 78/Exit[b]	135	-5.0 (63.3)	-2.0	-291 - 352	130	-1.3 (50.9)	1.0	-235 - 149

Source: EOT Table 23, 2001133-134addendum.doc, p 101

Table 33 Studies 133 & 134: Proportion of Subjects with Markedly Abnormal Values on Lipid Profiles in Extension Phase

Laboratory Test	Plc->TTS->TTS (N=167) n/m	(%)	TTS->TTS->TTS (N=154) n/m	(%)
Total Cholesterol (mg/dL)	0/135	(0.0%)	0/131	(0.0%)
HDL-Cholesterol (mg/dL)	0/129	(0.0%)	1/128	(0.8%)
LDL-Cholesterol (mg/dL)	1/129	(0.8%)	3/128	(2.3%)
Triglycerides (mg/dL)	5/135	(3.7%)	4/131	(3.1%)

Source: EOT Table 27, 2001133-134addendum.doc, p 105

Division comments:

- **On average, there were no clinically relevant changes in the lipid profile. It is notable, however, that as much as 3-4% of subjects exposed to testosterone for a year developed LDL or triglyceride levels more than 30% above baseline, although this does appear comparable to the rate seen in placebo subjects followed for six months.**
- **Subjects exposed to testosterone for up to 78 weeks showed small decreases from baseline in total cholesterol and LDL, small increases in HDL and changes in triglycerides ranging from about a 5% decrease to a small increase. None of these changes are likely to be of clinical significance.**

Hepatic Profile

Table 34 shows the changes from baseline in hepatic function experienced by subjects in the open label phase, which were of similarly small magnitude to those seen in the double blind phase. A single subject in the TTS->TTS group had a markedly abnormal value on ALT (baseline of 55 U/L rose to 104 at Week 24 and to 134 at Week 52). The subject acknowledged significant and increased alcohol use over the course of the study, to which the investigator attributed the ALT rise. An additional TTS->TTS subject had a markedly abnormal AST (baseline of 36 UL rose to 153 at Week 52).

Table 34 Studies 133 & 134: Changes in Hepatic Function in Open Label Phase

Laboratory Test	Placebo->TTS (N=418)				TTS->TTS (N=419)			
Visit	n	Mean (SD)	Median	Min - Max	n	Mean (SD)	Median	Min - Max
Alkaline Phosphatase (U/L)								
Baseline [a]	371	77.9 (24.6)	74.0	24 - 179	357	79.0 (21.9)	77.0	20 - 172
Week 52	323	0.8 (11.2)	1.0	-51 - 60	311	-0.1 (13.8)	0.0	-47 - 46
Week 52/Exit [b]	371	1.0 (11.3)	1.0	-51 - 60	357	-0.2 (13.9)	0.0	-47 - 46
Alanine Aminotransferase (SGPT) (U/L)								
Baseline [a]	371	22.0 (10.9)	19.0	7 - 86	357	21.1 (9.5)	19.0	7 - 78
Week 52	323	0.6 (9.7)	0.0	-76 - 55	311	1.0 (10.4)	0.0	-55 - 79
Week 52/Exit [b]	371	0.6 (9.4)	0.0	-76 - 55	357	1.2 (10.6)	0.0	-55 - 79
Aspartate Aminotransferase (SGOT) (U/L)								
Baseline [a]	371	22.5 (8.7)	21.0	8 - 126	357	21.8 (6.4)	21.0	9 - 71
Week 52	323	-0.7 (8.5)	-1.0	-114 - 32	311	0.4 (9.1)	0.0	-22 - 117
Week 52/Exit [b]	371	-0.5 (8.2)	-1.0	-114 - 32	357	0.3 (9.0)	0.0	-30 - 117

Source: Table 54, safety-sum.doc, p 285

Subjects with exposure to testosterone up to 78 weeks are displayed in Table 35. None of these subjects experienced markedly abnormal values on the four hepatic parameters evaluated.

Table 35 Studies 133 & 134: Changes in Hepatic Function in Extension Phase

Laboratory Test	Plc->TTS->TTS (N=167)				TTS->TTS->TTS (N=154)			
Visit	n	Mean (SD)	Median	Min - Max	n	Mean (SD)	Median	Min - Max
Alkaline Phosphatase (U/L)								
Week 52[a]	135	77.1 (20.9)	75.0	34 - 148	130	79.6 (22.8)	75.0	37 - 157
Week 78	120	0.0 (9.5)	0.0	-25 - 33	121	-0.7 (14.4)	-2.0	-36 - 68
Week 78/Exit[b]	135	0.5 (9.9)	0.0	-25 - 35	130	-0.6 (14.3)	-2.0	-36 - 68
Alanine Aminotransferase (U/L)								
Week 52[a]	135	23.6 (12.5)	21.0	10 - 81	130	22.9 (14.6)	19.0	8 - 134
Week 78	120	-0.7 (9.3)	0.0	-48 - 32	121	-0.3 (11.5)	0.0	-84 - 35
Week 78/Exit[b]	135	-0.6 (9.0)	0.0	-48 - 32	130	0.1 (12.5)	0.0	-84 - 57
Aspartate Aminotransferase (U/L)								
Week 52[a]	135	22.6 (7.9)	21.0	10 - 63	130	23.0 (14.2)	21.0	12 - 153
Week 78	120	0.0 (5.8)	0.0	-31 - 21	121	-1.1 (8.3)	-1.0	-48 - 21
Week 78/Exit[b]	135	0.0 (5.6)	0.0	-31 - 21	130	-0.8 (8.4)	-1.0	-48 - 23
Total Bilirubin (mg/dL)								
Week 52[a]	135	0.52 (0.24)	0.50	0.2 - 1.9	130	0.46 (0.22)	0.40	0.1 - 1.6
Week 78	120	-0.03 (0.16)	0.00	-0.6 - 0.5	121	0.00 (0.15)	0.00	-0.3 - 0.7
Week 78/Exit[b]	135	-0.03 (0.16)	0.00	-0.6 - 0.5	130	0.01 (0.15)	0.00	-0.3 - 0.7

Source: EOT Table 25, 2001133-134addendum.doc, p 103

Carbohydrate Metabolism

Changes in the open label phase were of similarly small magnitude (Table 36). The slight increase in insulin at Week 52 was not felt to be clinically meaningful. The proportion of subjects in the open label phase who developed markedly abnormal values on measures of carbohydrate metabolism is shown in Table 37. The change in glucose value for subjects with up to 78 weeks of testosterone exposure is shown in Table 38. Only two subjects, one who initially received TTS and one who initially received placebo, experienced markedly abnormal glucose levels over Weeks 53-78.

