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APPLICATION NUMBER:

021463Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA Resubmission
Application Number(s)	NDA 21-463
Priority or Standard	Standard (Complete Response to October 16, 2009, Action Letter)
Submit Date(s)	2010-06-30
Received Date(s)	2010-06-30
PDUFA Goal Date	2010-12-30
Division / Office	DRUP / ODE 3
Reviewer Name(s)	Guodong Fang
Review Completion Date	2010-12-01 (Final draft)
Established Name	Testosterone 2% Gel
(Proposed) Trade Name	Fortesta
Therapeutic Class	Topical Steroid Androgen
Applicant	ENDO Pharmaceuticals, Inc.
Formulation(s)	$C_{19}H_{28}O_2$ (MW 288.42)
Dosing Regimen	2% Testosterone Gel
Indication(s)	Adult Male Hypogonadism
Intended Population(s)	Adult Men with Hypogonadism

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

From a clinical perspective, this reviewer recommends that Fortesta, 2% testosterone transdermal gel, be **approved** for the indication of replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone:

- "Primary hypogonadism (congenital or acquired)" or
- "Hypogonadotrophic or secondary hypogonadism (congenital or acquired)".

Based on a recent inspection of the (b) (4) and evaluation of the Sponsor's response to the Form FDA-483 observations in 2009, the Office of Compliance determined that the firm's re-assay experimental design appeared sufficient, and the results are acceptable, and has recommended to accept the analysis of all available testosterone backup samples to replace the previous analysis. The Clinical Review Team and other disciplines through their reviews believe that the results of the re-assay and the re-analyses based on the original and re-assay data are acceptable. The results of the re-assay continue to demonstrate that Fortesta adequately replaces testosterone concentrations in hypogonadal men when used as per the Phase 3 protocol dose-titration procedures.

A Black Box Warning and a Medication Guide addressing the potential for skin transference of testosterone to children have been included in labeling and are acceptable.

With the corrections of these deficiencies identified in the 2009 CR action, this Clinical reviewer recommends an Approval action at this time.

1.2 Risk Benefit Assessment Based on Clinical Findings

1.2.1 Brief Overview of Clinical Program

Fortesta™ (2% testosterone gel), supplied in a metered dose canister, is a transdermal testosterone preparation indicated for testosterone replacement therapy in adult male hypogonadism associated with a deficiency or absence of endogenous testosterone. Fortesta was demonstrated to be effective for the treatment of hypogonadism and restored average serum testosterone (T) concentration (C_{avg}) to the normal range (300-1140 ng/dL) in hypogonadal men. Fortesta is approved in 23 countries (including 20 countries in Europe) and is currently marketed in 19 of these 23 countries.

The Applicant submitted the original NDA 21-463 on May 31, 2002. During the first review cycle, the submission received a "not approvable" action (dated July 3, 2003) based on: (1)

insufficient information to establish that high supraphysiologic daily serum testosterone C_{max} levels achieved in a significant proportion of participants were safe under conditions of chronic administration and (2) insufficient information to demonstrate that the drug dose could be adjusted to consistently prevent the high supraphysiological testosterone levels. The Sponsor re-submitted its application on April 17, 2009, as a Complete Response to the July 3, 2003, non-approvable action letter. The Complete Response included one pivotal, open-label, phase 3 study in hypogonadal males in the US (trial FOR01C), with supporting evidence from other Phase 3 and 2 studies (from previous submissions) and a Phase 3b/4 European study in hypogonadal men with either metabolic syndrome or type 2 diabetes mellitus. The data to support the safety and efficacy of Fortesta came primarily from study FOR01C. The sponsor sought the same indication as previously: testosterone replacement therapy in men with conditions associated with primary or secondary hypogonadism.

In the Action letter from DRUP for the second cycle review, conveyed on October 16, 2009, the Division informed the Sponsor that based on following reasons the application could not be approved:

- **CLINICAL:** The Division of Scientific Investigations (DSI) identified several deficiencies in the analytical methods and quality control measures used to analyze specimens from the single phase III clinical study (FOR01C) through an audit of the (b) (4) located in (b) (4) These deficiencies raised serious questions regarding the validity of the data needed to determine the efficacy and safety of the drug product. In the absence of reliable data upon which an approval decision could be based, this NDA could not be approved.

- **CLINICAL PHARMACOLOGY:** Safety data were needed to determine if secondary exposure to testosterone (transfer) could occur after washing of the application site.

In the action letter, the Applicant was informed that the means to address these two deficiencies were:

- **Information Needed to Address the Clinical Deficiency:** Adequate and reliable data must be provided to assess the safety and efficacy of this drug product. The previously submitted phase III data may be sufficient if the deficiencies identified in the DSI audit of the (b) (4) can be resolved. If these deficiencies cannot be adequately addressed, new phase III data will be required.

- **Information Needed to Address the Clinical Pharmacology Deficiency:** Conduct a pharmacokinetic "wash-off" study to evaluate the amount of testosterone remaining on the skin from an application of your product after washing.

The action letter also requested submission of the following items:

- **LABELING:** At the time of the action, labeling remained unresolved. The Sponsor was informed to include updated content of labeling in the CR [as per 21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm.

- **RISK EVALUATION AND MITIGATION STRATEGIES REQUIREMENTS**: In accordance with section 505-1 of the FDCA, a Risk Evaluation and Mitigation Strategy (REMS) was deemed necessary for Fortesta (testosterone) to ensure that the benefits of the drug outweigh the risk of secondary exposure of children to testosterone from men using this product. It was determined that under section 505-1, the REMS for this product must include a Medication Guide and a timetable for submission of assessments.

- **SAFETY UPDATE:** A safety update must be included in the CR as described at 21 CFR 314.50(d)(5)(vi)(*b*). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

RESUBMISSION ON JUNE 30, 2010

The Sponsor worked with the [redacted] (b) (4) to respond to the DSI audit deficiencies outlined in the FDA Form 483. Based on this work, the Sponsor believes and DSI has concurred that all of the FDA 483 observations have been successfully resolved. The reanalysis data generated at [redacted] (b) (4) support concordance with the original data; therefore, the data from the original NDA are considered reliable and accurate. After the Type C Meeting with the Division on June 10, 2010, the Sponsor provided a detailed description of the re-analysis and individual patient narratives associated with the pivotal Phase III study FOR01C. On June 30, 2010, the Sponsor submitted this CR amendment (RESUBMISSION) electronically to NDA 21-463, which provides data which supports the original assessment of safety and efficacy for FORTESTA.

1.2.2 Efficacy

The **primary efficacy endpoint** in the pivotal US Phase 3 trial FOR01C was the proportion of patients with an average testosterone concentration ($\mathbf{C_{avg}}$) in eugonadal range (300 – 1140 ng/dL) at Day 90. Important **secondary endpoints** included the proportion of subjects with maximum testosterone concentration ($\mathbf{C_{max}}$) ≤ 1500 ng/dL and the proportion with C_{max} between 1800 and 2500 ng/dL at Day 90**.**

For testosterone replacement products, the Division currently considers the following as evidence of acceptable efficacy:

- Primary endpoint (C_{avg}): The point estimate of subjects with C_{avg} in the normal range should be at least 75%, with a lower bound of 95% CI > 65%, at a predetermined time point.
- Secondary endpoints (C_{max}):
  a. A minimum of 85% of subjects with C_{max} ≤ 1500 ng/dL at a predetermined time point

b. Less than 5% of subjects with C_{max} between 1800 and 2500 ng/dl at a predetermined time point

Table 1.1 shows the results for the primary and secondary endpoints from the original data analysis and from the re-assay data analysis.

Table 1.1 Analysis of the Original and Re-assayed Results of Total Serum Testosterone C_{avg} and C_{max} at Day 90 for All Modified ITT (MITT) Subjects

Assay	N (number of samples)	% Subjects (95% CI) Who Met the Criterion: C_{avg} Within [300, 1140 ng/dL]	% Subjects Who Met the Criteria		
			$C_{max} \leq$ 1500 ng/dL	C_{max} Within [1800, 2500 ng/dL]	$C_{max} >$ 2500 ng/dL
Original	138 (1374)	76.1 (69.0-83.2)	91.3	4.3	0
Re-assay	129 (1247)	77.5 (70.3-84.7)	94.6	1.6	0
Re-assay imputing with valid original values[a]	138 (1368)	76.8(69.8-83.9)	92.8	2.9	0

Reviewer's comments: The reliability and accuracy of the original data are supported by the similarity of the statistical analysis results. The analysis of the original data and the re-assayed data both met the acceptance criteria for the primary and all of the secondary endpoints at Day 90. Thus the conclusions of the 2009 submission remain the same and support the 2009 assessment of the efficacy associated with the use of FORTESTA.

1.2.3 Safety

Since the previous Clinical review, there have been **no changes** for exposure to the drug, adverse events (AEs), vital signs, physical findings and other observations related to safety, and safety in special groups and situations.

1.2.3.1. PSA issues:

One of FDA's Form 483 observations regarded the accuracy and precision of the assay for PSA at (b) (4) specifically, that PSA values were below the (b) (4) validated range but in agreement with labeled assay range by the kit manufacturer. Since the observation only affects low PSA values, and clinical concern is primarily in regard to elevated values, the Sponsor does not believe that this observation impacts the clinical safety of FORTESTA. To address this concern regarding PSA, additional analyses were performed by the (b) (4) to confirm the accuracy and precision of the lower limit established by the kit manufacturer for the PSA assay results. The new data indicate that the PSA results are considered accurate and precise to 0.01 ng/mL, the lower limit of samples that were reported in the pivotal study, FOR01C. Thus the results reported in FOR01C are accurate and the conclusions for serum PSA are unchanged.

1.2.3.2. Postmarketing Safety data

FORTESTA has been approved in 20 EU member states and 2 other countries. The Sponsor provided postmarketing safety information from these countries, which comprised a total of 56 AE case reports. Of this total, there were 9 serious AE's (SAE's). During a 12-month period, 20 AE cases were reported including 6 SAE's, with 3 unexpected (tachycardia, acquired feminization, and vascular purpura), and 3 expected (one with blood T increased, and two of prostate cancer with increased PSA).

Reviewer's comments: In the patient with a very high serum T level, the patient's T concentration was re-assessed and determined to be within normal range while still on drug. Therefore, a lab error may have been responsible for the errant high value. Otherwise, the safety findings of Fortesta were expected of a transdermal testosterone replacement product. It is considered that the overall safety profile of FORTESTA (testosterone 2% gel) is well tolerated for use as testosterone hormone replacement in adult hypogonadal men with specific dose adjustment criteria outlined in the Prescribing Information.

1.2.4 Dose Regimen and Administration

Fortesta is supplied in 60 gm metered dose canisters with a pump that delivers 10 mg of testosterone (0.5 gm of gel) per one complete depression. The recommended starting dose is 40 mg of testosterone (2.0 gm of gel) applied once daily at approximately the same time in the morning to the front and inner thighs. Dose titration is based on serum testosterone levels at 2-hour post dosing at 14 days after initiating treatment, and if necessary, at 14 days after any subsequent change in dose. In the clinical trial that supported approval, dose titration occurred on Days 14, 35, and 60 (±3 days) after initiating treatment, with the final dose ranging between 10 mg to 70 mg testosterone per day.

1.2.5 Special Populations

No new data regarding special populations are included in this re-submission.

1.2.6 Drug Abuse and Dependence

No changes have been made since last review circle. Fortesta is a Schedule III controlled substance because it contains testosterone. The labeling has been reviewed by the Controlled Substances Staff (CSS) and all their comments have been incorporated.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

1.3.1 Black Box Warning

A black box warning has been instituted for the class of topical testosterone products due to the risk of adverse outcomes in children who are inadvertently exposed to testosterone by direct skin

contact at the application site of adult males. The Fortesta label will also contain this black box warning, which reads:

WARNING: SECONDARY EXPOSURE TO TESTOSTERONE

- **Virilization has been reported in children who were secondarily exposed to testosterone gel.**
- **Children should avoid contact with unwashed or unclothed application sites in men using testosterone gel.**
- **Healthcare providers should advise patients to strictly adhere to recommended instructions for use.**

1.3.2 Medication Guide

At the time of instituting the black box warning, the Agency also required manufacturers of topical testosterone products to distribute a Medication Guide to consumers. The Applicant's proposed Medication Guide will be the same as the Medication Guides instituted for the existing approved topical testosterone products. The Medication Guide and timetable for assessments constitutes the required Risk Evaluation and Minimization (REMS) program for this product and was submitted in its final form in the June 30th, 2010 CR submission.

Reviewer's comment: The Division of Risk Management (DRISK) has concurred with the elements of the proposed REMS.

1.4 Recommendations for Postmarket Requirements and Commitments

The sponsor has agreed to conduct a "hand- and application site- washoff" study as a postmarketing requirement study in order to demonstrate that Fortesta is effectively removed from the hands and application site by simple washing. The CR submission contains a detailed protocol synopsis for this study. On October 11, 2010, the sponsor committed to goal dates for this study, as follows:

For the hand washing and application site study (draft protocol submitted to IND January 22, 2010, Serial No. 0014), please note the following dates for the PMR:

- Final Protocol Submission: 02/2011
- Study/Trial Completion: 09/2011
- Final Report Submission: 04/2012

Reviewer's comment: The 7-month timeframe from submitting the study protocol to completing the study is needed for the Division to review the protocol and to discuss it with the Sponsor, and for the Sponsor to initiate and complete the study. The Sponsor is requesting only several months after the study completion to submit the final study report. These dates are acceptable.

2 Introduction and Regulatory Background

2.1 Product Information

Fortesta™ (2% testosterone gel) belongs to the pharmacological class of androgenic hormones. The formulation contains the active drug substance, 2% testosterone (a Schedule III controlled substance as defined by the Anabolic Steroids Act), and eight excipients. All excipients have USA/NP monographs.

Drug Product (proprietary name)	Fortesta™ 2% Gel
Drug Substance (non-proprietary or common name)	Testosterone
Sponsor Name	ENDO Pharmaceuticals Inc. (from ProStrakan Inc. 09/08/2009)
Dosage Form	Fortesta 2% Gel is supplied in 60 g metered dose canisters with a pump that delivers 0.5 g gel (10 mg of testosterone) per complete depression
Strength	2.0 % w/w
Route of Administration	Transdermal
Proposed Indication(s)	FORTESTA is an androgen indicated for testosterone replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone: • Primary hypogonadism (congenital or acquired) – testicular failure due to conditions such as cryptochidism, bilateral torsion, orchitis, vanishing testis syndrome, orchiectomy, Kleinfelter's syndrome, chemotherapy, or toxic damage from alcohol, heavy metals. • Hypogonadotropic hypogonadism (congenital or acquired) – idiopathic gonadotropin or luteinizing hormone-releasing hormone (LHRH) deficiency or pituitary-hypothalamic injury from tumors, trauma, or radiation.

2.2 Currently Available Treatments for Proposed Indications

Testosterone replacement therapy is used to treat conditions associated with a deficiency or absence of endogenous testosterone. FDA-approved testosterone products are shown in Table 2.1.

Table 2.1 Currently Available Testosterone Products in the United States

Drug Name	Adult Dose	Route of Administration	Dosage Forms and Strengths
Testosterone (AndroGel)	Starting: 5 gm once daily; may titrate up to 10 gm daily	Topical gel	1 % gel; transdermal; 2.5 and 5 gm unit-dose packets or multiple-dose pump with 1.25 gm doses per pump actuation
Testosterone (Testim)	Starting: 5 gm once daily; may titrate up to 10 gm	Topical gel	1 % gel; transdermal 5 gm unit-dose tubes
Testosterone (Androderm)	Starting: 5 mg system applied nightly; may titrate to 7.5 mg	Topical film (patch)	2.5 mg/24 hour and 5 mg/24 hour film, extended-release; transdermal
Testosterone (Striant)	Apply one system to gums, twice daily	Buccal	30 mg buccal tablet, extended-release; buccal
Testosterone (Testopel Pellets)*	150-450 mg SC every 3-6 months	Implant	75 mg pellet; subcutaneous (SC)
Testosterone cypionate (Depo–Testosterone)# Testosterone enanthate (Delatestryl)**	50-400 mg IM every 2-4 weeks 50-400 mg IM every 2-4 weeks	IM IM	100 mg/mL and 200 mg/mL injectable; intramuscular 200 mg/mL injectable; intramuscular
Methyltestosterone (Virilon, Testred, Android, Methitest)	10-50 mg daily§	Oral	10 mg capsule; oral 10 and 25 mg tablets; oral

* Prescribing information available from Slate: (www.slatepharma.com/wp-content/uploads/2008/12/testopelpi.pdf)
\# Prescribing information available from Pfizer (www.pfizer.com/files/products/uspi_depo_testosterone.pdf)
** Prescribing information available from Indevus (www.indevus.com/site/images/PDF/delatestryluspi.pdf)
§ Dose information available from Drug Facts and Comparisons, 4.0 (Wolters Kluwer Health, Inc; 2008)
Source: Division's Clinical Reviewer.

Limitations of the currently available products include the following:

- Injectable depot solutions may be associated with pain at the injection site. Mood swings are possible due to large fluctuations in testosterone levels.
- High dose, oral, methyltestosterone formulations have been associated with an increased incidence of liver disease.
- Transdermal patches may be associated with significant application site reactions.
- Pellet implants can be expelled from the insertion site and may result in infection.
- Testosterone gels incur the potential risk of secondary exposure to testosterone of children and women.