Table 36 Studies 133 & 134: Changes in Carbohydrate Metabolism Markers in Open Label Phase

Laboratory Test	Placebo->TTS (N=418)				TTS->TTS (N=419)			
Visit	n	Mean (SD)	Median	Min - Max	n	Mean (SD)	Median	Min - Max
Glucose (mg/dL)								
Baseline [a]	369	85.3 (8.6)	85.0	52 - 118	358	86.0 (8.4)	86.0	59 - 131
Week 52	321	2.2 (8.9)	2.0	-40 - 55	312	1.7 (10.6)	1.0	-28 - 84
Week 52/Exit [b]	369	2.0 (8.8)	2.0	-40 - 55	358	1.3 (10.3)	0.0	-28 - 84
Hemoglobin A1C (%)								
Baseline [a]	368	5.35 (0.36)	5.30	4.2 - 7.2	356	5.31 (0.35)	5.30	3.9 - 6.2
Week 52	320	-0.07 (0.19)	-0.10	-0.8 - 0.4	309	-0.05 (0.25)	0.00	-0.9 - 1.5
Week 52/Exit [b]	368	-0.06 (0.21)	-0.10	-0.8 - 0.6	356	-0.04 (0.25)	0.00	-0.9 - 1.5
Insulin (uIU/mL)								
Baseline [a]	367	8.7 (6.3)	7.0	1 - 40	354	8.2 (7.2)	6.0	2 - 68
Week 52	319	1.2 (7.7)	1.0	-22 - 81	307	2.5 (10.8)	1.0	-55 - 84
Week 52/Exit [b]	367	1.1 (7.5)	1.0	-22 - 81	354	2.6 (10.4)	1.0	-55 - 84

N = number of open-label patients; n = number of patients with data at that visit; SD = standard deviation

Source: Table 58, safety-sum.pdf, p 290

Table 37 Studies 133 & 134: Proportion of Subjects with Markedly Abnormal Values in Carbohydrate Metabolism Markers in Open Label Phase

Laboratory Test	Placebo->TTS N=418		TTS->TTS N=419 220	
	# abnl/ # with data	%	# abnl/ # with data	%
Glucose	0/374	0	1/361	0.28
Hemoglobin A1c	0/372	0	0/359	0
Insulin	7/371	1.89	14/357	3.92

Source: Appendix 5.9, Table 34, *2001133.pdf, p 11197* and Appendix 5.9, Table 29, *2001134.pdf, p 9893*

Table 38 Studies 133 & 134: Changes in Carbohydrate Metabolism Markers in Extension Phase

Laboratory Test / Visit	Plc->TTS->TTS (N=167)				TTS->TTS->TTS (N=154)			
	n	Mean (SD)	Median	Min - Max	n	Mean (SD)	Median	Min - Max
Glucose (mg/dL)								
Week 52[a]	135	86.5 (8.6)	86.0	51 - 109	130	87.6 (9.0)	87.0	71 - 115
Week 78	120	3.9 (12.0)	2.0	-34 - 65	121	2.1 (9.7)	2.0	-24 - 54
Week 78/Exit[b]	135	3.8 (11.7)	2.0	-34 - 65	130	1.4 (9.9)	1.0	-24 - 54

Source: EOT Table 24, 2001133-134addendum.doc, p 102

Division comment:

- **Overall, there were no clinically relevant changes in parameters of carbohydrate metabolism. The proportion of testosterone-exposed subjects who had markedly abnormal values for insulin after 12 months of exposure is similar to the proportion of placebo subjects who displayed such changes.**

Hematology

The change in hemoglobin during the open label phase was similar to that seen among the TTS subjects during the double blind phase (see Table 39).

Table 39 Studies 133 & 134: Changes in Hemoglobin in Open Label Phase

Laboratory Test / Visit	Placebo->TTS (N=418)				TTS->TTS (N=419)			
	n	Mean (SD)	Median	Min - Max	n	Mean (SD)	Median	Min - Max
Hemoglobin (g/dL)								
Baseline[a]	368	13.58 (0.91)	13.60	10.5 - 16.2	352	13.46 (0.98)	13.40	9.7 - 16.3
Week 52	320	0.14 (0.63)	0.10	-1.4 - 2.2	307	0.16 (0.69)	0.20	-2.2 - 4.0
Week 52/Exit[b]	368	0.13 (0.62)	0.10	-1.4 - 2.2	352	0.15 (0.69)	0.10	-2.2 - 4.0

Source: Table 62, safety-sum.pdf, p 294

At Week 78, hemoglobin declined slightly from baseline (Table 40); no subjects had markedly abnormal hemoglobin values with 52-78 weeks of testosterone exposure.

Table 40 Studies 133 & 134: Changes in Hemoglobin in Extension Phase

Laboratory Test / Visit	Plc->TTS->TTS (N=167)				TTS->TTS->TTS (N=154)			
	n	Mean (SD)	Median	Min - Max	n	Mean (SD)	Median	Min - Max
Hemoglobin (g/dL)								
Week 52[a]	131	13.69 (1.00)	13.70	11.6 - 16.0	129	13.65 (0.98)	13.60	10.0 - 16.6
Week 78	118	-0.17 (0.62)	-0.15	-1.9 - 1.7	120	-0.06 (0.68)	-0.10	-1.6 - 1.5
Week 78/Exit[b]	131	-0.17 (0.63)	-0.20	-1.9 - 1.7	129	-0.06 (0.67)	-0.10	-1.6 - 1.5

Source: EOT Table 26, 2001133-134addendum.doc, p 104

Coagulation Parameters

Changes in the open label phase, displayed in Table 41, were generally of greater magnitude, and the TTS->TTS group had a numerically greater increase in fibrinogen than did the placebo->TTS group, with a mean increase of almost 8% above baseline at Week 52. Markedly abnormal values are summarized in Table 42.

Table 41 Study 133: Changes in Coagulation Parameters in Open Label Phase

Laboratory Test / Visit	Placebo->TTS (N=229)				TTS->TTS (N=220)			
	n	Mean (SD)	Median	Min - Max	n	Mean (SD)	Median	Min - Max
Activated Partial Thromboplastin Time (sec)								
Baseline a	215	28.72 (3.86)	28.30	19.2 - 45.1	205	29.24 (4.06)	28.90	20.0 - 42.1
Week 52	191	1.16 (3.27)	1.00	-10.0 - 10.1	183	0.63 (3.51)	0.50	-13.3 - 11.7
Week 52/Exit b	215	1.03 (3.40)	1.00	-12.7 - 10.1	205	0.51 (3.41)	0.30	-13.3 - 11.7
ATIII								
Baseline a	217	105.8 (13.3)	105.0	40 - 138	203	104.5 (10.8)	105.0	58 - 130
Week 52	193	4.7 (13.0)	6.0	-52 - 68	181	4.6 (10.7)	4.0	-24 - 33
Week 52/Exit b	217	4.8 (12.6)	6.0	-52 - 68	203	4.9 (10.7)	5.0	-24 - 38
Fibrinogen (mg/dL)								
Baseline a	216	389.7 (80.3)	383.0	204 - 589	205	385.4 (87.5)	381.0	163 - 700
Week 52	192	10.9 (74.1)	19.0	-247 - 216	183	29.9 (86.4)	34.0	-313 - 282
Week 52/Exit b	216	13.5 (74.1)	19.0	-247 - 216	205	27.4 (85.6)	27.0	-313 - 282
Prothrombin Time (sec)								
Baseline a	216	10.62 (0.91)	10.50	9.3 - 21.0	205	10.78 (0.61)	10.80	9.1 - 13.8
Week 52	192	0.88 (1.61)	0.90	-9.9 - 16.2	183	0.67 (0.87)	0.60	-1.8 - 6.5
Week 52/Exit b	216	0.79 (1.55)	0.80	-9.9 - 16.2	205	0.62 (0.87)	0.60	-1.8 - 6.5

Source: Appendix 5.9, Table 39, *2001133.pdf, pp 11205-6*

Table 42 Study 133: Proportion of Subjects with Markedly Abnormal Values in Coagulation Parameters in Open Label Phase

Laboratory Test	Placebo->TTS (N=229) n/m (%)	TTS->TTS (N=220) n/m (%)
Activated Partial Thromboplastin Time (sec)	1/215 (0.5%)	0/206 (0.0%)
Fibrinogen (mg/dL)	2/216 (0.9%)	3/206 (1.5%)
Prothrombin Time (sec)	2/216 (0.9%)	2/206 (1.0%)

Source: Appendix 5.9, Table 40, *2001133.pdf, p 11207*

Data on coagulation parameters for subjects using testosterone for up to 78 weeks in the extension phase were not provided.

5.3.2.6 Vital signs and Weight

The open label and extension phases permitted assessment of changes from baseline or differences in blood pressure based upon duration of testosterone exposure. As some subjects had been exposed to placebo in the first six months (double blind phase) of the clinical trials, their baseline values were obtained from the visit just prior to their initiation of testosterone therapy. In the open label phase, the mean (SD) and median changes from baseline in systolic blood pressure were 1.6 (12.3) and 2.0 mm Hg in the placebo->TTS group, and 1.5 (14.0) and 0 mm Hg in the TTS->TTS group. For diastolic blood pressure, the mean (SD) and median changes from baseline were 0.9 (9.0) and 0 mm Hg in the placebo->TTS group, and 0.5 (9.7) and 0 mm Hg in the TTS->TTS group. In the extension phase, the mean (SD) and median changes from baseline in systolic blood pressure were 1.0 (12.9) and 2.0 mm Hg in the placebo->TTS->TTS group, and 0.2 (13.6) and 0 mm Hg in the TTS->TTS->TTS group. For diastolic blood pressure, the mean (SD) and median changes from baseline were 0.4 (9.1) and 0 mm Hg in the placebo->TTS->TTS group, and -0.4 (8.6) and 0 mm Hg in the TTS->TTS->TTS group.

In the open label phase, there was little further change in body weight; the median change from baseline (the visit just before starting testosterone) ranged from 0 to 0.05 kg, depending on the duration of testosterone exposure.

Overall, subjects in the extension phase gained about 0.6 kg by Week 78. One-third of subjects with 12 months exposure to testosterone gained weight from baseline to Week 78, as did 40% of subjects with 18 months of exposure.

Division comment:

- **Increases in systolic blood pressure as small as 1 mm Hg were observed in the WHI subjects on estrogen and progestin and were postulated as possible factors related to the increase in cardiovascular events in that arm.**
- **It appears that testosterone is associated with a small increase in weight (mean 0.63 kg) over that seen with placebo. This weight gain persists in subjects treated up to 78 weeks.**

5.3.3 Frequency and Incidence of Selected Adverse Events (Weeks 0-78)

Data on the incidence (Table 43) and frequency (Table 44) of selected adverse events are provided. The incidence rate provides information about the occurrence of new cases of a specific AE in the population remaining at risk for that AE; subjects who have previously experienced that AE are no longer considered at risk. Data on the frequency of AEs allows for the inclusion of an AE in a given subject in every treatment phase in which it occurred. In this analysis, the entire population remains at risk for AEs through all three phases of the studies.