Currently, the goal of testosterone replacement therapy in hypogonadal men is to replace testosterone levels at as close to physiological concentrations. Clinical guidance from the Endocrine Society indicates that testosterone replacement therapy should aim to achieve testosterone levels in the mid-normal range.

2.3 Important Safety Issues with Consideration to Related Drugs

Labeled risks of testosterone administration in hypogonadal men include worsening of clinical BPH symptoms, polycythmia, induction or exacerbation of sleep apnea, breast tenderness or enlargement, liver toxicity (with methyltestosterone formulations), and acne. Two major areas of concern in older men with aging-associated decline in serum testosterone are the unknown effects of long-term testosterone administration on the risks of prostate cancer and progression of atherosclerotic heart disease.

Topical testosterone gel preparations, which are applied directly to the skin, have been associated with a small number of events of secondary exposure of testosterone in children. Several exposed children have experienced significant clinical sequelae which prompted the FDA to mandate a Black Box Warning for all topical testosterone products.

2.4 Summary of Presubmission Regulatory Activity Related to Submission

Cellegy Pharmaceuticals opened IND (b) (4) (2% testosterone gel for the treatment of male hypogonadism) on August 24, 1998. An NDA (21-463) for 2% testosterone gel (formerly Fortigel) was filed on June 3, 2002, based on the results from a single Phase 3 trial (study T 00-03-01).

On July 2, 2003, NDA 21-463 received a "not approvable" action. The deficiencies noted in the marketing application were:

1) Lack of evidence to support that high supraphysiologic daily C_{max} is safe for chronic administration. This deficiency is evidenced by the observation that 9% of patients had maximum serum testosterone concentrations (C_{max}) of >1500 ng/dL but ≤ 1800 ng/dL, 14% had C_{max} > 1800 ng/dL but ≤ 2500 ng/dL, and 6% had C_{max} > 2500 ng/dL. (Table 2.2)
2) Lack of information to support that the dose of this product can be adjusted to consistently preclude achieving these high supraphysiological T levels.

Table 2.2 C_{max} Outliers from Study T 00-03-01 in Original Submission of NDA 21-463*

Product	C_{max} (ng/dL)				C_{avg} (ng/dL)	N
	between 1200 – 1500	between 1500 – 1800	between 1800 – 2500	> 2500	> 1100	
2% testosterone	20 (14%)	13 (9%)	20 (14%)	9 (6%)	0 (0%)	147

*6 months post treatment with 2% testosterone gel;
Source: Division's Clinical Analysis.

To resolve these deficiencies, the Division recommended a new clinical trial (s) using lower doses of 2% testosterone gel or another testosterone gel formulation to demonstrate that physiological levels of testosterone can be attained while avoiding high supraphysiologic C_{max} levels of testosterone.

On January 12, 2004, the sponsor submitted an amendment to NDA 21-463. This amendment contained the results of a second Phase 3 study (CP601B 02-02-01). The Division determined that the findings of this second phase 3 study did not adequately address the deficiencies outlined in the July 3, 2003, Non-Approvable letter.

Cellegy (b) (4), and transferred ownership of 2% testosterone gel to Strakkan Pharmaceutical in February, 2007. On April 6, 2007, Strakkan Pharmaceutical requested a Special Protocol Assessment for a new phase 3 study entitled, **"**An Open Label Phase 3 Study of Fortesta Testosterone Gel" (Study FOR01C). The protocol was assigned a new IND number (76,634). A Type A meeting was held with the sponsor on May 24, 2007, to discuss the protocol for Study FOR01C. The Division accepted the design and size of the proposed Phase 3 study in a regulatory letter dated August 23, 2007. Findings of study FOR01C form the basis of Complete Response #2 which was submitted on April 17, 2009.

During the review in 2009, it originally appeared that the efficacy and safety of Fortesta had been confirmed by results from the new study, FOR1C. However, the results of an audit by the Division of Scientific Investigations (DSI) of the (b) (4) located in (b) (4) raised some new concerns. The audit identified several deficiencies in the analytical methods and quality control measures used to analyze specimens from the phase III clinical study FOR01C. These deficiencies raised serious questions regarding the validity of the data that was submitted by the applicant in support of efficacy and safety of the drug product. In the absence of reliable data upon which an approval decision could be based, the NDA could not be approved, and a CR action was taken on October 16, 2009.

Subsequent to the CR action, the Division held a Type A teleconference with the Sponsor on December 1, 2009. The meeting included discussion of how to resolve the CR deficiency, including the Sponsor's plan to re-analyze all available serum samples from Study FOR01C for serum testosterone and compare those to the original analytical results. The Division met with the Sponsor on June 10, 2010, at a Type C Guidance meeting. At that time, the applicant stated that they believed that the deficiencies identified in the DSI audit of the (b) (4) had been adequately addressed and that the data from Study FOR01C should be considered reliable. Further, the applicant noted that their re-analysis of available samples provided strong support for the conclusions from the original analysis.

On June 30, 2010, the applicant submitted this Complete Response.

3 Ethics and Good Clinical Practices

No changes since last submission.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls (CMC)

The CMC review team notes that there have been no changes since last submission. In their final review, dated December 10, 2010, the CMC review team stated that for this review cycle, the label and labeling were re-reviewed in the context of a new labeling approach for the testosterone drug products and these items have been revised satisfactorily, making the previous "Approval" recommendation from the CMC perspective still effective.

4.2 Clinical Microbiology

No new microbiology data were submitted nor were they requested for the current Complete Response NDA submission.

4.3 Preclinical Pharmacology/Toxicology

No new pharmacology/toxicology data were submitted nor were they requested for the current Complete Response/NDA submission. In their final review, the PharmTox review team stated that labeling for this product would be consistent with class labeling for testosterone products. On December 13, 2010, Dr. Reid concurred with final labeling.

4.4 Clinical Pharmacology

In their final review dated December 15, 2010, the clinical pharmacology reviewer concluded that "The Division of Clinical Pharmacology 3, Office of Clinical Pharmacology finds the clinical pharmacology information submitted in NDA 021463 acceptable provided that an agreement is reached between the sponsor and the Division regarding the language in the package insert."

The clinical pharmacology reviewer also noted that a clinical trial entitled "Hand washing and application site washing trial following application of Fortesta" to assess the amount of residual T before and after washing primary user's hands as well as thighs (application sites of Fortesta) should be conducted as a Phase 4 post-marketing requirement.

The Executive Summary of the Clinical Pharmacology review points out the Office of Clinical Pharmacology requested a consult from DSI to inspect the analytical site where the back-up samples were analyzed. The review states that following the DSI inspection, the DSI reviewer recommended to accept the dataset provided by the sponsor.

4.5 Biostatistics

According to their final review dated November 19, 2010, the statistical review team believes that based on the re-assayed percentage of successful responders and the concordance between the original results and the re-assayed results, the re-assayed data seems acceptable. Results from re-assayed values and sensitivity analysis all met the study acceptance criteria. Biometrics concluded that the results from phase 3 study FOR01C with original and re-assayed values support the efficacy of Fortesta for testosterone replacement in male hypogonadism. The study confirmed that with the right starting dose of Fortesta, sampling time points and the titration schedules, testosterone levels were achieved within the physiologic range for the majority of the patients. Fortesta also minimized supraphysiologic concentrations of testosterone levels. From a statistical perspective, the Statistical Review Team recommended approval of the current Complete Response/NDA.

4.6 Consults from Other Divisions

4.6.1 Division of Medication Errors Prevention and Analysis (DMEPA)

In their final review dated November 2, 2010, DMEPA determined that the proposed tradename "Fortesta" is not vulnerable to name confusion that could lead to medication errors and does not object to use of the proposed tradename. On December 3, 2010, and December 12, 2010, DMEPA concurred with the final carton/container labeling and final package insert labeling, respectively.

4.6.2 Division of Risk Management (DRISK)

In a final review dated November 22, 2010, DRISK concurred with the elements of the proposed REMS. A final REMS Memorandum was completed by DRUP on December 9, 2010.

In another final review dated December 6, 2010, DRISK stated that the Medication Guide was acceptable with the accompanying recommendations for changes. The applicant made the recommended changes.

4.6.3 Division of Drug Marketing, Advertising and Communications (DDMAC)

DDMAC reviewed the proposed product labeling (PI), carton labeling and container labeling for Fortesta included in this re-submission. The DDMAC recommendations were considered and acted upon during label negotiations with the sponsor.

4.6.4 Division of Pharmacovigilance (DPV)

The DPV agreed with the Division that a REMS (including a Medication Guide) and labeling to include a black box warning should be required for all testosterone gel products. The risk of transfer of testosterone from patients to children was discussed at a June 23, 2009, Pediatric Advisory Committee Meeting. A Medication Guide and a black box warning have been instituted for the three currently approved testosterone gel products (AndroGel, Testim and Axiron).

4.6.5 Division of Scientific Investigation (DSI)

In their final reviews data November 6 and November 18, 2010, DSI commented upon the Applicant's response to the original FDA Form 483 deficiencies regarding (b) (4). DSI concluded the following:

- The analysis of all available testosterone backup samples to replace the previous analysis was considered acceptable. At the request of the Division of Clinical Pharmacology III, the backup sample analysis was inspected by DSI to assure the integrity of the analysis. At the time of the November 6, 2008 DSI memo, the re-evaluation of the failed FSH samples appeared acceptable but the free testosterone, estradiol, and DHT backup sample analyses were considered not acceptable due to lack of long term -70°C frozen stability assurance. The estradiol and DHT data were eventually accepted by DSI (see below for a summary of the November 18, 2010 DSI Addendum memo).
- Due to the endogenous nature of the analytes, the use of baseline values instead of nominal values for the six cycles of freeze/thaw (F /T) stability data for all analytes provided in the response can be accepted. The long term −70°C frozen stability data for total testosterone can be accepted, however (b) (4) was asked to provide a rationale explaining how evaluating stability versus baseline determinations is equivalent to using nominal concentrations. Additionally, only the FSH long-term frozen stability was initially considered to be within acceptable performance. The repeated values for free testosterone, estradiol and DHT were initially considered not acceptable as 2.6 year stability for these analytes had not been established. However, in their subsequent Addendum memo, the estradiol and DHT data were later found to be acceptable to DSI (see below).
- The backup sample experiment with active audit trail should be sufficient to reconstruct parameters changed during sample analysis.
- The firm's ISR experiment design appears sufficient.
- The DHT measurement concerns have been addressed sufficiently.

- Limiting LH reported values to the confirmed LLOQ of 0.24 mIU /mL is appropriate.

In their Addendum memo, which describes in greater detail the DSI audit of the re-assay of the analytical portion of the study FOR01C, DSI stated:

- The DHT and E2 long-term –70°C stabilities have been demonstrated up to 960 and 1025 days, respectively. The re-assay for the DHT and E2 samples are therefore acceptable.
- Less than 66% of the Free T stability samples were within 20% of their target values: However, the mean decrease for Free T from the original measurement was less than 15% indicating the degradation was not significant. Further evaluation of the Free T stability data showed that there was large variability in the stability data but there was no clear indication of Free T degradation. Overall, DSI has decided to recommend accepting data of the re-assayed Free T samples.
- SHBG long term –70°C storage stability has been established to 168 days.

Additionally, in DSI's second addendum review for the 2009inspection, sent to the review division August 9, 2010, DSI concluded that the firm's ISR experiment design appeared sufficient. The ISR data were reviewed at the 2010 inspection and the results are acceptable.

4.6.6 Pediatric Review Committee (PeRC)

PeRC granted a full pediatric waiver for Fortesta on August 20, 2009 based on the following:
1) Studies would be highly impracticable to conduct and,
2) The disease/condition does not exist in children and,
3) The product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.

The PeRC requested that the Division modify the pediatric page to indicate that the primary reason for waiver as being too few children with disease/condition to study. PeRC also reiterated that Fortesta did not need PREA. There have been no changes in the PeRC position since the last review cycle.

4.6.7 Controlled Substance Staff (CSS)

In their final review dated October 20, 2010, CSS provided final recommended labeling for the Drug Abuse and Dependence section of the label. The Sponsor’s proposal was generally acceptable with the addition of one sentence. There were no CSS changes since last submission.

5 Sources of Clinical Data

5.1 Size of the Testosterone dataset and the number of invalid results

During review of NDA 21-463 2009 submission, the DSI identified 290 (8%, 290/3696) serum testosterone results that did not meet the bioanalytical criteria. These 290 samples were from 64 subjects who had at least one specimen in a previous invalidated run. The sponsor decided to re-assay all available back-up samples for total serum testosterone, except for five (5) back-up samples which were not re-assayed because of an assay requisitioning issue. In addition, all 5 of these samples had valid assay results. For the 290 serum testosterone results which were invalid, Table 5.1 showed that number of invalid results by study day, and the number which were re-assayed. Of these 290 invalid results, 90% were re-assayed. The results of Day 90 from those of MITT population are the basis of the trial's primary and secondary endpoints. For the Day 90 MITT population, 95% of the invalid results were re-assayed.

Table 5.1 Summary of the Number of Samples by Day Which Had Invalid Results (All Subjects)

Day	Number of invalid results[a]	Number of invalid results which did not have a valid re-assay	Number of invalid results for which valid results could be obtained by re-assaying a backup sample (%)
Any day in study	290	29	261 (90%)
Day 90[b]	153	7	146 (95%)
Day 35[b]	97	7	90 (93%)
Screening, Baseline, Day 14, or Day 60[c]	40	15	25 (63%)

[a] Invalid results are those that came from assays which did not meet the bioanalytical acceptance criteria
[b] Samples collected on Days 35 and 90 comprise complete 24-hour profiles. Each profile includes up to 10 samples.
[c] Samples collected at baseline, Day 14, or Day 60 were only from 2 hours post-FORTESTA application.

The numbers of the valid and invalid results from Day 90 are shown in Table 5.2, providing evidence that a high percentage of Day 90 valid and invalid samples were re-assayed. In particular, for the MITT population, of the original 1222 samples that had valid results, re-assayed results are available for 1101 of those samples (90%); and of the 152 invalid sample, re-assayed results are available for 146 of those samples (96%).

Table 5.2 Number of Original Valid and Invalid Results Summarized by Original Assay and Re-assay on Day 90

Study Day	Category of Original Assay Result	Number of Original Samples with Results	Number of Original Samples Which Were Re-assayed
Day 90	Valid	1228	1107 (90.1%)
	Invalid	153	146 (95.4%)
	Total	1381	1253 (90.7%)
Day 90 MITT Population	Valid	1222	1101 (90.1%)
	Invalid	152	146 (96.1%)
	Total	1374	1247 (90.8%)

In addition, complementary information in the form of a data flow starting with the original results and ending with the number of samples which have at least one valid result (from an original valid assay or a re-assay) is shown in Table 5.3. For Day 90, there were originally 1381 samples. Through re-assaying backup samples, 1374 had at least 1 valid result and only 7 samples did not have at least 1 valid result. Between original results which were valid and results from the re-assay, very little data (< 1%) are missing with over 99% of the samples having at least one valid result. Thus, for the analysis, missing values from the re-assay can be effectively addressed by imputing valid values from the original analysis.

Table 5.3 Summary of the Number of Samples That Were Originally Assayed, Re-assayed, and the Number of Valid and Invalid Results on Day 90

Study Day	Original Results, N	Re assayed Results, N (% of Original)	Re-assayed Results Not Available, N (% of Original)	Re-assayed Results Not Available But Original Assay Valid, N	# of Samples Which Did Not Have Any Valid Assay Results	Samples Which Had at Least One Valid Assay Result, N (% of Original)
Day 90	1381	1253 (90.7%)	128 (9.3%)	121	7	1374 (99.5%)
Day 90 MITT Population	1374	1247 (90.8%)	127 (9.2%)	121	6	1368 (99.6%)

Reviewer's comment: From the clinical review point of view, the database of reassay for reanalysis is adequate and acceptable.

5.2 Concordance of the original results and the re-assayed results

To demonstrate that the original results were sufficiently similar to the re-assayed results such that the original results can be considered reliable, the Sponsor performed a concordance correlation analysis.

Figure 5.1 and Figure 5.2 are scatter plots of all pairs of the original assay results versus the re-assayed results from all of the study days and Day 90, respectively. The Sponsor determined that the Pearson Correlation Coefficient (95% confidence interval [CI]) between the difference and the average of the original assay value and re-assayed value for total testosterone was 0.09 (0.06-0.13), so only untransformed data were used to generate scatter plots and the Concordance Correlation Coefficients (CCC). The CCCs were "excellent" and for all study days: CCC [2-sided 95% CI] = 0.947 [0.943-0.950]; for Day 90: CCC = 0.941 [0.935-0.947]). Closer examination of the valid and invalid results separately gives confidence in both the concordance approach and the reliability of the invalid original results. Figure 5.3 and Figure 5.4 are scatter plots of the valid original values versus the re-assayed values for all of the data and the Day 90 data, respectively. The CCCs were very strong (all valid original data: CCC [2-sided 95% CI] = 0.948 [0.945-0.952]; Day 90 valid original data: CCC [95% CI] = 0.941 [0.934-0.947]). The

Sponsor believes that this strong concordance between the valid original values and the re-assayed values demonstrates that the concordance approach is appropriate.