Table 43 Incidence of Adverse Events by Duration of Testosterone Exposure

Duration of Testosterone Exposure	None	6 months		12 Months		18 Months
Treatment History (Treatment phase, length), N	Placebo (DB, Wks 0-24) N=703*	TTS (DB, Wks 0-24) N=696*	P->TTS (OL, Wks 25-52) N=418**	TTS-TTS (OL, Wks 25-52) N=419**	P->TTS->TTS (Extension, Wks 53-78) N=167**	TTS->TTS->TTS (Extension, Wks 53-78) N=154**
Incidence Rate						
Death	0.001	0	0	0	0	0
SAE w/o ASRs	0.024	0.024	N/A	N/A	N/A	N/A
W/D due to AE	0.052	0.057	NA	N/A	N/A	N/A
Acne	.0.081	0.102	0.064	0.078	N/A	N/A
Alopecia	0.030	0.039	0.033	0.052	0.031	0.066
Hirsutism	0.056	0.079	0.164	0.189	0.036	0.068
Voice Deepening	0.019	0.026	0.023	0.029	N/A	N/A
ASRs**	0.501	0.424	0.055	0.049	N/A	N/A
Hot Flushes	0.027	0.031	0.014	0.012	0.031	0.007
Breast Pain	0.056	0.047	0.019	0.017	0.006	0.021
Wt Gain ≥7%	0.057	0.162	0.034	0.036	N/A	N/A
Laboratory AEs	0.023	0.036	0.033	0.043	0.012	0.028

DB=Double Blind phase, OL=Open Label phase
*Includes Studies 068, 092, 133 & 134
** Includes Studies 133 & 134 only
Incidence rate is computed per 100 person-time units, where time unit is the number of weeks in that phase of study

The incidence data provide the clearest assessment of the change in occurrence over increasing duration of testosterone exposure. It can be seen that the incidence of acne varies little with increasing duration of exposure (i.e., there is no increase in new presentations over time), up to one year, and remains similar to the rate observed in subjects on placebo. In contrast, the incidence of alopecia increases in each interval of testosterone exposure examined, and is more than double the placebo rate by 18 months of testosterone treatment. The rate of voice deepening remains relatively stable up to one year of exposure, and is numerically slightly higher than that seen in placebo subjects. Incidence data on the remaining AEs are too variable to suggest clear trends with increasing length of exposure to testosterone.

Table 44 Frequency of Adverse Events by Duration of Testosterone Exposure

Duration of Testosterone Exposure	**None**	**6 months**		**12 months**		**18 months**
Time in Study	**6 months**		**12 months**		**18 months**	
Population (Treatment phase, length), N	**Placebo (DB, Wks 0-24) N=703***	**TTS (DB, Wks 0-24) N=696***	**P->TTS (OL, Wks 25-52) N=418****	**TTS-TTS (OL, Wks 25-52) N=419****	**P->TTS->TTS (Extension, Wks 53-78) N=167****	**TTS->TTS->TTS (Extension, Wks 53-78) N=154****
% with Adverse Event						
Death	**0.1**	0	**0**	0	**0**	0
SAE	**2.1**	2.2	**1.7**	1.7	**3.0**	0.6
W/D due to AE	**8.4**	8.2	**6.0**	8.4	**5.4**	5.2
All AEs	**75.8**	76.1	**56.2**	58.0	**53.9**	51.3
Androgenic AEs	**14.4**	17.7	**N/A**	N/A	**10.2**	13.6
Acne	**5.1**	6.7	**6.5**	7.9	**3.0**	1.3
Alopecia	**2.9**	4.2	**3.3**	5.0	**3.6**	5.8
Hirsutism	**5.9**	7.3	**15.8**	17.2	**4.2**	7.1
Voice Deepening	**2.2**	2.7	**2.4**	2.9	**2.4**	0.6
ASRs	**34.1**	30.4	**5.5**	5.7	**4.8**	2.6
Hot Flushes	**2.4**	2.7	**1.4**	1.2	**3.0**	0.6
Breast Pain	**4.8**	4.2	**1.9**	1.7	**0.6**	1.9
Wt Gain>= 3.5%	**11.9**	20.2	**N/A**	N/A	**15.5#**	13.2#
Laboratory AEs	**1.99**	2.87	**3.59**	4.30	**1.20**	2.60
Markedly Abnormal Lipids**	**4.59**	3.68	**7.18**	7.22	**4.5**	6.2
Markedly Abnormal Markers of Carbohydrate Metabolism**	**3.41**	2.70	**1.89**	4.20	**0.7**	0.8
Markedly Abnormal Coagulation Labs##	**1.23**	3.92	**2.31**	2.43	**N/A**	N/A
Markedly Abnormal Hepatic Labs**	**0.44**	0.44	**0**	0.55	**0**	0
Markedly Abnormal Hematology Labs**	**0.41**	0.90	**0**	0.66	**0**	0

Bold rates apply to subjects who initially received placebo, and are used to help visually group them as they move through the different phases of the trials; similarly, the unbolded rates apply to subjects who were initially assigned to TTS.
DB=Double Blind phase, OL=Open Label phase
*Includes Studies 068, 092, 133 & 134 ** Includes Studies 133 & 134 only
#Percent reported only for those gaining over 5% ## Includes Study 133 only

Division comment:

- **This frequency table allows for comparison of AE rates both by duration of testosterone exposure and by duration of study participation. Some AEs may be dependent upon**

time in study, (e.g., application site reactions [ASRs]) rather than on duration of testosterone exposure (e.g., alopecia). As an example of a time-dependent AE, the frequency data on application site reactions suggests that the rate is highest (range 30-34%) in the first six months of exposure to the patch in general, rather than to testosterone specifically. Subjects continuing into the open label phase, who had already worn the patch for six months, reported a low rate (range 2.6-5.7%) of this AE. In contrast, a drug-dependent AE such as alopecia shows that the frequency rises with duration of testosterone exposure (rates in subjects who started the trials in the placebo arm rise from 2.9 to 3.3 to 3.6, while rates in subjects initially randomized to TTS rise from 4.2 to 5.0 to 5.8 as exposure to testosterone continues).

5.3.4 Relationship of Serum Free Testosterone Levels to Androgenic Adverse Events

The association of androgenic AEs in the double blind phase with maximum serum levels of total testosterone, free testosterone and DHT was assessed by categorizing hormone levels into quartiles and evaluating the rates of individual androgenic AEs within these quartiles (Table 45 shows data for free testosterone). The only association identified was one of increasing hirsutism with increasing free testosterone. However, a threshold free testosterone level reliably associated with hirsutism could not be defined by the Applicant.

Table 45 Incidence of Androgenic AE by Serum Free Testosterone Quartiles in Double Blind Phase

		TTS (N=696)					
Patients	Placebo (N=703)	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)
Acne	49 (7%)	9 (7.6%)	11 (7.4%)	8 (5.5%)	19 (13.3%)	16 (11.3%)	63 (9.1%)
Alopecia	19 (2.7%)	5 (4.2%)	6 (4.1%)	6 (4.1%)	2 (1.4%)	5 (3.5%)	24 (3.4%)
Hirsutism	35 (5%)	6 (5.1%)	5 (3.4%)	9 (6.2%)	15 (10.5%)	14 (9.9%)	49 (7%)
Voice Deepening	12 (1.7%)	3 (2.5%)	2 (1.4%)	4 (2.8%)	3 (2.1%)	4 (2.8%)	16 (2.3%)

Source: Table 43, safety-sum.pdf, p 273

Division comment:

- **The incidence of acne appears to show a trend when comparison is made between rates in the lower two quartiles (7%) and those in the upper two quartiles (11-13%).**

Four TTS subjects attained free testosterone levels above 20 pg/ml during the double blind phase (normal range for reproductive age women 0.9-7.3 pg/ml). Two, with maximal levels of 32.1 pg/ml and 25.3 pg/ml, had no androgenic AEs. Another subject with a maximal level of 61.8 pg/ml at Week 12 and 16.5 pg/ml at Week 24 reported mild facial hair growth and mild acne with onset three and four months, respectively, after randomization. She continued into the extension phase with a Week 52 free testosterone level of 3.2 pg/ml. The fourth subject developed mild chin hirsutism at three months and withdrew three months later due to lack of efficacy. Her Week 12 free testosterone level was 6.2 pg/ml and her exit level about six months after starting testosterone was 30.4 pg/ml. She reported resolution of the hirsutism one month after discontinuation of testosterone.

In the open label phase, seven subjects developed free testosterone levels above 20 pg/ml. Two, with maximal values of 21.5 pg/ml and 45.7 pg/ml, had no androgenic AEs. A subject who had a level of 107.7 pg/ml at Week 52 reported mild acne, which was ongoing at the end of the open label phase; she did not continue into the extension study. A subject with mild hirsutism had a maximal level of 24.2 pg/ml, and entered the extension study with the side effect ongoing. A

third subject experienced mild acne with a maximal free testosterone level of 24.1 at Week 52; the acne resolved shortly after she began the extension phase. A subject experienced mild hoarseness after 11 months on testosterone and had a Week 52 level of 63.1 pg/ml. She did not continue in the extension phase, but reported resolution one month after discontinuing the drug. The final subject had mild acne, mildly increased fasting insulin and experienced a DVT during the double blind phase. Her Week 52 testosterone level was 23.7 pg/ml. Both the acne and the laboratory abnormality resolved shortly after her entry into the extension phase.

Division comment:

- **There does appear to be an increased risk of hirsutism and possibly acne with rising free testosterone levels. Review of outliers on serum free testosterone levels does not identify any additional patterns of adverse events associated with attainment of supraphysiological free testosterone levels in a small number of subjects.**

5.3.5 Pharmacokinetics of Free and Total Testosterone

The Applicant submitted data descriptive of the normal range of free and total testosterone in reproductive aged women (ages 18-49 years). The reference range for free testosterone in this population was 0.9-7.3 pg/ml, and the reference range for total testosterone was 12-50 ng/dl.

The serum concentrations of free and total testosterone in participants on testosterone in Studies 133 and 134 who had blood samples collected within 5 days of applying the last patch prior to the scheduled study visit are presented in Table 46. While mean concentrations of total testosterone exceeded the upper limit of normal for reproductive-aged women at all treatment visits, mean concentrations of free testosterone remained at the upper of the normal range throughout treatment.

Table 46 Studies 133 & 134: Free and Total Testosterone Concentrations

Analyte Statistic	Week 0	Week 12[a]	Week 24	Week 52	Week 78
Free Testosterone (pg/mL)					
n	544	209	412	287	91
Mean	0.92	5.52	4.36	4.44	5.94
SE	0.03	0.41	0.16	0.31	0.47
Median	0.80	4.00	3.60	3.10	4.60
Min	0.0	0.3	0.1	0.3	0.5
Max	8.8	61.8	30.4	63.1	25.1
P-value*					0.3917
Total Testosterone (ng/dL)					
n	547	210	413	288	91
Mean	17.6	90.3	79.7	74.8	91.1
SE	0.4	4.4	2.7	3.6	6.0
Median	15.0	72.5	69.0	62.0	83.0
Min	0	7	3	6	14
Max	119	511	516	461	342
P-value*					0.0510

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.
n = number of patients with available data at timepoint; SE = standard error; 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, total, and bioavailable testosterone and total dihydrotestosterone, and across all visits for sex hormone binding globulin, using repeated measures analysis of variance (ANOVA) adjusted by study and visit.
[a] Total dihydrotestosterone was not collected at Week 12 in either study, according to the protocol.

Source: EOT Table 34, 2001133-134.pdf, p 114

Percentages of subjects in the double blind and open label phases whose maximal free or total testosterone level exceeded the normal range in reproductive age women are presented in Table 47.