The DSI observation identified 290 serum testosterone samples that did not meet the bioanalytical acceptance criteria, and were judged as "invalid" results. Re-assayed values are available for 261 of these samples. On Day 90, there were 153 invalid results of which 146 re-assayed values are available. Figure 5.5 and Figure 5.6 are scatter plots of the invalid original values versus the re-assayed values for all of the study days and Day 90, respectively. The CCCs were very strong: for all original invalid data: CCC [2-sided 95% CI] = 0.927 [0.910-0.944]; for Day 90 invalid data: CCC [2-sided 95% CI] = 0.941 [0.923-0.960]. The Sponsor believes that this "excellent" concordance between the invalid original data and the re-assayed data demonstrates that the original invalid data were, in fact, reliable.

Table 5.4 Concordance Correlation Coefficients (CCC)

	All original data from all days vs. the re-assayed for all days	Day 90 original vs. re-assayed	All valid original data vs. the re-assayed for all days	Day 90 valid original data vs. the re-assayed for Day 90	All invalid original data vs. the re-assayed for all days	All invalid original data vs. the re-assayed for Day 90
Subjects	**3318**	**1253**	**3052**	**1107**		
CCC	**0.947**	**0.941**	**0.948**	**0.941**	**0.927**	**0.941**
CI	**(0.943, 0.950)**	**(0.935, 0.947)**	**(0.945, 0.952)**	**(0.934, 0.947)**	**(0.910, 0.944)**	**(0.927, 0.960)**

Figure 5.1 Scatter Plot of All of the Original Results Versus Re-assayed Results for Total Testosterone (N=3318)

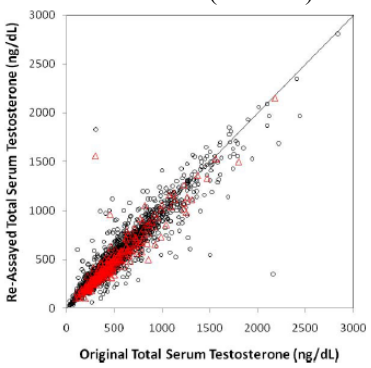


Figure 5.2 Scatter Plot of Day 90 Results Versus Re-assayed Results for Total Testosterone (N=1253)

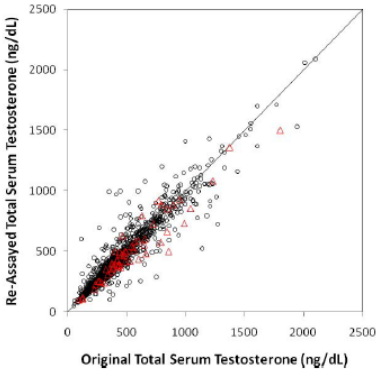


Figure 5.3 Scatter Plot of the Original Values from Assay Runs Which Met Bioanalytical Criterion (Valid) Versus Re-assayed Values for Total Testosterone (N=3052)

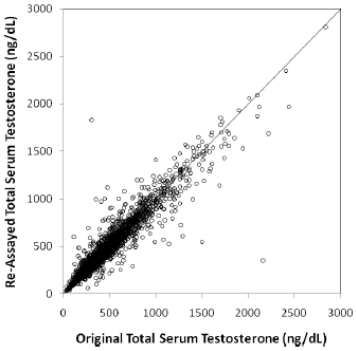


Figure 5.4 Scatter Plot of Day 90 Original Values from Assay Runs Which Met Bioanalytical Criterion (Valid) Versus Re-assayed Values for Total Testosterone (N=1107)

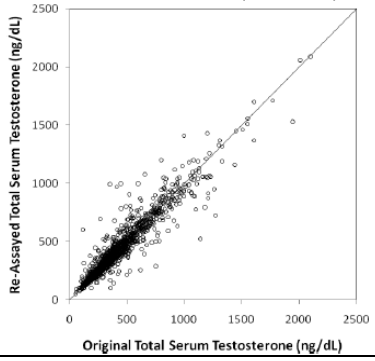


Figure 5.5 Scatter Plot of the Original Values from Assay Runs Which Did Not Meet Bioanalytical Criteria (Invalid) Versus Re-assayed Values for Total Testosterone (N=261)

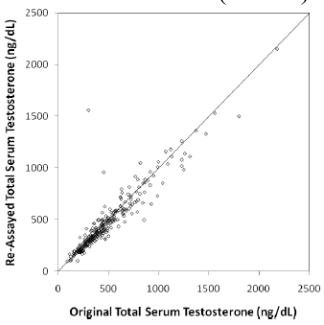
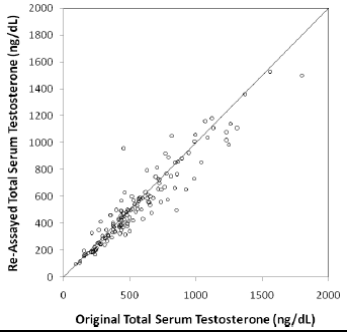


Figure 5.6 Scatter Plot of Day 90 Original Values from Assay Runs Which Did Not Meet Bioanalytical Criteria (Invalid) Versus Re-assayed Values for Total Testosterone (N=146)



Reviewer's comment: The method of concordance correlation analysis is acceptable and based on the high percentage of re-assayed data and strong concordance between the two groups of samples, the re-assayed samples are acceptable; the results from this analysis demonstrated that the original data including the "invalid data" are acceptably reliable.

6 Review of Efficacy

Efficacy Summary

The original efficacy summary from the 2009 submission remains the same:

Fortesta is effective in restoring mean serum testosterone (T) level (C_{avg}) within the physiologic range in men with hypogonadism. Supra-physiologic T concentrations may be prevented by the proposed starting dose of Fortesta 40 mg once daily, titrating in 10 mg increments as needed, to a final dose ranging from 10 mg to 70 mg once daily.

6.1 Re-analyses of Primary and Secondary Endpoints

6.1.1 Methods

The current resubmission mainly includes the results of the re-assayed data and re-analyses to support the original assessment of the efficacy and safety data of Fortesta. The primary focus of this review is on the validity of the re-assayed data and the reanalysis of the data.

As shown in Table 6.1, of the 138 subjects in the original MITT population, 129 subjects' re-assayed total serum testosterone values were available for the re-analysis. Table 6.2 shows the analysis of the original values from the clinical study report (submitted April 17, 2009) and the analysis using the re-assayed values only. In the original MITT population, there were 5 subjects with a BMI ≥ 35 kg/m^2, who by strict, per-protocol definition were not eligible for study participation, but were included nonetheless; 4 of these obese men had samples available for re-assay and 1 did not.

Table 6.1 Analysis subjects sets

	Based on Original Assay	Based on Re-assay
Number of subjects who had at least one application of the study drug and had more than one of the total serum testosterone values at Day 90 (MITT population)	**138**	**129**
Number of subjects who had at least one application of the study drug and had more than one of the total serum testosterone values at Day 90 and whose BMI < 35 kg/m^2	**133**	**125**

Since some subjects did not have back up samples a supportive statistical analysis of re-assayed values using imputation is also given in Table 6.2. Imputation means that when re-assayed values are not available, original values are substituted for the missing re-assayed value. This analysis was provided by the Sponsor to support the analysis using all available re-assayed values only.

This supportive analysis uses all valid values: re-assayed values with imputation of original valid values when re-assayed values were not available; thus excluding the 6 invalid original values which did not have backup samples available for re-assay.

Based on re-assayed values only, among 129 patients with valid re-assayed values, 77.5% of the patients had their testosterone levels within the normal range with the lower bound of the 95% CI of 70.3% on Day 90, which met the threshold. For the re-assayed C_{max} assessment on Day 90, the results also met the predefined threshold for demonstrating efficacy criteria. As shown in Table 6.2, more than 94.6% patients had C_{max} less than 1500 ng/dL, fewer than 2% of patients exceeding 1800 ng/DL and none exceeding 2500 ng/DL.

Table 6.2 Analysis of the Original and Re-assayed Results of Total Serum Testosterone C_{avg} and C_{max} at Day 90 for All Modified Intent-to-Treat (MITT) Subjects

Assay	N (number of samples)	% Subjects (95% CI) who met the criterion: C_{avg} within [300, 1140 ng/dL]	% Subjects who met the criteria		
			$C_{max} \leq$ 1500 ng/dL	C_{max} within [1800, 2500 ng/dL]	$C_{max} >$ 2500 ng/dL
Original	**138 (1374)**	**76.1 (69.0-83.2)**	**91.3**	**4.3**	**0**
Re-assay	***129 (1247)***	***77.5 (70.3-84.7)***	***94.6***	***1.6***	***0***
Re-assay imputing with valid original values[a]	**138 (1368)**	**76.8(69.8-83.9)**	**92.8**	**2.9**	**0**

The Sponsor concludes that the reliability and accuracy of the original data are further supported by the similarity of all the statistical analysis results. The analysis of the original data, the re-assayed data, as well as the supportive analysis (re-assay combined with imputed valid original results), all met the acceptance criteria for the primary and the secondary endpoints. Thus the conclusions of the original submission remain the same and support the original assessment of the efficacy associated with the use of FORTESTA.

Reviewer's comment: Based on the results from re-analyses, and the similarity of the results between the original analyses and the re-analyses, the reliability and accuracy of the original data are accepted, and this reviewer agrees with the Sponsor's conclusion that the efficacy conclusions of the 2009 submission remain the same.

In the original MITT population, there were 5 subjects with a BMI $\geq$ 35 kg/m^2 who by strict definition of study eligibility should not have been included but participated nonetheless; 4 had samples available for re-assay and 1 did not. DRUP requested that a sub-analysis of the MITT population be performed on subjects who had a body mass index (BMI) < 35 kg/m^2, which serves to exclude these "protocol violators". This analysis of subjects with BMI < 35 kg/m^2 shown in **Table 6.3** was provided by the Sponsor to support the analysis using re-assayed values. This supportive analysis uses all valid values: re-assayed values with imputation of original valid values when re-assayed values are not available. Removal of the subjects with a BMI $\geq$ 35 kg/m^2

did not substantially affect the analysis, and the analysis of this population meets all criteria of the study acceptability.

Table 6.3 Supportive Analyses of the Original and Re-assayed Results of Total Serum Testosterone C_{avg} and C_{max} at Day 90 for Subjects in the MITT Population with BMI < 35 kg/m^2

Assay	N (number of samples)	% Subjects (95% CI) who met the criterion: C_{avg} within [300, 1140 ng/dL]	% Subjects who met the criteria		
			$C_{max} \leq$ 1500 ng/dL	C_{max} within [1800, 2500 ng/dL]	$C_{max} >$ 2500 ng/dL
Original	132 (1316)	75.0 (67.6-82.4)	91.7	3.8	0
Re-assay	124 (1202)	76.6 (69.2-84.1)	94.4	1.6	0
Re-assay imputing with valid original values[a]	132 (1310)	75.8 (68.5-83.1)	93.2	2.3	0

Since male hypogonadism is associated with obesity, the Sponsor believes that it is appropriate to include the obese subjects in the analysis set.

Reviewer's comment: It is acceptable to include the obese subjects in the analysis set. Even though to enroll these subjects was considered as a violation of the study protocol, these obese subjects should be included in the analysis set. The Sponsor is correct in stating that male hyogonadism may be associated with obesity.

6.2 Details of Day 90 Samples Which Were Not Available for Re-assay (N=128)

In a preliminary response to sponsor's questions for the Type C meeting on June 10, 2010 (preliminary response to Question 1.2), the Division asked about the 128 samples that did not have backup samples available for re-analysis. The Sponsor replied that 121 of these missing re-assay samples had valid original bioanalytical results while only 7 of the samples had invalid bioanalytical results originally and did not have backup samples. A total of 89 missing backup samples came from 9 subjects who had no backup samples at all, and 32 missing backup samples came from 22 subjects who had 1 to 3 missing backup samples. The Sponsor provided further details about these 128 missing samples and these are discussed herein.

6.2.1 89 Day 90 samples, from 9 subjects with no backup samples available, had valid bioanalytical results originally

The 9 subjects with no backup samples came from 5 different sites. The Sponsor provided 2 reasons why backup samples were unavailable for re-assay for these subjects: 4 of the subjects had their backup samples used during the original assay, and 5 did not have their backup samples shipped to the lab in error. This error was not detected by the CRO monitoring the sites at the termination visit. This error was uncovered recently, so the samples have been in long term storage at the involved sites for approximately 2 years, where the storage conditions have not been adequately monitored to ensure sample integrity.

Table 6.4 C_{avg} and C_{max} from the 9 subjects who did not have any Day 90 samples available for Re-assay (N = 89 Samples)

Subject ID	Why Backup Samples Were Not Available for Re-assay	Original C_{avg} (ng/dL)	Original C_{max} (ng/dL)	# Valid Original Values
006-003	Backup samples used for primary testing	264.8	356	10
010-007	Backup samples were not shipped to lab but remained under storage conditions for ≈2 yrs that would not ensure sample integrity	517.1	1550	10
010-008	Backup samples were not shipped to lab but remained under storage conditions for ≈2 yrs that would not ensure sample integrity	107.2	250	10
010-010	Backup samples were not shipped to lab but remained under storage conditions for ≈2 yrs that would not ensure sample integrity	545.0	1130	10
021-001	Backup samples were not shipped to lab but remained under storage conditions for ≈2 yrs that would not ensure sample integrity	169.1	948	10
021-004	Backup samples were not shipped to lab but remained under storage conditions for ≈2 yrs that would not ensure sample integrity	748.0	1470	10
026-006	Backup samples used for primary testing	458.9	721	10
032-028	Backup samples used for primary testing	224.9	410	10
032-042	Backup samples used for primary testing	1132.3	1930	9

Reviewer's comment: The explanations for the 89 missing backup samples from the 9 subjects are acceptable. Of these 9 subjects, one subject had a C_{avg} below normal range (#006-003), one had a C_{max} modestly above 1500 ng/dl (#010-007), and one had a C_{max} between 1800 ng/dL and 2499 ng/dL (#032-042).

6.2.2 32 samples from 22 subjects who were missing 1 to 3 backup samples, had valid bioanalytical results originally but backup samples were not available for re-assay

32 missing backup samples came from 22 subjects who were missing 1 to 3 back-up samples. All of these had valid bioanalytical results originally but back-up samples were not available for re-assay. The reasons for a backup sample not being available for re-assay included that (1) backup sample was used in the original assay run, (2) there was insufficient volume (QNS) of serum in the backup for the assay, (3) the backup could not be found, and (4) issue in requisitioning of the assay resulted in the sample being tested but not for total T.

Table 6.5 Samples with Valid original assay but no re-assayed results (N=32 samples from 22 subjects)

Subject ID	Nominal Sample Time	Serum Testosterone Value (ng/dL)	Why Backup Samples Were Not Available
003-005	2:00	536	Backup used for original assay
	4:00	632	Backup not found in storage
	8:00	458	Backup not found in storage
003-006	0:00	376	Backup used for original assay
004-003	2:00	727	No backup received
007-003	2:00	1130	Backup used for original assay
009-004	6:00	368	Backup not found in storage
009-006	2:00	642	Backup not found in storage
012-012	12:00	223	Backup not found in storage
012-019	1:00	354	Backup not found in storage
	2:00	428	Backup not found in storage
014-068	4:00	470	Backup used for original assay
014-070	0:30	611	Backup not found in storage
	10:00	293	Assay requisition issue
016-003	0:00	228	Assay requisition issue
016-006	12:00	719	Backup not found in storage
016-008	8:00	385	Backup used for original assay
016-010	4:00	778	Backup used for original assay
018-001	2:00	2460	Backup used for original assay
018-008	12:00	426	Backup not found in storage
026-015	0:00	187	Backup used for original assay
028-007	4:00	820	Backup used for original assay
	8:00	462	Backup not found in storage
028-011	24:00	410	Backup used for original assay
031-002	4:00	373	Backup used for original assay
	6:00	189	Backup used for original assay
	10:00	113	Backup used for original assay
032-019	10:00	415	Backup used for original assay
032-048	0:00	159	Assay requisition issue
	1:00	130	Assay requisition issue
	2:00	675	Backup QNS
	6:00	725	Assay requisition issue

6.2.3 7 samples from Day 90 did not have valid original assay results and no backup sample was available (6 Samples from MITT population)

There were a total of 7 missing backup samples from a total of 6 subjects on Day 90 which were not originally assayed in a valid bioanalytical run and did not have backup samples available for re-assay. 6 samples came from the MITT population and 1 sample came from a subject who was not part of the MITT population. Values of Day 90 C_{avg} of these subjects are shown on Table 6.6. The Sponsor believes that absence of these values does not change the interpretation of the primary or secondary endpoints as indicated by the supportive analysis. In addition, the Sponsor

has supplied narratives and pharmacokinetic data (tables and figures) for each of these subjects to support their contention that these 7 missing samples had no effect on the interpretation of the primary or secondary endpoints.