Table 47 Percent of Subjects with Free and Total Testosterone Levels Beyond Normal Range for Reproductive Aged Women

Maximal Free Testosterone (Normal range 0.9-7.3 pg/ml)								
	Double Blind Phase				Open Label Phase			
Testosterone Values	Placebo		TTS		Placebo->TTS		TTS->TTS	
	N	%	N	%	N	%	N	%
Within normal range	434	99.8	351	80.0	272	87.7	256	85.9
Above normal range	1	0.2	88	20.0	38	12.3	42	14.1

Maximal Total Testosterone (Normal range 12-50 ng/dl)								
	Double Blind Phase				Open Label Phase			
Testosterone Values	Placebo		TTS		Placebo->TTS		TTS->TTS	
	N	%	N	%	N	%	N	%
Within normal range	434	99.3	91	20.7	109	35.0	118	39.5
Above normal range	3	0.7	349	79.3	202	65.0	181	60.5

Division comment:

- **The proportion of TTS treated subjects experiencing above normal values of total testosterone was much greater than the proportion with elevated free testosterone levels. The increased total testosterone levels may not reflect bioactive testosterone because of increased levels of sex hormone binding globulin (SHBG).**

5.3.6 Special Safety Studies

5.3.6.1 Mammographic Study

Study 2003082 was a 24-week, randomized (1:1), double-blind, placebo-controlled trial designed to evaluate the effects of the 300 mcg TTS on mammographic breast density and breast epithelial proliferation in 99 naturally menopausal women who were also taking combined estrogen/progestogen hormone products. Entry criteria for this study included amenorrhea for at least 12 months or FSH >40 IU/L, no sex hormone treatment for three months before enrollment, and no prior history of breast disease, cancer or abnormal mammogram. Subjects received mammograms and fine needle aspirations (FNA) at baseline and after 6 months of treatment.

Proliferation of breast epithelium was assessed by immunostaining of epithelial breast cells obtained by FNA with Ki67, a monoclonal antibody that reacts with a human nuclear antigen that is only present in proliferating cells. Mammographic breast density was classified into four categories according to the Wolfe classification:

- N1 – essentially normal breast
- P1 – prominent ductal pattern in up to ¼ of breast volume
- P2 - prominent ductal pattern in more than ¼ of breast volume
- DY – extremely dense parenchyma, usually denoting connective tissue hyperplasia

Mammograms were also classified into one of five categories of percentage of dense parenchymal tissue, ranging from 0-20, 21-40, 41-60, 61-80 and 81-100%.

The average exposure of the testosterone-exposed subjects was 171 days; 99% of subjects were compliant with dosing, defined as application of 80% of assigned patches. Eighty-eight subjects (47 on TTS) completed the study.

FNA biopsies were obtained on two occasions from all 88 subjects completing the study; however, only 125 biopsies were evaluable based on sufficient number of cells in the aspirate. Just over half (45/88) of the subjects had paired samples available for pre- and post-treatment comparison. Mean and median percent of Ki67 positive cells for each group are displayed in Table 48. The difference in change from baseline between TTS and placebo groups, which was not significant, suggested a trend toward reduced epithelial proliferation in the TTS group, but this difference disappeared when results were adjusted for the higher percent of Ki67 positive cells at baseline in the TTS group. When all evaluable biopsies were evaluated (not just paired samples), there were no statistically significant differences between placebo and TTS subjects at either baseline or end of treatment.

Table 48 Percent Ki67 Positive Cells in Subjects with Paired Samples

	Placebo (N=22)	Testosterone (N=23)
Baseline		
Mean (SEM)	1.13 ± 0.40	1.90 ± 0.45
Median	0	1.46
Month 6		
Mean (SEM)	3.60 ± 0.63	2.55 ± 0.56
Median	2.92	2.06
LSMean (SEM)	3.64 ± 0.61	2.51 ± 0.60
Month 6 Change From Baseline		
Mean (SEM)	2.47 ± 0.60	0.65 ± 0.79
Median	2.44	0.01
LSMean (SEM)	2.12 ± 0.61	0.99 ± 0.60

LSMean is the adjusted mean from the ANCOVA model

Source: Table 4, Karolinska.pdf, p 17

There were no mammographic abnormalities detected in any subjects in this study. A total of 87 subjects had mammograms evaluable for change in density. Changes from baseline in Wolfe classification and percent change are presented in Table 49. No subjects in either treatment arm experienced a decrease in breast density, and the proportions experiencing an increase by either classification did not differ significantly between the two groups. Actual scores on each classification at baseline and at the end of treatment are displayed in Table 50. Both groups showed shifts toward denser breast tissue, with neither reaching the highest categories of density.

Table 49 Change in Mammographic Breast Density

	Placebo (N=41)		Testosterone (N=46)		Overall (N=87)	
	n	(%)	n	(%)	n	(%)
Increase in breast density according to Wolfe Classification	7	(18%)	10	(22%)	17	(20%)
Decrease in breast density According to Wolfe Classification	0	(0%)	0	(0%)	0	(0%)
Increase in breast density according to the percentage scale	12	(29%)	14	(30%)	26	(30%)
Decrease in breast density according to the percentage scale	0	(0%)	0	(0%)	0	(0%)

Source: Table 6, Karolinska.pdf, p 19

Table 50 Mammographic Breast Density at Baseline

	Placebo (N=41)		Testosterone (N=46)		Overall (N=87)	
	n	(%)	n	(%)	n	(%)
Wolfe Classification						
N1	1	(2%)	2	(4%)	3	(3%)
P1	19	(46%)	23	(50%)	42	(48%)
P2	21	(51%)	21	(46%)	42	(48%)
DY	0	(0%)	0	(0%)	0	(0%)
Percentage scale						
0% to 20%	18	(44%)	12	(26%)	30	(34%)
21% to 40%	13	(32%)	20	(43%)	33	(38%)
41% to 60%	8	(20%)	13	(28%)	21	(24%)
61% to 80%	2	(5%)	1	(2%)	3	(3%)
81% to 100%	0	(0%)	0	(0%)	0	(0%)