Table 6.6 Subjects with Day 90 samples which were not assayed in a valid bioanalytical assay and their C_{avg} (N=7 samples; 6 from MITT Population)

Subject ID	Nominal sample time	Invalid[a] serum T Value (ng/dL)	Why backup sample is missing	C_{avg} (ng/dL)		
				Based on original values including invalid value	Based on Re-assay values only	Based on Re-assay values with imputation of valid original value[b]
004-004	2:00	600	Used in original assay	276.6	251.1	251.1b
012-012	2:00	330	Used in original assay	350.0	332.0	333.7
026-008	0.00	412	No backup in storage	523.9	466.6	466.6b
031-002	2:00	177	Used in original assay	171.0	190.7	187.4
031-003	10:00	169	No backup received	253.0	233.1	233.1b
031-003	1:00	1070				
032-052	non-MITT	380	N/A	N/A	N/A	N/A

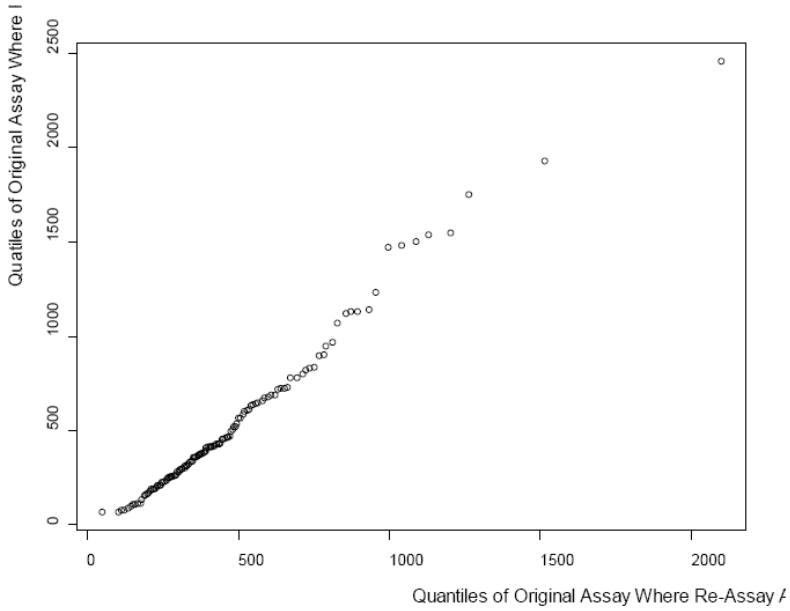
[a] The assay runs for these samples did not meet bioanalytical acceptance criteria, so these values are invalid.
[b] Column 3 of C_{avg} value is the same as column 2, because where imputation was needed the original value was invalid, so no imputation could be performed

6.2.4 Are there bias due to missing backup samples or invalid assays?

The Sponsor believes that bias due to missing backup samples or invalid assays is unlikely based on the following reasons:

1) There was no bias induced in the selection of which samples to re-assay.
2) Visual inspection of the distribution of valid and invalid samples which were re-assayed (Figure 5.1) appears random.
3) The statistical analysis of the re-assayed values met all the study acceptance criteria.
4) Multiple supportive analyses met all the study acceptance criteria and indicate that the original analysis is reliable and robust.
5) To further demonstrate the robustness of the results against bias from missing values, a QQ-plot (Figure 6.1) of all the subjects' original total serum testosterone values which had re-assayed values available versus those where re-assayed values were unavailable on Day 90 was produced to demonstrate the similarity of the distributions of these 2 groups of data. From Figure 5, it is clear that the quantiles of these 2 distributions fall on a straight line, indicating the similarity of the 2 distributions. The QQ-plot shows the distribution of the original values with back up samples and the distributions of the original values without back up sample are similar. Thus, the total serum T values from those subjects without re-assayed values are similar to those with re-assayed values.

Figure 6.1 QQ-Plot of original total serum T values (ng/dL) separated by availability of the Re-assay, All available Pairs, at Day 90 (N [Re-assay available, Re-assay unavailable] = 1253, 128)



6.2.5 Review of the Narratives from 34 subjects

Before the June 10, 2010 meeting between the Sponsor and the Division, the Division made the following information requests to the Sponsor:

- Nine (9) were excluded due to lack of serum samples on Day 90, and four were excluded due to BMI $\geq$ 35 kg/m^2. The exclusion of 8 patients with BMI < 35 kg/m^2 and insufficient data for re-analysis on Day 90 will be a major review issue. Clarify the reason for excluding these 8 patients.
- Provide individual narratives for each of these 8 patients to include (1) test summary related to missing data, (2) table of testosterone concentrations and (3) testosterone PK curve showing missing testosterone concentrations.

The Sponsor stated during the discussion of the Meeting, that the total number of samples from Days 35 and 90 that did not meet original bioanalytical acceptance criteria and were included in the concordance analysis was 250, not 290. The total number of back-up samples available for re-analysis was 236 (of 250). Therefore, the concordance analysis includes 94% of the original samples, lacking just 14 pairs. The Sponsor stated that 90 of 97 samples from Day 35, and 146 of 153 samples from Day 90 were available for the re-analysis. The Division acknowledged that the percentage of missing data is less than originally stated in the Sponsor's meeting package. The Sponsor reiterated their belief that the concordance analysis supports the reliability of the original data.

In the current NDA re-submission, individual narratives from 34 subjects were provided by the Sponsor. This reviewer carefully assessed these narratives and divided then into three categories:

- 9 subjects who did not have any Day 90 samples available for re-assay (89 backup samples missing): Due to lack of any backup samples for Day 90, no concordance could be seen at all;
- 22 subjects (total of 32 backup samples missing), all with valid original assay results (thus, partially missing backup samples): 17 subjects showed good concordance even with some missing samples, but 5 showed not good concordance with missing samples from key time points (including subject # 018-001 with original Day 90 C_{max} = 2460; and one subject #032-042 with original Day 90 C_{max} =1930, both shown in Table 6.7);
- Additional 3 subjects (total of 4 samples) who did not have valid original assay results and no backup sample was available: only one subject showed relative good concordance and other 2 showed not good concordance with missing samples from key time points.

Reviewer's comment: The narratives provided by the Sponsor do not include one subject who was not included in MITT population and did not have valid original assay results and no backup sample was available for re-assay.

6.3 Subjects with C_{max} Values >1800 ng/dL on Day 90

One of the secondary endpoints for the pivotal trial FOR01C is the percentage of subjects with C_{max} values between 1800 ng/dL and 2500 ng/dL. The analysis of the original results, the analysis of the re-assayed results, and all the supportive analyses met the predefined acceptance criteria of <5% of the population having C_{max} values in this range. Table 6.7 lists the subjects with C_{max} values which were >1800 ng/dL. The re-assayed values were similar to the original values. Narratives were provided for the subjects who did not have backup samples available for re-assay. There were no new subjects with C_{max} values >1800 ng/dL based on the re-assay of backup samples. The subject with the highest C_{max} value, 2460 ng/dL, did not have a backup sample for re-assay, but the original assay which generated this result was from a valid bioanalytical run.

Table 6.7 Subjects with C_{max} Values >1800 ng/dL on Day 90

Subject ID	Original Value (ng/dL)	Original Assay Valid (Y/N)	Re-assayed Value (ng/dL)
018-001	2460	Y	N/A[a]
018-002	2100	Y	2090
016-003	2010	Y	2060
016-006	1944	Y	1560
032-042	1930	Y	N/A[a]
005-001	1800	N	1500

6.4 Subjects with Body Mass Index (BMI) > 35 kg/m^2

There were 5 subjects in the MITT population in FOR01C who had a BMI > 35 kg/m^2. Inclusion of these subjects was a protocol deviation, since there was an upper BMI limit of 35kg/m^2 in the inclusion criteria. Analysis of the original data and the re-assayed data both including and excluding subjects with BMI > 35 kg/m^2, does not substantially change the primary or secondary endpoints. Table 6.8 lists the 5 subjects who have BMIs > 35 kg/m^2 and includes their Day 90 C_{avg} and C_{max}. These 5 subjects came from 3 different sites. One subject did not have any Day 90 samples available for re-assay. By inspection, the Sponsor believes that there does not seem to be obvious differences between the serum testosterone results for these 5 obese subjects and the remainder of the subjects in the study. Since hypogonadism is associated with obesity, the Sponsor believes that it is appropriate to include the obese subjects in the analysis set.

Table 6.8 Subjects in MITT Population with a BMI >35 kg/m^2

Subject ID	BMI (kg/m^2)	Dose on Day 90 (mg)	Original Assay		Re-assay	
			C_{avg}-D90*	C_{max}-D90	C_{avg}-D90	C_{max}-D90
003-005	41.5	70	362.5	632	331.2	376
003-006	40.8	50	644.0	896	641.5	887
004-008	35.4	60	807.0	1270	707.3	1100
032-042	35	60	1132.3	1930	N/A	N/A
032-051	35	40	474.6	987	453.7	731

Reviewer's comments: The results from above 5 subjects may be included in the analytic data set because obesity may be associated with hypogonadism.

6.5 Summary and conclusions for the efficacy based on total Serum T

1) In the FDA483, issues were raised about [redacted] (b) (4) measurement of total serum testosterone. These issues were addressed as following: 1) all available backup samples were re-assayed; 2) the number of samples with invalid original results represented about 8% (290/3696) of the total samples originally assayed (the Sponsor notes that 250 total samples were from invalid runs) 3) for the Day 90 samples, 91% (1253/1381) were available for re-assay, and just 6 samples from the MITT population were ultimately not assayed in a valid assay; 4) therefore, for the Day 90 samples, when the re-assayed results and the original valid results are combined, over 99% of the samples have at least one valid assay result.
2) A concordance approach was used to confirm the reliability of the original data. The strength of this concordance analysis is based on the completeness of the dataset, the strong concordance correlation of the original results with the re-assayed results, and the robustness of the data and the conclusions that were supported by multiple analyses. Using this concordance approach, the original data have been shown to be reliable.
3) In addition, the statistical analysis of the re-assayed results, like that of the original results, meets all the acceptance criteria of the study for both the primary and secondary endpoints.

4) Therefore, the conclusion of efficacy remains the same and supports the original assessment of the efficacy associated with the use of FORTESTA in the FOR01C study.

Reviewer's comment: Based on the similarity of the results from original analyses and the results from re-assay analyses with all available back-up samples, this reviewer believes that the efficacy conclusion of submission in 2009 remains the same and approval is warranted.

6.6 Efficacy Assessment based on Other Hormones (DHT/T ratio, FSH)

In addition to total testosterone, the Form 483 raised concerns related to other hormone analytes, including dihydrotestosterone (DHT), estradiol, follicle stimulating hormone (FSH), and free testosterone (free T). The Form 483 commented upon the following"

1. In Observation 1 - Failure to demonstrate accuracy of the DHT RIA assay.
2. In Observation 5 - Many analytical runs "failed", including runs for DHT, estradiol, FSH, and free T.

In the Sponsor's re-submission on June 30, 2010, the Observation 1 of failure to demonstrate accuracy of the DHT RIA assay has been addressed; however, there were "failed" analytical runs during the original analysis of DHT, estradiol, FSH, and free T; for the same reasons as the "failed" runs for total testosterone. Therefore, the Division requested that the Sponsor provide more information to address this concern, using data from the original analysis but excluding samples from failed runs, including:

1. Provide an analysis (mean and SD) for the concentrations of DHT, DHT:T ratio, estradiol, FSH, and free T at different time points (baseline AND 2 hours after application on Days 14, 35, 60, and 90).
2. Provide the SAS transport file for the concentrations of T, DHT, DHT:T ratio, free T and estradiol.

The requested analyses of concentrations of DHT, DHT:T ratio, estradiol, FSH and free T are shown in Table 6.9.

Table 6.9 Analysis of DHT, DHT/T ratio, estradiol, FSH and free T at baseline and 2 hours after FORTESTA application on Days 14, 35, 60, and 90 for the MITT population

		Baseline		Day 14 H2		Day 35 H2		Day 60 H2		Day 90 H2	
		N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
DHT (ng/dL)	Original	137	22 (7.6)	135	68.2 (40.6)	134	74.2 (42.3)	137	79.2 (47.8)	137	76.5 (41.8)
	Original w/o FR*	121	21.7 (7.7)	122	65.9 (37.4)	122	73.4 (42.2)	128	79.3 (49.0)	110	77.0 (43.9)
DHT/T Ratio	Original	137	.13 (.072)	135	.147 (.077)	134	.126 (.069)	137	.141 (.104)	136	.129 (.061)
	Original w/o FR*	120	.134 (.078)	117	.143 (.07)	116	.122 (.065)	120	.141 (.109)	99	.127 (.059)
Estradiol (ng/dL)	Original	133	1.692 (0.786)	n/a^	n/a	132	2.794 (1.468)	n/a	n/a	131	2.988 (1.704)
	Original w/o FR*	87	1.715 (0.795)	n/a	n/a	85	2.748 (1.37)	n/a	n/a	103	2.991 (1.674)
	Reassay of failed runs	27	1.562 (0.639)	n/a	n/a	22	2.655 (1.246)	n/a	n/a	14	2.779 (0.967)
FSH (IU/L)	Original	137	10.51 (15.942)	n/a	n/a	132	5.395 (11.425)	n/a	n/a	133	4.058 (11.48)
	Original w/o FR*	80	11.513 (17.692)	n/a	n/a	62	5.42 (11.425)	n/a	n/a	48	3.536 (8.14)
	Reassay of failed runs	45	7.868 (12.505)	n/a	n/a	43	4.23 (8.482)	n/a	n/a	57	3.055 (9.672)
Free T (pg/mL)	Original	136	33.1 (16)	136	118.9 (112.1)	134	168.4 (176.4)	137	178.1 (160.2)	137	160.8 (118.3)
	Original w/o FR*	119	33.7 (15.8)	123	117.1 (110.8)	116	172.1 (185.5)	124	170.6 (149.4)	119	161 (118.9)
	Reassay of failed runs	13	32.5 (18.4)	12	145.2 (140.3)	10	159.3 (142.3)	12	224.7 (234)	9	159.2 (107.7)

* *original data excluding samples from failed runs (FR)*
^ *samples not collected per protocol on days 14 and 60 for estradiol and FSH.*

The results of the analysis of the original data and of the original data excluding data from the failed runs are similar. The small changes in the results do not change the clinical interpretation of the findings from the original report. Thus, the conclusion regarding the clinical efficacy and safety of FOR01C in the original resubmission remains unchanged and supports the original assessment of the efficacy associated with the use of FORTESTA.

Reviewer's comment: For both DHT and DHT/T ratio, the analysis of the original data excluding the data from the failed runs is similar to the analysis of the original data. As expected, the DHT levels rise with T supplementation, but the DHT/T ratio remains similar at Day s 14, 35, 60 and 90 as well as prior to T supplementation. Therefore, there was no excessive conversion of T to DHT with the administration of FORTESTA.

As requested by DRUP, the Sponsor did provide the SAS transport file for the concentrations of T, DHT, DHT:T ratio, free T and estradiol. The analysis of DHT is considered of particular clinical relevance and is shown herein.

The change from baseline values in DHT/T ratio for Day 35 and Day 90 is calculated as the difference of Day 35 or Day 90 C_{avg} DHT / C_{avg} T – baseline DHT/ baseline T.

Table 6.10 is a summary of the change from baseline of the 24 hour C_{avg} of DHT/Total T ratio for the MITT population. In calculating C_{avg} for either analyte, if there were fewer than 2 valid values for the analyte for the subject, then no C_{avg} was calculated. The results of the analyses are similar to the original results, so the clinical interpretation and conclusions are unchanged from those in the first Complete Response.

Table 6.10 DHT/T ratio and change from baseline for the MITT Population

Baseline Mean (SD) (ng/dL)		Mean (SD) Change from Baseline (ng/dL)			
		Visit 4 (Day 35)		Visit 6 (Day 90)	
Original[a] (N=137)	Re-analyzed[b] (N=120)	Original[a] (N=137)	Re-analyzed[b] (N=109)	Original[a] (N=137)	Re-analyzed[b] (N=96)
0.13 (0.072)	0.134 (0.078)	0.042 (0.084)	0.039 (0.097)	0.039 (0.088)	0.039 (0.096)

[a] Original results from FOR01C Section 11.4.1.3 [Module 5, Volume 1]
[b] Original data with invalid results removed
N=Number of subjects

For serum FSH, the Division requested that the Sponsor provide data for "concentrations of FSH reported in the original assay excluding the failed runs" and "concentrations of FSH reported in re-assay for failed runs". In particular, the Sponsor is requested to provide an analysis (mean and SD) for the concentrations of FSH at different time points (baseline AND 2 hours after application) on Days 35 and 90.

Table 6.11 Analysis of FSH at baseline and 2 hrs after application on Days 35 & 90 for the MITT population, and the re-assay values from runs which initially failed

		Baseline		Day 35 H2		Day 90 H2	
		N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
FSH (IU/L)	Original	137	10.51 (15.942)	132	5.395 (11.425)	133	4.058 (11.48)
	Original w/o FR*	80	11.513 (17.692)	62	5.42 (12.117)	48	3.536 (8.14)
	Original values from FR	57	9.103 (13.123)	70	5.373 (10.864)	85	4.352 (13.03)
	Re-assay values from FRs	45	7.868 (12.505)	43	4.23 (8.482)	57	3.055 (9.672)

**original data excluding samples from failed runs (FR)*

The results of the analysis of the original FSH data and of the original FSH data excluding data from the failed runs are similar. As expected, T supplementation suppresses FSH levels. The re-analysis of the small number of samples from failed runs was similar to the analysis of the corresponding original data. The small changes in the results from excluding the data from the failed runs do not change the clinical interpretation of the findings from the original report. Thus, the conclusion regarding the clinical efficacy and safety of FOR01C in the original resubmission

regarding FSH remains unchanged and supports the original assessment of the safety and efficacy associated with the use of FORTESTA.