Mammographic Breast Density at End of Treatment

	Placebo (N=41)		Testosterone (N=46)		Overall (N=87)	
	n	(%)	n	(%)	n	(%)
Wolfe Classification						
N1	0	(0%)	0	(0%)	0	(0%)
P1	13	(32%)	17	(37%)	30	(34%)
P2	28	(68%)	29	(63%)	57	(66%)
DY	0	(0%)	0	(0%)	0	(0%)
Percentage scale						
0% to 20%	11	(27%)	8	(17%)	19	(22%)
21% to 40%	13	(32%)	17	(37%)	30	(34%)
41% to 60%	13	(32%)	16	(35%)	29	(33%)
61% to 80%	4	(10%)	5	(11%)	9	(10%)
81% to 100%	0	(0%)	0	(0%)	0	(0%)

Source: EoT Tables 3&4, *Karolinska.pdf, p 24-5*

Division comments:

- **Although the proposed indication is for use in surgically menopausal women, who would only be using estrogen therapy, the Applicant provided data comparing testosterone to placebo in women using combined estrogen/progestin therapy. It is known that progesterone itself increases breast density, and thus any effect of testosterone may be obscured by the progesterone effect in this study.**

- **No formal power or sample size calculations are provided for this study. It is unclear whether the power was sufficient to detect differences between placebo and TTS-exposed subjects in breast epithelial proliferation or mammographic density that may be of clinical relevance.**
- **The duration of this study was relatively short. With regard to detection of breast cancer itself, data from the WHI studies on estrogen plus progestin found that rates of breast cancer did not diverge from those found in placebo subjects until 2-4 years following randomization.**

An additional anecdotal report arose in Study 133, where a subject in the Placebo->TTS->TTS group was diagnosed with breast cancer during the extension study. Her baseline mammogram had shown fibroglandular densities bilaterally and a six-month follow-up was recommended. She continued into the open label and extension phases, not obtaining a repeat mammogram until she had had 37 weeks exposure to testosterone. The follow-up mammogram showed microcalcifications in the left breast, and a biopsy revealed an infiltrating breast cancer with marked lobular features, which was ER and PR positive. The subject was discontinued from both testosterone and estrogen therapy.

5.3.6.2 Bone Mineral Density and Bone Turnover

Bone mineral density measurements were made of the lumbar spine at baseline and Week 24 in a subset of 120 subjects from Study 068 (Subgroup 1) and from 60 subjects in Study 092 (Subset 1), and markers of bone turnover (serum N-telopeptide, serum type 1 C-terminal procollagen peptide and serum bone specific alkaline phosphatase) were drawn at baseline and Weeks 4, 12 and 24 in the same subsets.

Although the differences were not statistically significant, the 300 mcg group increased lumbar BMD slightly from baseline to Week 24 (0.52%), while the placebo group decreased slightly from baseline (-0.11%) in Study 068. In Study 092, the difference in the change from baseline between testosterone and placebo subjects was statistically significant. Testosterone subjects showed a 0.5% increase in lumbar BMD at Week 24, compared to a 0.9% decrease seen in the placebo subjects.

In Study 068, the only statistically significant difference in markers of bone turnover between subjects receiving placebo and those taking 300 mcg testosterone was on serum N-telopeptide, a marker of bone resorption. Testosterone subjects showed a 10.1% decrease from baseline in this marker, while placebo subjects decreased by 5.7%. There were no statistically significant differences between placebo and testosterone groups in any bone markers in Study 092.

Division comment:

- **The effect of testosterone on bone mineral density appears to be neutral to slightly favorable.**

5.3.6.3 Vascular Pulsatility Study

A second 120-subject subgroup (Subgroup 2) from Study 068 and a 9-subject subset (Subset 2) from Study 092 were used for the measurement of the vascular pulsatility index by Doppler ultrasound of internal carotid artery blood flow. This was conducted at baseline and Week 24. Measurements were reported for right and left internal carotids, for the average of the two and for the worst (most increased from baseline) index for the two arteries. There were no significant changes from baseline seen in the vascular pulsatility index in the 300 mcg testosterone group vs. the placebo group in Study 068. Due to the small number of subjects (9) from Study 092, their data were not analyzed.

Division comment:

- **The effect of testosterone on vascular reactivity and impedance to blood flow appears minimal in this small exploratory analysis.**

5.3.6.4 Platelet Aggregation

Subgroup 2 from Study 068 and Subset 2 from Study 092 were also used for platelet aggregation tests, done at baseline and Week 24. Subjects were instructed to avoid aspirin for seven days prior to this test. No statistically significant changes or percent changes from baseline were seen in platelet aggregation in the 300 mcg testosterone group vs. the placebo group in Study 068. Due to the small number of subjects from Study 092, their data were not analyzed.

5.3.6.5 Total Body Composition

In Studies 068 and 092, a dual energy x-ray absorptiometry evaluation for total body composition (lean body mass and fat content) was conducted in Subgroup 1 and Subset 1 at baseline and Weeks 12 and 24. No statistically significant changes or percent changes from baseline were seen in total lean body mass, percent total body fat, trunk fat or trunk lean body mass in the 300 mcg testosterone group vs. the placebo group in Study 068. In Study 092, total lean body mass increased from baseline by 865 gm (2.4%) in the TTS group, as compared to a 226 gm (0.7%) increase in the placebo group; this difference was statistically significant. There were no significant differences in other parameters measured.

5.3.6.6 Local Tolerance

Local tolerance was evaluated in three phase 2 studies (T96002, 1999098 and T96001), which were designed to evaluate the incidence of contact sensitization and dermal irritation following repetitive applications over three weeks of active and placebo patches. Study T96002 found no evidence of contact sensitization to either the active or the placebo patch. Study 1999098 used 5 cm^2 patches cut from 14 cm^2 and 18 cm^2 patches delivering 150 mcg of testosterone per day, smaller than that used in the phase 3 trials. This cumulative irritation study found that these smaller patches showed evidence of irritation ranging from " a slight potential for very mild cumulative irritation" for samples cut from the 14 cm^2 patch to "a moderate potential for mild cumulative irritation" for the samples cut from the 18 cm^2 patch. Study T96001, which also used 5 cm^2 patch samples, found that the testosterone patch was a "probably mild" irritant in normal use, and was not a cumulative skin irritant.