Reviewer's comments: The FSH data, either from the original samples or from the original samples with exclusion of failed runs all have large SDs. This is also true for the FSH data from original samples from failed runs, as well as for re-assay (back-up) samples from the original failed runs. However, the analysis results from the original data and from the original data excluding data from those from the failed runs are similar, thus the interpretation of the findings from the original report remains unchanged.

6.7 Final Conclusions for Efficacy

Results from phase 3 study FOR01C with original and re-assayed values support the efficacy of Fortesta for testosterone replacement in male hypogonadism. The study confirmed that with the right starting dose of Fortesta, the appropriate single sampling time point (2 hours after the dose), and the titration schedules, testosterone levels were achieved within the physiologic range for the majority of the patients with minimized occurrence of supraphysiologic concentrations of serum testosterone levels.

7 Review of Safety

Safety Conclusions from the Clinical review of the previous Complete Response submission of April 17, 2009

- The safety and tolerability of Fortesta (testosterone gel 2%) at a daily dose of 40 mg with a dose adjustment ranging between 10 mg to 70 mg depending upon serum testosterone level, was overall acceptable.
- No deaths occurred with Fortesta treatment and a majority of non-fatal SAEs were not drug-related.
- The most common reason for drug discontinuation was application site reactions.
- The most common adverse events considered to be related to Fortesta were application site reactions (ASRs) including contact dermatitis, application site erythema, dryness, and skin reaction. The majority of ASRs were mild to moderate in severity and required no further medical intervention.
- The next common treatment-related AEs were increase in hematocrit (that was not clinically significant) and prostate specific antigen (PSA), and a decrease in HDL-cholesterol (also not clinically significant).
- The safety findings in the Fortesta safety database are consistent with the known safety profile of other testosterone products (transdermal and non-transdermal).
- No cases of testosterone secondary transfer to children have been reported in the post-marketing experience with Fortesta.

The only new safety data included in this resubmission are spontaneously reported adverse events from post-marketing use in 20 countries in the European Union and 2 other countries and these cases are included in the submitted Periodic Safety Update Report (PSUR) covering the 12-month period April 1, 2009 to March 31, 2010.

7.1. No changes between this submission and the submission in 2009

Although the extent of postmarketing exposure to the drug has increased, there have been no changes in the nature of adverse events, vital signs, physical findings or other observations related to safety, and no change in safety in special groups or special situations.

7.2 PSA issue:

One of the analytes subject to the FDA's 483 observations was the observation regarded the validation (accuracy and precision) of the assay for PSA at (b) (4) specifically that values were reported in the 2009 Complete response NDA submission that were below the (b) (4) validated range but in agreement with labeled assay range by the kit manufacturer. The Sponsor does not believe that this observation would impact the clinical safety of FORTESTA, because the observation only affects low PSA values, and clinical concern is primarily in regard to elevated values. To address this concern regarding PSA, additional analyses were performed

by the (b) (4) to confirm the accuracy and precision of the lower limit established by the kit manufacturer for the PSA assay results. The new data indicate that the lower limit of quantitation (LLOQ) was demonstrated at 0.0059 ng/mL, the current cutoff of 0.01 ng/mL is acceptable. Therefore, the PSA results are considered accurate and precise to 0.01 ng/mL, the lower limit of samples that were reported in the pivotal study, FOR01C. Thus the results reported in FOR01C are accurate and the conclusions for serology are unchanged.

7.3 Postmarketing Safety data

7.3.1 Exposure Estimates

FORTESTA has marketing authorizations in 20 member states of European Union (EU) and 2 other countries. Since first launch in 2005, 56 case reports of AE cases have been received by the Marketing Authorization Holder (MAH) possibly related to the use of the product, including 9 SAE's and 47 non-serious.

A submitted Periodic Safety Update Report (PSUR) covers the 12 month period April 1, 2009 to March 31, 2010, and estimated packs of testosterone 2% gel distributed to market during this period were (b) (4), and the estimated patient exposure (excluding patients treated in clinical trials) during the 12 month period covered by the PSUR is 5,053 patient-years.

7.3.2 Adverse Reactions

Overall, the adverse reactions observed are consistent with the expected safety profile for topical testosterone preparations.

7.3.2.1 Serious Adverse Events (SAE's)

During the 12-month period covered by the submitted PSUR, 20 AE cases possibly related to the use of the product were reported.

A total of 6 SAE's were reported with possible relationship to the use of the product. Three SAEs were considered as "unexpected" (tachycardia, Case # 2009-UK-0036; acquired feminization, Case # 2010-DE-0013; and vascular purpura, Case #2009-GR-0001;) and 3 SAEs were considered as "expected" (one with blood T increased, Case # 2009-NL-0009; and two of prostate cancer with increased PSA, Case # 2009-SE-0016 and Case #2009-SE-0017). Among these cases, Case # 2009-GR-0001 had unknown brand/route of testosterone product; and Cases # 2009-SE-0016 and # 2009-SE-0017 had minimal data available and it was impossible to make full evaluation. For two of the 6 SAE's (Case # 2010-DE-0013 and Case # 2009-NL-0009, case narratives were previously received by the Division. An additional 2 SAEs have also been previously received by the Division, for a total of 4 SAE cases previously received by the Division as 15-day safety reports for Fortesta.

Narratives of new SAE's based on the already received 15-day safety reports

Case #1 (submitted to IND 76,634 as a 15-day IND safety report, serial # 047, Case 2010-DE-0013). This case is reported as "acquired feminization".

A 70 year-old male consumer who received Tostran (testosterone gel) experienced a resolution of heavy and therapy-resistant depression, "indescribable happiness", progressive gynecomastia, elimination of maleness, mind "changed completely to female", and smooth and silky skin. The patient had a medical history of depression for approximately 50 years, type II diabetes, and was overweight. The report also notes signs of Klinefelter's syndrome. No concomitant medications were reported. The patient started Tostran 50 mg in December, 2009 for an unknown indication, and the dose was increased to 60 mg in February, 2010, and then to 80 mg in March, 2010. The dose was reduced to 50 mg in May 2010. On the 2nd day after the therapy, the patient stated that he felt an "indescribable happiness." His heavy and therapy-resistant depression "vanished abruptly". He is also experiencing progressive gynecomastia, and one the basis of vitality and energy caused by Tostran, his "happiness is getting stronger each day." The patient reported that during his puberty he had had an intensive desire to be a woman and this was "taken up" by the use of Tostran. Before starting Tostran, the baseline testosterone level of the patient was 228 ng/dL (normal range 400-1200 ng/dL).

Reviewer's comment: Gynecomastia is a listed adverse reaction effect of testosterone replacement therapy, and it has been suggested by some that testosterone may have an antidepressant effect in depressed patients, especially those with hypogonadism. However, the change of gender alignment/reactivation of a desire to be female is not expected, and hard to be judged as possibly related.

Case #2 (submitted to IND 76,634 as a 15-day safety report, Case # 2010-GR-0001). This case is reported as "vascular purpura".

A 57-year-old male with no relevant medical history was treated with Fortigel because of "androgenic deficiency" due to his age. After a few days of treatment, the patient developed some erythematous and pruriginous patches with edema of lower limbs. No details of the dose and the duration of the therapy were reported. No further report of the action taken and the outcome of the events were available. The reporter considered this event as serious due to its medical importance.

Reviewer's comment: The event may reflect an allergic reaction to the testosterone gel and it would be expected that the drug use would be discontinued.

Case #3 (submitted to IND 76,634 as a 15-day safety report; Serial #062 and #067; Case # 2010-ES-0002).

A 19-year-old male was prescribed with Itnogen (testosterone gel at dose of 60 mg/day) in July 2008 for decrease of the libido due to use of isotretinoin for his acne, and he misused the product

by applying directly to his genitals. He has experienced loss of sensibility in the glan and loss of orgasm in 2008 and the treatment was stopped sometime later in 2008. No improvement has been seen even with other treatments. The reporter considered these events as serious as they involve significant disability or incapacity.

Reviewer's comment: This reviewer believes that loss of sensitivity of the glan in this patient may be related to the misuse of the Fortesta gel on his genitals.

Case #4 (submitted to IND 76,634 as a 15-day safety report, Serial #056, Case # 2009-NL-0009). The case was reported as "blood T increased".

A 69-year-old male received Tostran 2% gel and experienced a very high serum level of testosterone. The patient's medical history included bilateral orchidectomy in 2007 and 2008 because of nodal non-Hodgkin's lymphoma; cardiac arrhythmia, enlarged prostate, and chronic sinusitis. The patient has been on testosterone replacement therapy for 1.5 years, including Testim 50 mg/day, and then Andriol Testocaps 40 mg, 2-4 tablets daily. On 08/23/2009, he switched to Tostran because of his repeated low T levels (1.7 and 7.7 mmol/L, respectively) as well as inconvenient side effects, mainly, flatulence. Two months after starting Tostran, on 10-28-2009, approximately 1 hour after applying Tostran, a blood level of 118 mmol/L was measured (normal range 12.2-35.8). However, repeated tests three weeks later, on 11/17/2009 and 11/18/2009, several hours after and immediately before applying Tostran, respectively, showed blood T levels within normal range (33.9 mmol/L, on 11/17/2009, 1 hr after application; and 17.4 mmol/L, on 11/18/2009, immediately before application). The case was upgraded to serious medically important.

Reviewer's comment: According to the case report, if the patient did not overuse the product, an error of laboratory measurement needs to be excluded.

Case #5 (submitted by the Sponsor with the current CR submission, Case 2009-UK-0036). The case is reported as "tachycardia, malaise" and is considered "unexpected".

A report was received from a nurse via a representative concerning a male patient in his 30's. The patient had started Tostran 2% gel 3 g daily transdermally for an unknown indication and approximately 3 weeks later was admitted to hospital with tachycardia (heart rate 110+) and remained hospitalized for approximately 2 days. The reporter confirmed that the patient had high stress levels which could have led to his admission to hospital. The patient was also receiving long-term hydrocortisone and thyroxine. The Tostran 2% gel dose was reduced (timing in relation to event unknown) and the patient had recovered.

Reviewer's comment: It is noted by the reporter that the patient was hospitalized due to high stress levels. In addition, the patient was receiving thyroxine (dose unknown). It is unclear if sinus or non-sinus tachycardia was diagnosed and his cardiac condition is unknown. There are several known causes of sinus tachycardia including hyperthyroidism and exercise. Tachycardia is a listed ADR for thyroxine. There is no known drug interaction between thyroxine and

testosterone. The patient recovery after the testosterone gel dose was reduced may be coincident because of the unknown timing relationship.

7.3.2.2 Other non-serious Adverse Events

Table 7.1 is the summary tabulation of all 41 individual adverse events reported in the PSUR.

Table 7.1 Summary of AE case reports from all sources sort by MedDRA system

Body System Adverse Drug Reaction (ADR) Term	Spontaneous/ Regulat Bodies	Clinical Trials	Literature
Cardiac disorders	1	0	0
Tachycardia* (S)	1	0	0
Gastrointestinal disorders	1	0	0
Nausea	1	0	0
General disorders & adminis. site conditions	16	0	0
Application site alopecia	1	0	0
Application site burn	1	0	0
Application site erythema	1	0	0
Application site irritation	1	0	0
Application site pain	2	0	0
Application site paraesthesia	1	0	0
Application site pruritus	2	0	0
Application site urticaria	1	0	0
Drug ineffective*	2	0	0
Malaise* (S)	1	0	0
Medication residue	1	0	0
No adverse event	3	0	0
Edema peripheral	1	0	0
Therapeutic response unexpected* (S)	2	0	0
Injury, poisoning and procedural complications	4	0	0
Device failure*	1	0	0
Drug administered at inappropriate site*	1	0	0
Incorrect dose administered*	2	0	0
Investigations	3	0	2
Blood test abnormal	1	0	0
Blood testosterone decreased	1	0	0
Blood testosterone increased (S)	1	0	0
Prostatic specific antigen increased (S)	0	0	2
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	0	2
Prostate cancer (S)	0	0	2
Nervous system disorders	1	0	0
Headache*	1	0	0
Psychiatric disorders	2	0	1
Drug abuse (S)	0	0	1
Euphoric mood	1	0	0
Generic identity disorder* (S)	1	0	0
Reproductive system and breast disorders	1	0	0
Feminisation acquired* (S)	1	0	0
Gynaecomastia	1	0	0
Skin & subcutaneous tissue disorders	1	0	1
Rash	1	0	0
Vascular purpura* (S)	0	0	1
Total number of events	35	0	6
Total number of cases	17	0	3

* Unlisted event; (s) = serious event

Overall, the adverse reactions observed are consistent with the expected safety profile for topical testosterone preparations. No new safety concerns have been identified from post-marketing experience since the resubmission of NDA 21-463 on April 17, 2009.

Reviewer's comment: From the data reviewed, this reviewer believes that the overall safety profile of Fortesta (testosterone 2% gel) has not changed since the time of the 2009 re-submission. The reviewer's conclusion from 2009 remains the same.

7.4 Overall Safety Conclusions

In the last re-submission in 2009, based on the results of 6 Phase III studies, including 2 extension studies and 5 Phase I/II studies that enrolled a combined total of 578 hypogonadal men, and 8 healthy men, FORTESTA had been demonstrated to be well tolerated and acceptably safe for the indication.

In addition, as described in Postmarketing experience, overall, the adverse reactions observed are consistent with the expected safety profile for topical testosterone preparations. No new safety concerns have been identified since the resubmission of NDA 21-463 on April 17, 2009. From the data reviewed, it is considered that the overall safety profile of FORTESTA (testosterone 2% gel) is favorable for a product used for the treatment of hypogonadism.

In conclusion, the clinical safety data presented in the current submission demonstrates that a starting dose of 40 mg testosterone (2 g FORTESTA) topically applied daily to the thighs, with specific dose adjustment criteria outlined in the Prescribing Information, is tolerated for use as testosterone hormone replacement in adult hypogonadal men.

8 Postmarket Requirement

As part of the Complete Response action taken on October 11, 2009, the Division stated that the Sponsor would need to conduct a hand washing study as a postmarket requirement (PMR). The Sponsor submitted a hand washing and application site washing study protocol (draft) to the original IND (IND 76,634) on January 22, 2010 (Serial No. 0014). This protocol was also included in the current CR submission. The Division was in general overall agreement with the objectives, design and procedures of the study.

After the re-submission of June 30, 2010, the Sponsor made its final commitment on October 11, 2010, and proposed the following dates for the PMR:

- Final Protocol Submission: 02/2011
- Study/Trial Completion: 09/2011
- Final Report Submission: 04/2012

Reviewer's comment: The Division has agreed with the Sponsor's proposed dates for PMR.

9 Labeling

Labeling discussions were held with the entire review team on November 15 and November 18, 2010. Another review team meeting was held on November 23, 2010 to discuss just the Dosage & Administration section of the label. The Division's edited label was conveyed to Sponsor on November 26, 2010. The Sponsor accepted most of the Division's edits and returned the document on November 30, 2010. A second set of Division edits were conveyed to Sponsor on December 7, 2010. The Sponsor again accepted the Division's edits in large part, and returned the document on December 9, 2010.

On December 6, 2010, the Division received the edited version of the Medication Guide from DRISK. This document was conveyed to Sponsor on December 7, 2010. The Sponsor accepted all the Agency's edits to the Medication Guide and returned the document on December 9, 2010.

Reviewer comments: This reviewer concurs with the labeling submitted by the Sponsor on December 9, 2010. The reviewer has no further recommendations for edits.

10 Appendices

No appendices

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

GUODONG FANG
12/15/2010

MARK S HIRSCH
12/15/2010
I concur.

Deputy Division Director
Summary Review for Regulatory Action

Date	**October 15, 2009**
From	**George S. Benson, MD**
Subject	**Deputy Division Director Review**
NDA#	**21-463**
Applicant	**Endo Pharmaceuticals, Inc.**
Date of Submission	**April 17, 2009**
PDUFA Goal Date	**October 17, 2009**
Proprietary Name/ Established name	**Fortesta** **Testosterone 2% gel**
Dosage forms/Strength	**Metered dose canister which delivers 0.5 g gel (10 mg testosterone) per complete depression**
Proposed Indication	**Testosterone replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone**
Recommendation	**Complete response**

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DDMAC: Division of Drug Marketing, Advertising and Communications
DRISK: Division of Risk Management
CCS: Controlled Substances Staff
DSI: Division of Scientific Investigations

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1. Introduction:

NDA 21-463 for Fortesta (testosterone) Gel 2% for the indication testosterone "replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone" was submitted on April 17, 2009. This NDA submission is a complete response to a not approvable action which was taken on July 3, 2003. The major deficiencies delineated in the "not approvable" letter were 1) "lack of evidence to support that high supraphysiologic daily C_{max} (of testosterone) is safe for chronic administration" and 2) **"**lack of information to support that the dose of this product can be adjusted to consistently preclude achieving these high supraphysiological testosterone levels." The sponsor subsequently submitted an additional phase 3 protocol (FOR01C) in which the starting dose was lowered and dose titration was revised. The results of this study form the basis for the resubmission of NDA 21-463.