Division comment:

- **These data appear to be borne out in the phase 3 trials, where the incidence of application site reactions was greatest upon initial exposure, and did not appear to increase with cumulative exposure to the patch (see Table 44).**

5.4 SUMMARY OF OVERALL SAFETY

One overarching concern in evaluating the safety of the proposed testosterone patch for use in surgically menopausal women is that the proposed labeled indication is for use in women "receiving concomitant estrogen therapy." Risks associated with use of estrogen alone in surgically menopausal women, as documented in the WHI study, include increased incidence of nonfatal stroke and deep vein thrombosis. While there appears to be a reduction in hip and vertebral fracture risk in estrogen users, estrogen alone has a neutral effect on the incidence of coronary heart disease, breast and colorectal cancer, and death.

Current black box warnings on estrogen and combined estrogen/progestin products used for treatment of vasomotor symptoms and vulvovaginal atrophy associated with menopause state that these products "should be prescribed at the lowest effective doses and for the shortest

duration consistent with treatment goals and risks for the individual woman." The American College of Obstetrics and Gynecology[3] recommends that women review their decision to use hormonal products annually with their physician. However, Intrinsa is a product that will potentially be used on a chronic, long-term basis, and thus, might induce women to continue use of estrogen well beyond the duration that would be recommended for management of menopausal symptoms.

5.4.1 Special Concerns

Areas of special concern regarding the use of testosterone in surgically menopausal women include the unknown risks of cardiovascular disease and breast malignancy potentially arising from chronic use of this hormone.

5.4.2 Unknown Risks

The primary trials reviewed enrolled surgically menopausal women, who had had a hysterectomy and bilateral salpingo-oophorectomy prior to enrollment. Thus, in this population, there is no concern about potential effects of testosterone on the endometrium. The product however, has the potential for off-label use, either in naturally menopausal women or even in pre- and perimenopausal women with intact uteri, who may be at risk for endometrial hyperplasia, cancer and pregnancy.

The proposed label notes the potential for edema as a serious complication of high doses of testosterone administered to women with preexisting cardiac, renal or hepatic dysfunction. The current trials were conducted in generally healthy women, with a mean age of 49; therefore the potential for this adverse event arising from use of Intrinsa has not been evaluated.

The major areas of unknown risk, however, concern the long-term impact of chronic use of testosterone, especially when combined with estrogen treatment. While the short-term effects of testosterone treatment appear relatively benign and easy to monitor, long-term effects cannot be appreciated from the clinical trial data available to date. The alarm generated by the publication of the WHI results following decades of widespread use of estrogen/progestin therapy highlights the need for proactive assessment of the risks of chronic use of testosterone in women.

6 PHARMACOVIGILANCE PROGRAM

The Applicant has proposed a Pharmacovigilance plan utilizing a pharmaceutical claims-based database. The proposed plan is detailed below.

[3] ACOG Task Force on Hormone Therapy, Hormone Therapy – Vasomotor Symptoms, Obstet & Gynecol, 104 (4S): 106S-117S, 2004

Pharmacoepidemiologic Study Overview

We propose a retrospective cohort study of Intrinsa patients in the Ingenix Lab/Rx Database™ to assess the incidence and risk of potential adverse health outcomes of interest. The Ingenix Lab/Rx Database™ covers over 20 million lives and includes longitudinal data representing health care services from professional, 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%). In addition, our lease agreement with Ingenix provides access to complete claims data from January 2000 through December 2008, as it becomes available in 6-month updates. We anticipate that this database will have an adequate number of patients exposed to Intrinsa to conduct analyses as early as 18 months post-launch. We expect approximately 60% formulary coverage.

In the proposed study, we will identify a population of Intrinsa users and an individually matched comparison group. Both cohorts will be followed for a period of up to five years with analyses performed as warranted for the purposes of signal detection. We would make a concerted effort to validate outcome measures by contracting with Ingenix to abstract critical data elements from the medical records. In the data analysis phase, current and recent use of Intrinsa will be defined based on prescription patterns, and age-adjusted relative risk estimates for pre-specified subgroups will be computed using Poisson regression. We will evaluate the available data in the Ingenix database 18 months post launch (receipt of updated database is expected at 24 months post launch due to lag). We will plan for subsequent analyses based on additional 6 month updates. Specific protocol details and analysis plans will be discussed and agreed upon with the Division prior to conduct.

The advantages of a cohort study design include the ability to examine multiple outcomes, minimal selection bias, and the ability to compute incidence rates for adverse events of interest. Key disadvantages are the time required to complete the study and the limited adjustment variables that are included in claims databases. This study would provide real world, observational data with the ability to assess the long-term safety of Intrinsa.

Division comment:

- **The Office of Drug Safety (ODS) was asked to provide consultation on the potential utility of this pharmacovigilance plan. They concluded that the proposed retrospective cohort study was unlikely to provide adequate information about potential risks of the product and recommended that a prospective, long-term randomized, controlled study of sufficient power, which incorporates prespecified endpoints of particular concern, would be most likely to provide meaningful answers about the long-term risks of treatment with TTS (Intrinsa). Specific comments from the ODS epidemiologist regarding the Applicant's proposed pharmacovigilance study included a concern that drug use and hospitalizations might cease to be captured by the proposed pharmacovigilance study when postmenopausal women treated with TTS shifted to Medicare as their primary health insurer at age 65. The ODS epidemiologist also had concerns that the sample size and duration of the proposed study might not provide adequate power to detect an increase over the background rate of potential adverse events of interest in women of the age group for whom TTS would be indicated.**