Testosterone for replacement therapy in men is currently available in a variety of dosage forms and routes of administration including intramuscular injection, testosterone implants, buccal tablets, and transdermal patches and gels. Two testosterone gels, AndroGel and Testim are currently approved.

The transfer of testosterone gel products from patients to others (particularly children) has been recognized as a significant safety concern. An Advisory Committee meeting regarding this issue was held on June 23, 2009. Both AndroGel and Testim currently have black box warnings and Medication Guides relating to the increased awareness of secondary exposure of children to testosterone gels.

2. Background

NDA 21-463 was submitted on June 3, 2002 and received a "not approvable" action on July 2, 2003. The deficiencies noted in the action letter were:

a) Lack of evidence to support that high supraphysiologic daily C_{max} is safe for chronic administration. This deficiency is evidenced by the observation that 9% of patients had testosterone $1500 \leq C_{max} \leq 1800$, 14% had $1801 \leq C_{max} \leq 2500$, and 6% had $C_{max} > 2500$ ng/dL.

b) Lack of information to support that the dose of this product can be adjusted to consistently preclude achieving these high supraphysiological testosterone levels.

Protocol FOR01C ("An Open Label Phase 3 Study of Fortesta Testosterone Gel") was submitted for Special Protocol Assessment on April 6, 2007. The protocol called for a lower starting dose and a more rigorous dose adjustment strategy. Following modifications, the Division agreed with the design of the trial. The results of study FOR01C form the basis of this NDA submission.

Fortesta is approved in 23 countries (including 20 in Europe) and is currently marketed in 19 of those countries.

3. CMC

The CMC reviewer concluded that: "This NDA has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product. However, the final recommendation from the Office of Compliance involving all facilities pertaining to the cGMP inspections of drug substance and drug product manufacturing and testing operations is Pending. Until a final recommendation is made by the Office of Compliance, the recommendation from a CMC perspective is a COMPLETE RESPONSE. If the Office of Compliance issues an ACCEPTABLE recommendation, then the NDA would be recommended for APPROVAL from a CMC standpoint.

Final labeling has not been agreed upon as yet. Labeling will be added in a subsequent memo prior to the PDUFA date."

The CMC reviewer also commented: "As proposed and committed to by the sponsor in the Complete Response submission dated 17-Apr-2009, it is acceptable to establish a specification for in vitro release within 12 months following product approval."

Comment: Compliance has determined that the inspections of the drug substance and drug product manufacturing and testing operations are acceptable. Although product labeling negotiations with the sponsor were substantially completed, a subsequent Division of Scientific Investigation's inspection of (b) (4) *revealed significant deficiencies which precluded approval of NDA 21-463. (See Section 11.a. of this review.) Labeling will be readdressed at the time of submission of a Complete Response.*

4. Nonclinical Pharmacology/Toxicology

The pharmacology/toxicology reviewer stated that "based on pharmacology/toxicology information submitted and reviewed under the original NDA dated May 31, 2002, there are no safety concerns from the pharmacology/toxicology perspective." There are no unresolved toxicology issues. The reviewer recommended that "nonclinical data support approval of the resubmitted NDA 21-463."

5. Clinical Pharmacology

The clinical pharmacology reviewer concluded that "The Division of Clinical Pharmacology 3, Office of Clinical Pharmacology, finds the clinical pharmacology information submitted in NDA 21-463 acceptable provided that the findings of DSI inspection are acceptable and agreement is reached between the sponsor and the Division regarding the language in the package insert.

The clinical pharmacology reviewer also believes that a "wash off" study to determine the amount of testosterone left on the skin following washing with soap and water should be performed as a Phase 4 commitment.

Comment: Following a teleconference on October 1, 2009, the sponsor agreed to perform a hand "wash-off" study as a Post Marketing Requirement. The sponsor's proposed timeline for completing this study is:

- *Date for submission of the study protocol – April 16, 2010*
- *Study projected to end – October 16, 2010*
- *Study report submission date – December 16, 2010*

Although product labeling negotiations with the sponsor were substantially completed, a subsequent Division of Scientific Investigation's inspection of (b) (4) *revealed significant deficiencies which precluded approval of NDA 21-463. (See Section 11.a. of this review.) The clinical-pharmacology review team concluded that the hormonal data could not be considered reliable and that NDA 21-463 should not be approved.*

Labeling will be readdressed at the time of submission of a Complete Response.

Because of the decision to issue a complete response action, the previously agreed upon Post-Marketing Requirement ("wash-off" study) will be converted to a pre-approval requirement as recommended by Clinical Pharmacology.

A review completed by Clinical Pharmacology on October 14, 2009, concluded that the clinical pharmacology information submitted in NDA 21-463 is "not acceptable" based on the DSI inspection findings.

6. Clinical Microbiology

The microbiology review was performed during the original submission and the microbiology reviewer recommended approval of the application from a microbiology perspective.

7. Efficacy/Statistics

Fortesta was evaluated in a multicenter, 90 day open-label, non comparative trial of 149 men conducted in the United States (32 clinical sites).

Inclusion criteria included:

- BMI (body mass index) >22 kg/m2 and <35 kg/m2
- Screening serum total testosterone of < 250 ng/dL or two consecutive serum total testosterone levels of < 300 ng/dL

Patients were white Caucasian (80.5%), Black (10.1%), Hispanic (7.4%), and other (2.0%).

Fortesta was applied once each morning to the thighs at a starting dose of 2.0 g gel (40 mg) per day. The dose was adjusted between a minimum of 10 mg and a maximum of 70 mg testosterone on the basis of total serum testosterone concentration obtained two hours post drug application on Days 14, 35, and 60 (+/- 3 days) according to parameters described in Table 1.

Table 1. Dose Adjustment Criteria for Study FOR01C

Total serum Testosterone Concentration (C2)	Dose Titration
C2 ≥ 2500 ng/dL	**Decrease daily dose by 20 mg T (1 g gel)**
1250 ≤ C2 < 2500 ng/dL	**Decrease daily dose by 10 mg T (0.5 g gel)**
500 ≤ C2 < 1250 ng/dL	**No change continue on current dose**
C2 < 500 ng/dL	**Increase daily dose by 10 mg T (0.5 g gel)**
If a patient had a C2 total serum T value > 2500 ng/dL at 2 successive visits, then the patient was withdrawn from the study.	

KEY: T = testosterone Source: Module 5.3.5.1 FOR01C Main Report.

The primary efficacy endpoint for trial FOR01C was serum total testosterone C_{avg} within physiological range in ≥ 75% of patients with the lower bound of 95% CI at 65% on Day 90. (Table 2.)

Table 2. Study FOR01C: Results of Primary Efficacy Endpoint

Primary Efficacy endpoint Day 90 C_{avg} (ng/dL)	Target	Results (N=138 in mITT population)
Mean±SD		442.41±177.73
% patients 300 ≤ C_{avg} ≤ 1140	≥ 75	76.1
95% CI limit	lower bound at 65%	(69.0, 83.2)

Source: Module 5.3.5.1 Study Report for Study FOR01C.

The secondary endpoint for trial FOR01C was Day 90 serum testosterone C_{max} < 1500 ng/dL in ≥ 85% of patients, C_{max} between ≥ 1800 and < 2500 in < 5% of patients and C_{max} > 2500 ng/dL in no patients. (Table 3).

Table 3. Study FOR01C: Results of Secondary Efficacy Endpoint

Secondary Efficacy Endpoint Day 90 C_{max} (ng/dL)	Target	Results (N=138 in mITT population)
Mean±SD		863.92±408.01
% patients C_{max} ≤ 1500	≥ 85	93.1
% patients 1800 ≤ C_{max} ≤ 2500	< 5	4.3
C_{max} > 2500	none	0

Source: Module 5.3.5.1 Study Report for Study FOR01C.

Statistical review:

The statistical reviewer concluded: "Results from phase 3 study FOR01C support the efficacy of Fortesta for testosterone replacement in male hypogonadism. The study confirmed that with the right starting dose of Fortesta, sampling time points and the titration schedules, testosterone levels were achieved within the physiologic range for the majority of the patients. Fortesta also minimized supraphysiologic concentrations of testosterone levels."

Comment: The testosterone PK parameters pre-specified as the primary and secondary endpoints were met. Two prior studies had shown unacceptably high C_{max} values. Study FOR01C used a lower starting dose and a more rigorous dose titration scheme which probably resulted in the acceptable C_{max} levels demonstrated in this trial.

The Division of Scientific Investigation's inspection of (b) (4) *identified significant deficiencies (see Section 11.a. of this review). The hormone levels upon which the primary and secondary endpoints of Trial FOR01C are based can not currently be relied upon to form the basis for approval of NDA 21-463. The primary medical officer, clinical pharmacology reviewer, and the cross discipline team leader believe that a Complete Response action should be taken.*

8. Safety

The primary trial submitted to support efficacy was FOR01C. In addition to evaluating this trial for safety, three additional phase 3 trials (2 with safety extensions) were also reviewed (Table 4).

Table 4. Summary of studies included in the ISS

Study	Study design	No. of Subjects Enrolled/Safety	Subjects	Length of Study
Phase III Studies				
FOR01C	Open-label, non-vehicle controlled	149/149	Hypogonadal men	3 months
T 00-03-01	Open-label, non-vehicle controlled	204/204	Hypogonadal men	6 months
T 00-03E 01 Extension	Open-label, non-vehicle controlled 12-mo. (to 24-mo.) extension study	83/83 (11/11)	Hypogonadal men	12-24 months
T 02-03-01	Open-label, non-vehicle controlled	68/68	Hypogonadal men	8 weeks
T 02-03E-01 Extension	Open-label, non-vehicle controlled l2-mo. extension study	55/55	Hypogonadal men	12 months
TSX/01/C	Double-blind placebo-controlled, randomized, Phase IIIb/IV study	108/108	Hypogonadal men of metabolic synd. or type 2 diabetes	2 years

Source: Module 5.3.5.3: Integrated Summary of Safety.

Phase 1/2 studies included in the ISS are shown in Table 5.

Table 5. Summary of studies included in the ISS (Cont.)

Study	Study design	No. of Subjects Enrolled/Safety	Subjects	Length of Study
Phase I/II Studies				
T 98-03-01	Open-label, non-vehicle-controlled, randomized, 7 treat-ment regimen, 3-way, 3-period, matrix-type crossover (Treatment G added by amendment)	18/18	Hypogonadal men	21 days (28 days)
T 00-03-03	Open-label, non-vehicle-controlled, randomized, 2-treatment, 2-period crossover	7/7	Hypogonadal men	14 days
T 00-03-07	Open-label, non-vehicle-controlled, randomized, 3-treatment, 3-period crossover	12/12	Hypogonadal men	24 days
T 00-03-08	Open-label, non-vehicle-controlled, randomized, 3-treatment, 3-period crossover	15/15	Hypogonadal men	24 days
T 00-03-09[a]	Open-label, randomized, 3-treatment, parallel groups	72/72	Healthy volunteers	56 days
T 01-03-02[b]	Open-label, vehicle-controlled, randomized, 3-period crossover	8/8 males	Healthy volunteers	3 months[C]

Source: Module 5.3.5.3: Integrated Summary of Safety.

Deaths: One death occurred in the Phase 3 trials (including the primary phase 3 study FOR01C) and Phase 1/2 studies listed above. The death was secondary to a myocardial infarction in a man assigned to placebo.

Serious adverse events (SAE's):

In the Phase 3 studies, 32 (6.1%) out of 526 subjects experienced a total of 47 treatment-emergent serious adverse events (TEAE's). Five of the treatment-emergent serious adverse events were considered by the investigator to be at least possibly related to study drug. These five TEAE's were congestive heart failure, polycythemia in 3 subjects, and deep vein thrombosis. The subject who experienced congestive cardiac failure had a medical history significant for rheumatic fever.

In the primary phase 3 study FOR01C, 5 SAE's were reported. Narratives for these 5 patients are detailed on pages 70-73 of the primary medical officer review. I agree with the medical officer's opinion that none of these SAE's was likely related to study medication.

There were no SAEs reported in the Phase 1 or 2 studies.

Comment: The lack of a placebo control group in these trials complicates the analyses of adverse events. Polycythemia and deep vein thrombosis are widely recognized complications of testosterone replacement therapy and can be adequately labeled.

Common adverse events:

In primary phase 3 trial FOR01C, the most common TEAE's were skin reaction (16.8%), upper respiratory infection (6.7%), sinusitis (4%), and hypertension (2.7%).

Those adverse events judged at least possibly related to study drug and reported in >1% of patients in Trial FOR01C (N=149) were skin reaction 24 (16.1%), PSA increased 2 (1.3%), and abnormal dreams 2 (1.3%).

Subjects with adverse events leading to study discontinuation in Trial FOR01C are shown in Table 6.

Table 6. Patients with Adverse Events Leading to Discontinuation of Study Medication

Patient Number	Preferred Term	Severity	Relationship
006-004	Dermatitis contact	Moderate	Probably related
014-058	Dyspnea	Severe	Unrelated
027-004	Skin reaction	Moderate	Probably related
032-024	Contusion	Moderate	Unrelated
032-052	Gastric Hypomotility	Moderate	Possibly related

Source: Module 5.3.5.1 FOR01C: Main Report.

Application site reactions:

The results of dermatologic assessment in Trial FOR01C are shown in Table 7.

Table 7. Findings of Dermato1ogic Exam of Thigh Application Sites by Visit (Safety Population)

	Day 14	Day 35	Day 60	Day 90
Number of patients with an assessment	147	143	140	146
Dermal Response	**n (%)**			
0= No evidence of irritation	146 (99.3%)	139 (97.2%)	134 (95.7%)	138 (94.5%)
1 = Minimal erythema, barely perceptible	1 (0.7%)	4 (2.8%)	3(2.1%)	4 (2.7%)
2 = Definite erythema. readily visible, minimal edema or minimal popular response	0	0	3(2.1%)	3 (2.1 %)
3 = Erythema and papules	0	0	0	1 (0.7%)
4 = Definite edema	0	0	0	0
5 = Erythema, edema and papules	0	0	0	0
6 = Vesicular eruption	0	0	0	0
7 = Strong reaction spreading beyond the test site	0	0	0	0
Other Dermal Effects	**n (%)**			
A = No other dermal effects	144 (98.0%)	138 (96.5%)	132 (94.3%)	140 (95.9%)
B = Slight glazed appearance	3 (2.0%)	4 (2.8%)	4 (2.9%)	3 (2.1 %)
C = Marked glazing	0	1 (0.7%)	1 (0.7%)	1 (0.7%)
D = Glazing with peeling and cracking	0	0	3 (2.1%)	2 (1.4%)
E = Glazing with fissures	0	0	0	0
F = Film of dried serous exudates covering all or Part of the application site	0	0	0	0
G = Small petechial erosions and/or scabs	0	0	0	0

Source: Module 5.3.5.1 FOR01C: Main Report.

Comment: The dermatologic adverse event profile is acceptable. Only 2 of the 149 subjects in Trial FOR01C discontined because of dermatologic adverse events (both judged as "moderate.")

Laboratory assessment:

Hematology:

There were 4 patients in study FORO1C in whom the hematocrit went from normal at baseline to high at Day 90. In one patient the hematocrit was high at baseline and continued to be high at Day 90.

PSA:

Two (1.3%) of the 149 subjects in trial FOR01C had increases in PSA over baseline in this 90 day study.

Comment: The PSA elevations are difficult to evaluate in the absence of a control group.

Post-marketing experience:

Fortesta is approved in 23 countries (including 20 in Europe) and currently marketed in 19 of these countries. The drug was first launched in Sweden in September 2005; the remaining approvals have occurred since 2007.

Based on the recommended daily dose of Fortesta, the total estimated patient exposure from first launch to December 21, 2008 is 6,767 patient years.

Since the first launch, the sponsor has received a total of 20 spontaneous reports from health care professionals and consumers of adverse events which occurred during the use of Fortesta up to and including the data lock point of December 21, 2008. The 20 cases comprised 31 individual adverse events. None of these reported cases were considered serious by the reporters.

All adverse events (irrespective of causality) are summarized in Table 8, sorted by MedDRA SOC (System Organ Class) and Preferred Term.

Table 8. Postmarketing Adverse Events Reported for Fortesta

System Organ Class	MedDRA Preferred Term
Blood and lymphatic system disorders	**Polycythemia**
Eye disorders	**Vitreous detachment**
Gastrointestinal disorders	**Abdominal symptoms**
General disorders and administrative site conditions	**Application site erythema, irritation, pruritus, and swelling; fatigue, influenza like illness, and malaise.**
Investigations	**Decreased blood testosterone, increased hematocrit and hemoglobin**
Musculoskeletal and connective tissue	**Pain in extremity**
Nervous system disorders	**Dizziness, headache, and migraine**
Reproductive system and breast disorders	**Erectile dysfunction, and priapism**
Skin and subcutaneous tissue disorders	**Allergic dermatitis, erythema, rash, and popular rash.**

Source: Module 5.3.5.3 ISS, modified by this reviewer.

Comment: Post-marketing adverse event reporting raises no new safety concerns.

Testosterone transfer from patients to partners:

An open-label, vehicle controlled, pharmacokinetic study in healthy couples evaluated whether Fortesta could be transferred from a male patient to a female partner following skin contact and whether any transfer could be prevented by covering the application site in the male with clothing. Two hours after Fortesta application, the female partner engaged in vigorous skin to skin contact with the application site for 15 minutes. Mean C_{avg} and C_{max} values for testosterone were significantly higher (approximately two-fold) in the female partners. Despite this increase, mean testosterone values remained within the physiologic range for women of reproductive age. Transfer of testosterone to the female was prevented by covering the male application site with clothing.

Effect of showering on testosterone pharmacokinetics:

An open-label, randomized, two-treatment, two-period crossover study evaluated the effects of showering on the PK of testosterone following application of Fortesta. Based on the analysis of C_{avg}, C_{max}, and C_{min}, showering 2 hours after the application of Fortesta has no meaningful effect on the PK of testosterone.

Comment: No testosterone "wash-off" study was submitted. This study was initially planned to be performed as a Post-Marketing Requirement. Because of the Division of Scientific Investigation's (b) (4) *inspection results (see Section 11.a. of this review), the "wash-off" study will be requested to be performed prior to approval (as recommended by the clinical pharmacology reviewer) and the results are to be submitted with a Complete Response.*

Safety summary:

- The safety profile of Fortesta is acceptable and appears to be comparable to other approved testosterone products.

- The most common treatment emergent adverse events considered to be related to Fortesta were dermatologic adverse events at the application site. The majority of these events was mild to moderate in severity and uncommonly resulted in study discontinuation.
- The treatment-related AEs of increase in hematocrit and prostate specific antigen (PSA) are well recognized events seen with testosterone replacement therapy and can be adequately labeled.
- No cases of secondary transfer to children have been reported to date, including the post-marketing experience.

9. **Advisory Committee Meeting**

No advisory committee was convened to discuss the approval of this drug. There are multiple approved testosterone preparations and Fortesta would be the third testosterone gel to be approved. An Advisory Committee was held on June 23, 2009, to discuss the transfer potential of testosterone gels from patients to others, including children. The Advisory Committee agreed with the Division's plans to require labeling revisions (including a black box warning) and a Medication Guide for Androgel and Testim. The same labeling and a Medication Guide dealing with the potential transfer of testosterone to others will be applied to Fortesta.

10. Pediatrics

Fortesta was granted a full pediatric waiver by the Pediatric Review Committee (PeRC) on August 20, 2009. The Fortesta (testosterone gel) full waiver was reviewed by the PeRC PREA Subcommittee on August 19, 2009. The Division recommended a full waiver because studies would be impossible or highly impracticable in children and because the disease/condition does not exist in children and because the product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.

An e-mail was received from the PeRC on August 26, 2009 which stated that "The PeRC has received an update from OCC that their initial reaction that this product triggered PREA was not correct. Therefore we now ask that you modify the pediatric page to reflect that PREA does not apply."

11. Other Relevant Regulatory Issues:

a. Division of Scientific Investigations (DSI):

DSI forwarded (on October 1, 2009) copies of 483 forms issued to a) Mark R Akerson, MD and b) (b) (4)

Dr. Akerson's form 483 contained a) four instances in which adverse conditions were identified within the subjects' medical charts and not reported in the CRF's per the protocol b) four instances in which the subjects full medical history was not captured during screening and not reported on the CRF's per the protocol c) three instances in which subject inclusion/exclusion criteria were not met to enroll subjects per the protocol

d) failure to report promptly to the IRB all unanticipated problems involving risk to human subjects or others (a patient who was hospitalized was not reported), and e) failure to report to the sponsor adverse effects that may reasonably be regarded as caused by, or probably caused by, an investigational drug (this adverse event involved a subject being hospitalized).

(b) (4) form 483 contained multiple deficiencies including "the incurred sample reproducibility (ISR) of the LC/MS/MS method for TT (total testosterone) was not evaluated. TT concentrations determined by this method were used to calculate the primary and secondary efficacy endpoints of the study."

A meeting involving DSI, clinical-pharmacology, and the clinical review team was held on October 7, 2009, and a draft report from DSI reviewed. The DSI review was finalized on October 8, 2009, and stated:

"Data from the subjects listed in Attachment 6 should be omitted from data evaluation. The review division should consider if subjects with high number of failed samples be entirely removed." (More than 20 patients with multiple numbers of failed samples are included in Attachment 6).

"The DHT assessments are not acceptable at this time. The firm should provide data to demonstrate that solvent calibrators used in the DHT RIA are equivalent to serum-based calibrators, and did not affect accuracy of data generated by this assay."

"PSA measurements <0.5 ng/ml should be considered BLOQ. The remaining measurements can be accepted for review."

"LH measurements <0.59 mIU/ml can not be assured and should be considered BLOQ."

"The accuracy of the F/T and long term frozen storage stability data are questionable, as freshly prepared standard curves were not used in these stability experiments. The response provided by the firm is not adequate. The firm should repeat the F/T and long term frozen storage stability studies of all the analytes using freshly prepared standard curves."

"To confirm that the "Analyst" software audit trails are available, the firm should provide the audit trail records of the analytical runs in Attachment 5 to DSI for review."

"Panhandle Family Care Associates enrolled subjects that did not meet the study inclusion/exclusion criteria. DSI recommends that data from subjects 032-014, 032-051, and 032-050 be excluded from study evaluation.

Panhandle Family Care Associates failed to report all adverse conditions within four subject's medical chart in the CRF's; failed to capture full medical history of four subjects during screening and did not report them on the CRF's: did not report the SAE

(032-042) to the sponsor and promptly to the IRB. The medical reviewer should evaluate any impact of these findings on the safety evaluation of Fortesta."

Additional material was forwarded from DSI on October 9, 2009, which stated:

The application is not acceptable based on the results of audits conducted and arranged by the Division of Scientific Investigations (DSI) for phase III study (FOR01C). The major deficiencies identified in this study can be summarized as follows:

- Although (b) (4) response to the FDA 483 explains a silent audit trail was active during the study, it did not provide evidence that the audit trail was active for the total testosterone measurements. To confirm that the 'Analyst' software audit trails are available, the firm should provide the audit trail records for the following analytical runs for the total testosterone assay to DSI for review:
    - 07082326, 07091884, 07092604, 07100219, 07100531, 07100939, 07101142, 07101967, 07102375, 07102479, 07102786, 07110103, 07111226, 07111634, 07111635, 07111740, 07112146, 07112655, 07113065, 07113068, 07120578, 07120783, 07120786, 07121194, 07121397, 07121813, 07122019, 07122124, 07122433, 08010244, 08010653, 08011168, 08011375, 08011580, 08011992, 08012298, 08013029, 08020134, 08020240, 08021584, 08021481, 08022208, 08022310, 08022717, 08030228, 08030637, 08030638, 08031255, 08032804, 08041447
- The accuracy of the F/T and long term frozen storage stability data for all the analytes is questionable, as freshly prepared standard curves were not used in the stability experiments. (b) (4) should repeat the F/T and long term frozen storage stability studies of all the analytes using freshly prepared standard curves and provide the data to DSI for review.
- Due to inaccurate QCs, testosterone data from the subjects listed below are not acceptable. The original samples, if still available, must be reanalyzed to determine accurate testosterone concentrations and provided to DSI for review. The stability evaluations noted above must cover the storage time for the study samples until reanalysis.
    - 001-001, 003-005, 003-006, 004-004, 005-001, 005-002, 005-007, 005-010, 006-010, 007-001, 007-004, 007-009, 008-003, 009-003, 009-004, 009-010, 010-004, 011-001, 012-001, 012-019, 012-023, 013-003, 014-001, 014-014, 014-016, 014-048, 014-057, 014-064, 014-065, 014-068, 015-003, 015-006, 015-008, 015-009, 016-003, 018-009, 018-017, 022-001, 024-003, 024-004, 024-005, 025-001, 025-009, 026-001, 026-006, 026-008, 026-013, 026-019, 026-021, 027-009, 027-013, 027-014, 028-009, 028-012, 031-002, 031-003, 032-026, 032-036, 032-038, 032-040, 032-041, 032-042, 032-051, 032-052.

- The dihydroxytestosterone (DHT) radioimmunoassay (RIA) measurements are not acceptable. (b) (4) should demonstrate the accuracy of the DHT RIA by comparing the results of QC samples back calculated from: (1) calibrators prepared in solvent and (2) calibrators prepared in serum (including extraction and oxidation) and provide these data to DSI for review.
- Due to improper application of enrollment criteria as noted in the 483 for Panhandle Family Care Associates, the data from subjects 032-014, 032-051, and 032-050 should be excluded from study evaluation.

An internal meeting which included participants from DSI and the clinical, clinical-pharmacology, pharmacology/toxicology, chemistry, and statistical teams was held on October 8, 2009, and teleconferences were held with the sponsor on October 8 and 9, 2009. Representatives from (b) (4) were present on the October 9, 2009, teleconference after obtaining a letter of authorization from them to discuss the DSI findings with Endo.

Following all of these discussions concerning the deficiencies noted in the DSI (b) (4) inspection, the clinical and clinical-pharmacology reviewers concluded that the inability to rely on the laboratory values currently precludes the approval of Fortesta. The testosterone PK values are used to calculate the primary endpoint (C_{avg}) and the C_{max} of testosterone is an important secondary safety endpoint. The extent of the problems at (b) (4) is not entirely clear. However, after discounting only those patients whose testosterone levels enabled them to be classified as "responders" in the MITT population, the primary endpoint would not be met. In addition, the uncertainty concerning the audit trail complicates matters further. In addition, the results of the clinical site inspection requires that three patients be removed from the analysis. The status of the other hormonal evaluations is also in question. In summary, the data submitted to support the efficacy and safety of this product can not currently be relied upon.

b. Compliance:

Compliance determined that the inspections of the drug substance and drug product manufacturing and testing operations are acceptable.

c. Office of Surveillance and Epidemiology (OSE):

- **Division of Pharmacovigilance (DPV):**

  The DPV agreed with the Division that a REMS (including a Medication Guide) and labeling to include a black box warning should be required upon approval of Fortesta. As previously discussed, transfer of testosterone from patients using testosterone gel products to others (including children) was the subject of a June 23, 2009, Advisory Committee Meeting. A Medication Guide and a black box warning have been instituted for the two currently approved testosterone gel products.

Risk Evaluation and Mitigation Strategy (REMS):

The sponsor submitted a REMS consisting of a Medication Guide and Timetable for Assessments. These were being reviewed by the Division and by DRISK at the time the Division of Scientific Investigation's report of the (b) (4) was received by the Division. The REMS (including the Medication Guide) will be re-assessed following submission of a Complete Response.

- **Division of Medication Error Prevention and Analysis (DMEPA):**

The DMEPA review stated: "Fortesta is the proposed proprietary name for Testosterone Gel. This proposed name was evaluated from a safety and promotional perspective based on the product characteristics provided by the Applicant. We sought input from pertinent disciplines involved with the review of this application and considered it accordingly. Our evaluation did not identify concerns that would render the name unacceptable based on the product characteristics and safety profile known at the time of this review. Thus, DMEPA finds the proposed proprietary name, Fortesta, conditionally acceptable for this product. The proposed name must be re-reviewed 90 days before approval of the NDA."

Comment: The tradename Fortesta will be re-assessed at the time of submission of a Complete Response.

- **Division of Risk Management (DRISK):**

DRISK reviewed the Prescribing Information and the Medication Guide.

Comment: The label and the Medication Guide will be re-assessed at the time of submission of a Complete response.

d. Division of Drug Marketing, Advertising and Communications (DDMAC):

DDMAC reviewed the proposed product labeling (PI), carton labeling, and container labeling for Fortesta submitted on April 17, 2009. The labeling comments were based on the revised version of the draft label sent to DDMAC on September 24, 2009. The DDMAC recommendations were considered during labeling negotiations with the sponsor. DDMAC had no comments concerning the container and carton labeling.

Comment: The label, carton labeling, and container labeling will be reassessed at the time of submission of a Complete Response.

e. Controlled Substance Staff (CSS):

The Controlled Substance Staff recommended revised labeling under Section 9 in the label ("Drug Abuse and Dependence"). The recommended changes (specifically dealing with abuse, addiction, and dependence) were incorporated verbatim into the label.

f. Financial Disclosure:

The primary medical officer noted that financial disclosure information was submitted for all required studies submitted to the NDA and stated that "there is no evidence to suggest that a financial relationship had any impact on the study results."

12. Labeling:

Labeling negotiations were substantially completed on October 1, 2009.

The "Indications and Usage" statement was changed to more accurately reflect the indication and to be consistent with the labeling of other testosterone products.

The black box warning, contraindications, and warnings are now consistent with the two previously approved testosterone gel products. The potential for secondary exposure of children is adequately presented in labeling.

The Drug Abuse and Dependency Section 9 of the label was updated following consultation with Controlled Substance Staff.

The Patient Counseling Information (Section 17) is now consistent with other labeling, the Medication Guide, and the labeling for the other two approved testosterone gels.

Comment: Following receipt of the DSI inspection report and a determination made that the data could not be relied upon to approve NDA 21-463, further review of the label was suspended. Labeling may be re-negotiated following receipt of a Complete Response.

13. Decision/Action/Risk Benefit Assessment:

Upon initial review, the cross discipline team leader, primary medical officer, clinical pharmacology reviewer, pharmacology/toxicology reviewer, chemistry reviewer, and statistical reviewer all believed that NDA 21-463 could be approved pending inspection of the drug substance and drug product manufacturing and testing operations, inspection of the clinical sites and the (b) (4), the sponsor's agreement to perform a Post-Marketing Requirement ("wash-off" study), review of the REMS (including Medication Guide), and labeling.

Compliance determined that the inspections of the drug substance and drug product manufacturing and testing operations are acceptable.

Following a teleconference on October 1, 2009, the sponsor agreed to perform a hand "wash-off" study as a Post-Marketing Requirement. The sponsor's proposed timeline was:

- Date for submission of the study protocol – April 16, 2010
- Study projected to end – October 16, 2010
- Study report submission date – December 16, 2010

The DSI inspection of the (b) (4) found significant deficiencies which questioned the reliability of the hormonal evaluations which formed the basis for approval of NDA 21-463 (see Section 11.a. of this review). Specifically, the data which formed the basis for the primary and secondary endpoints for Trial FOR01C can not currently be relied upon. The cross discipline team leader, primary medical officer, statistician, and clinical pharmacology reviewers all believe that NDA 21-463 can not be approved at this time and I agree.

A complete response action will be taken. The REMS (including the Medication Guide) and labeling will be re-considered at the time of a Complete Response submission. The "wash-off" study will be a pre-approval requirement.

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/s/

GEORGE S BENSON
10/16/2009

CLINICAL REVIEW

Application Type	NDA Resubmission
Application Number(s)	NDA 21-463
Priority or Standard	Standard (Complete Response to July 3, 2003, Action Letter)
Submit Date(s)	2009-04-17
Received Date(s)	2009-04-17
PDUFA Goal Date	2009-10-17
Division / Office	DRUP / ODE 3
Reviewer Name(s)	Guodong Fang
Review Completion Date	2009-10-14
Established Name	Testosterone 2% Gel
(Proposed) Trade Name	Fortesta
Therapeutic Class	Topical Steroid Androgen
Applicant	ENDO Pharmaceuticals, Inc.
Formulation(s)	$C_{19}H_{28}O_2$ (MW 288.42)
Dosing Regimen	2% Testosterone Gel
Indication(s)	Adult Male Hypogonadism
Intended Population(s)	Adult Men with Hypogonadism

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

From a clinical perspective, this reviewer recommends that Fortesta, 2% testosterone transdermal gel, be **approved** for the indication of replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone:

- "Primary hypogonadism (congenital or acquired)" or
- "Hypogonadotrophic or secondary hypogonadism (congenital or acquired)".

Pending the Office of Compliance's recommendation regarding the acceptability of study site and manufacturing facility inspections and the Division of Scientific Investigation's (DSI) recommendation for clinical and analytical site inspections. This recommendation is based on the demonstration of substantial evidence of effectiveness in one appropriately designed Phase 3 trial and an acceptable safety profile consistent with other approved products in the testosterone drug class.

A Black Box Warning and a Medication Guide addressing the potential for skin transference of testosterone to children are recommended.

Addendum to Recommendation on Regulatory Action:
The Division of Scientific Investigations (DSI) in their final report submitted on October 7th, 2009, identified major quality control (QC) deficiencies during their analytical site inspection of (b) (4) *Additionally, there were some minor deficiencies identified at one of the clinical site inspections. With these uncorrected deficiencies and after having considered the recommendation of DSI, this clinical reviewer recommends a Complete Response (CR) action at this time.*

1.2 Risk Benefit Assessment Based on Clinical Findings

1.2.1 Brief Overview of Clinical Program

Fortesta™ (2% testosterone gel), supplied in a metered dose canister, is a transdermal testosterone preparation indicated for testosterone replacement therapy in adult male hypogonadism associated with a deficiency or absence of endogeneous testosterone. Fortesta was demonstrated to be effective for the treatment of hypogonadism and restored average serum testosterone (T) concentration (C_{avg}) to 300-1140 ng/dL in hypogonadal men. Fortesta is approved in 23 countries (including 20 in Europe) and is currently marketed in 19 of these 23 countries.

The Applicant submitted the original NDA 21,463 on May 31, 2002. During the first review cycle, the submission received a "not approvable" action (dated July 3, 2003) based on: (1) insufficient information to establish that high supraphysiologic daily serum testosterone C_{max} levels achieved in a significant proportion of participants are safe under conditions of chronic administration and (2) insufficient information to demonstrate that the drug dose could be adjusted to consistently prevent the high supraphysiological testosterone levels. The current submission, the subject of this NDA review, is a Complete Response to the July 3, 2003, non-approvable action letter. The Complete Response includes one pivotal, open-label, phase 3 study in hypogonadal males in the US (trial FOR01C), with supporting evidence from other Phase 3 and 2 studies (from previous submissions) and a Phase 3b/4 European study in hypogonadal men with either metabolic syndrome or type 2 diabetes mellitus. The data to support the safety and efficacy of Fortesta came primarily from study FOR01C. The sponsor seeks the indication of testosterone replacement therapy in men with primary or secondary hypogonadism.

1.2.2 Efficacy

The **primary efficacy endpoint** in the pivotal US Phase 3 trial FOR01C was the proportion of patients with an average testosterone concentration (**Cavg**) in eugonadal range (300 – 1140 ng/dL) at Day 90. Currently, this endpoint is an accepted primary endpoint in phase 3 clinical trials evaluating testosterone replacement therapy. At Day 90, Fortesta treatment resulted in 76% of patients, with a lower bound of 95% CI of 69%, achieving testosterone Cavg in the normal physiologic range (see Table 1.1). The mean testosterone Cavg (± SD) was 442 ng/dL (± 178)

Table 1.1 Study FOR01C: Proportion of subjects with average testosterone concentration in eugonadal range at Day 90 (mITT)

	Target	N=138
% patients with $300 \le C_{avg} \le 1140$	75	76.1
Lower bound of 95% CI limit	65	(69.0, [83.3])

Source: Module 5.3.5.1 Study Report for Study FOR01C.

Important **secondary endpoints** included the proportion of subjects with maximum testosterone concentration ($\mathbf{C_{max}}$) ≤ 1500 ngldL and the proportion with C_{max} between 1800 and 2500 ng/dL at Day 90. At Day 90, 93% of subjects had $C_{max} \le 1500$ ng/dL, 4% of subjects with C_{max} between 1800 and 2500 ng/dL, and no subjects with $C_{max} > 2500$ ng/dL.(see Table 1.2). The mean C_{max} (± SD) was 864 ng/dL (± 408).

Table 1.2 Study FOR01C: Results of Secondary Efficacy Endpoint

Secondary Efficacy Endpoint Day 90 C_{max} (ng/dL)	Target	Results (N=138 in mITT population)
% patients $C_{max} \le 1500$	≥ 85	93.1
% patients $1800 \le C_{max} \le 2500$	< 5	4.3
$C_{max} > 2500$	0	0

Source: Module 5.3.5.1 Study Report for Study FOR01C.

Reviewer's comment: For testosterone replacement products, the Division currently considers the following as evidence of acceptable efficacy:

- Primary endpoint (C_{avg}): The point estimate of subjects with C_{avg} in the normal range should be at least 75%, with a lower bound of 95% CI > 65%, at a predetermined time point.
- Secondary endpoints (C_{max}):
  a. A minimum of 85% of subjects with $C_{max} \leq 1500$ ng/dL at a predetermined time point
  b. Less than 5% of subjects with C_{max} between 1800 and 2500 ng/dl at a predetermined time point

The results of trial FOR01C Fortesta met all of the above targets for the primary and secondary efficacy endpoints at Day 90.

1.2.3 Safety

Safety data are drawn from 578 hypogonadal men and 8 healthy subjects who received at least one dose of Fortesta in six Phase 3 studies (including two extension studies) and five Phase 1 / 2 studies. The integrated safety database from the phase 3 studies included 526 hypogondal men who received at least one dose of Fortesta (ISS safety population). The study population was similar to the target population. Overall, this is an adequate safety database.

Clinical studies with Fortesta, as with other testosterone replacement products, did not include a placebo or other controls. Therefore, safety data are descriptive and not comparative. A summary of adverse events (AEs) in the integrated safety database from the phase 3 studies is shown in Table 1.4.

Table 1.4 Number and Percentage of Subjects with Treatment-Emergent Adverse Events in Integrated Safety Studies (ISS Safety Population)

	N=526 (100%)	
	n	**%**
Any AE ***Drug-related**	361 *246	68.6 *46.8
Serious AE (deaths?)	32	6.1
AEs leading to drug discontinuation	73	13.9
Drug-related AEs leading to drug discontinuation	60	11.4
Severe AEs	42	8.0

Source: Module 5.3.5.3 Integrated Summary of Safety.

In the integrated safety database, 33 patients (6.25%) reported 43 serious AEs (SAEs). Seven of these SAEs were considered to be drug-related and included the following: congestive heart failure (1), polycythemia (5), and severe deep vein thrombosis (1).

Table 1.5 shows the drug-related AEs in trial FOR01C reported in at least 0.5% of subjects. Common drug-related AEs in trial FOR01C were application site reactions (16.1%), PSA

increased (1.3%), and abnormal dreams (1.3%). The majority of AEs (> 88%) were mild to moderate in intensity.

Table 1.5 Drug-related AEs in Pivotal Study FOR01C (Safety population)

Probably or possibly related treatment-emergent adverse events (TEAEs)	Number (%) of Patients N = 149
Skin reactions	24 (16.1)
PSA increased	2 (1.3)
Abnormal dreams	2 (1.3)
Sinusitis	1 (0.7)
Vomiting	1 (0.7)
Muscle spasms	1 (0.7)
Hematuria	1 (0.7)
Hypertension	1 (0.7)
Nervous system disorders	1 (0.7)

Source: Module 5.3.5.1 Study Report for Study FOR01C.

The adverse changes in laboratory measures of hematocrit, Prostate Specific Antigen (PSA), and high-density lipoprotein (HDL) cholesterol associated with Fortesta were not unexpected for a testosterone product.

In summary, the safety findings of Fortesta were expected of a transdermal testosterone replacement product.

1.2.4 Dose Regimen and Administration

Fortesta is supplied in 60 g metered dose canisters with a pump that delivers 0.5 g gel (10 mg of testosterone) per one complete depression. The recommended starting dose is 2.0 g Fortesta gel (testosterone 40 mg) applied once daily at approximately the same time in the morning to the front and inner thighs. Dose titration is based on serum testosterone levels at 2-hour post dosing on Days 14, 35, and 60 (±3 days), with the final dose ranging between 10 mg to 70 mg testosterone per day.

1.2.5 Special Populations

Gender difference: Gender differences were not explored because Fortesta is contraindicated in women.

Racial difference: The effect of race on Fortesta pharmacokinetics has not been studied. The number of non-Caucasian patients in the phase 3 clinical trials is too small to draw meaningful conclusions.

Issues with elderly: The effect of age on Fortesta pharmacokinetics and pharmacodynamics were evaluated in study T 00-02-01 (N= 201, of which 89 patients were ≥ 55 years old). Testosterone

exposure (AUC and C_{max}) did not differ between subjects ≥ 55 years old and the younger age group. No overall differences in safety were observed between the older and younger age groups. There are insufficient long term safety data in geriatric patients to assess the potential risks of cardiovascular outcomes.

Hepatic or renal impairment: Effects of renal or hepatic impairment on Fortesta pharmacokinetics have not been evaluated.

Pediatric: A pediatric waiver was requested and granted by the Pediatric Review Committee.

Pregnancy: Fortesta is contraindicated in women. Fortesta is pregnancy category X based on known teratogenic effect on female fetuses. Fortesta label contains adequate warnings about the effect of Fortesta exposure in pregnancy.

1.2.6 Drug Abuse and Dependence

Fortesta is a Schedule III controlled substance because it contains testosterone.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

1.3.1 Black Box Warning

The FDA has issued a black box warning for the class of transdermal testosterone due to significant adverse outcomes in women and children inadvertently exposed to testosterone by direct skin contact at the application site of male partners. The Fortesta label must contain the following black box warning:

WARNING: SECONDARY EXPOSURE TO TESTOSTERONE

- **Virilization has been reported in children who were secondarily exposed to testosterone gel.**
- **Children should avoid contact with unwashed or unclothed application sites in men using testosterone gel.**
- **Healthcare providers should advise patients to strictly adhere to recommended instructions for use.**

1.3.2 Medication Guide

The Applicant's proposed Medication Guide was finalized on October 7th, 2009, and incorporated into the label.

1.3.3 Communication Plan

1.4 Recommendations for Postmarket Requirements and Commitments

As a postmarketing requirement, the sponsor has been asked to conduct a pharmacokinetic "wash off" study in humans to demonstrate that there is no residual Fortesta at the site of application after it has been washed with soap and water.

Reviewer's comment: This was communicated to the sponsor on October 1st, 2009, during a Teleconference call and an agreement was obtained with proposed time lines for the completion of such a study.

2 Introduction and Regulatory Background

2.1 Product Information

Fortesta™ (2% testosterone gel) belongs to the pharmacological class of androgenic hormones. The formulation contains the active drug substance, 2% testosterone (a Schedule III controlled substance as defined by the Anabolic Steroids Act), and eight excipients. All excipients have USA/NP monographs.

Drug Product (proprietary name)	Fortesta™ 2% Gel
Drug Substance (non-proprietary or common name)	Testosterone
Sponsor Name	ENDO Pharmaceuticals Inc. (from ProStrakan Inc. 09/08/2009)
Dosage Form	Fortesta 2% Gel is supplied in 60 g metered dose canisters with a pump that delivers 0.5 g gel (10 mg of testosterone) per complete depression
Strength	2.0 % w/w
Route of Administration	Transdermal
Proposed Indication(s)	FORTESTA is indicated for testosterone replacement therapy in adult male hypogonadism: • Primary hypogonadism (congenital or acquired) – testicular failure due to cryptochidism, bilateral torsion, orchitis, vanishing testis syndrome, orchiectomy, Kleinfelter's syndrome, chemotherapy, or toxic damage from alcohol, heavy metals or age related degeneration. • Secondary hypogonadism (congenital or acquired) – idiopathic gonadotropin or luteinizing hormone-releasing hormone (LHRH) deficiency or pituitary-hypothalamic injury from tumors, trauma, radiation, age related degeneration or drug induced hypopituitarism.

2.2 Currently Available Treatments for Proposed Indications

Testosterone replacement therapy is used to treat the signs and symptoms of adult male hypogonadism. FDA-approved testosterone products are shown in Table 2.1.

Table 2.1 Currently Available Testosterone Products in the United States

Drug Name	Adult Dose	Route of Administration	Dosage Forms and Strengths
Testosterone (AndroGel)	Starting: 5 g once daily; titrate up to 10 g daily	Topical gel	1 % gel; transdermal; 2.5 and 5 g unit-dose packets or multiple-dose pump with 1.25 g doses
Testosterone (Testim)	Starting: 5 g once daily; titrate to 10 g	Topical gel	1 % gel; transdermal 5 g unit-dose tubes
Testosterone (Androderm)	Staring: 5 mg system applied nightly; titrate to 7.5 mg	Topical film (patch)	2.5 mg/24 hour and 5 mg/24 hour film, extended-release; transdermal
Testosterone (Striant)	Apply one system to gums, twice daily	Buccal	30 mg tablet, extended-release; buccal
Testosterone (Testopel Pellets)*	150-450 mg SC every 3-6 months	Implant	75 mg pellet; subcutaneous (SC)
Testosterone cypionate (Depo–Testosterone)# Testosterone enanthate (Delatestryl)**	50-400 mg IM every 2-4 weeks 50-400 mg IM every 2-4 weeks	IM IM	100 mg/mL and 200 mg/mL injectable; intramuscular 200 mg/mL injectable; intramuscular
Methyltestosterone (Virilon, Testred, Android, Methitest)	10-50 mg daily§	Oral	10 mg capsule; oral 10 and 25 mg tablets; oral
Pharmacy-compounded testosterone products		Various	Various

* Prescribing information available from Slate: (www.slatepharma.com/wp-content/uploads/2008/12/testopelpi.pdf)
\# Prescribing information available from Pfizer (www.pfizer.com/files/products/uspi_depo_testosterone.pdf)
** Prescribing information available from Indevus (www.indevus.com/site/images/PDF/delatestryluspi.pdf)
§ Dose information available from Drug Facts and Comparisons, 4.0 (Wolters Kluwer Health, Inc; 2008)
Source: Division's Clinical Reviewer.

Limitations of the available products include the following:

- Injectable depot solutions are associated with pain at the injection site and mood swings due to large fluctuations in testosterone levels.
- High dose oral formulations have been associated with an increased incidence of liver disease.
- The transdermal patch is associated with significant application site reactions affecting tolerability.
- Pellet implants can result in rejection and infection.
- Testosterone gels involve application of large volumes that may be difficult to titrate and handle.

A consensus reached by WHO, NIH, and FDA stated that the major goal of testosterone therapy is "to replace testosterone levels at as close to physiological concentrations as possible." Clinical guidance from the Endocrine Society indicates that testosterone therapy should aim to achieve testosterone levels in the mid-normal range.

2.3 Availability of Proposed Active Ingredient in the United States

The active pharmaceutical ingredient, Testosterone USP, is manufactured and controlled according to DMFs (b) (4) by the drug substance manufacturers, (b) (4), respectively. The source of drug substance testosterone is from either of the following:

(b) (4)

Both facilities conform to current Good Manufacturing Practices (GMPs). Letters of Authorization to access the above referenced Drug Master Files (DMFs) were provided.

2.4 Important Safety Issues with Consideration to Related Drugs

Labeled risks of testosterone administration in hypogonadal men include erythrocytosis, induction or exacerbation of sleep apnea, breast tenderness or enlargement, liver toxicity, and acne. Two major areas of concern in older men with aging-associated decline in serum testosterone are the effects of long-term testosterone administration on the risks of prostate cancer and progression of atherosclerotic heart disease..

Transdermal testosterone preparations, which are applied to the skin, have been associated with secondary exposure of testosterone in women and children via direct skin to skin transference. The exposed women and children have experienced significant clinical sequelae which prompted the FDA to mandate a Black Box Warning for all transdermal testosterone products.

2.5 Presubmission Regulatory Activity Related to Submission

Cellergy Pharmaceutical opened IND (b) (4) (2% testosterone gel for the treatment of male hypogonadism) on August 24, 1998. A pre-NDA meeting was held on October 29, 2001. An NDA (21-463) for 2% testosterone gel (formerly Fortigel) was filed on June 3, 2002, and included the results of a single Phase 3 trial (study T 00-03-01).

On July 2, 2003, NDA 21-463 received a "not approvable" action. The deficiencies noted in the marketing application were:

1) Lack of evidence to support that high supraphysiologic daily C_{max} is safe for chronic administration. This deficiency is evidenced by the observation that 9% of patients had testosterone $1500 \leq C_{max} \leq 1800$, 14% had $1801 \leq C_{max} \leq 2500$, and 6% had $C_{max} > 2500$ ng/dL. (Table 2.2)
2) Lack of information to support that the dose of this product can be adjusted to consistently preclude achieving these high supraphysiological T levels.

Table 2.2 C_{max} Outliers from Study T 00-03-01 in Original Submission of NDA 21-463*

Product	C_{max} (ng/dL)				C_{avg} (ng/dL)	N
	between 1200 – 1500	between 1500 – 1800	between 1800 – 2500	> 2500	> 1100	
2% testostero	20 (14%)	13 (9%)	20 (14%)	9 (6%)	0 (0%)	**147**

*6 months post treatment with 2% testosterone gel;
Source: Division's Clinical Analysis.

To resolve these deficiencies, the Division recommended a new clinical trial (s) using lower doses of 2% testosterone gel or another testosterone gel formulation to demonstrate that physiological levels of testosterone can be attained while avoiding high supraphysiologic C_{max} levels of testosterone.

On January 12, 2004, the sponsor submitted Complete Response #1 as an amendment to NDA 21-463 (Serial N000BC) which contained the results of a second Phase 3 study (CP601B 02-02-01). The Division determined that the findings of this second phase 3 study did not adequately address the deficiencies outlined in the July 3, 2003, Non-Approvable letter.

Cellegy (b) (4), and transferred ownership of 2% testosterone gel to Strakkan Pharmaceutical in February, 2007. On April 6, 2007, Strakkan Pharmaceutical requested a Special Protocol Assessment for a new phase 3 study entitled, **"**An Open Label Phase 3 Study of Fortesta Testosterone Gel (FOR01C)." The protocol was assigned new IND number 76,634. The Division held a Type A meeting with the sponsor on May 24, 2007, to discuss this phase 3 study (protocol FOR01C). The Division accepted the design and size of the proposed Phase 3 study (**"**An open label phase 3 study of Fortesta testosterone Gel 2% in hypogonadal males") in a letter dated August 23, 2007. Findings of study FOR01C form the basis of Complete Response #2 and is the subject of this NDA submission.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

Sponsor has in place standard operating procedures consistent with ICH Good Clinical Practice, which include archiving of source data, data validation of CRF data, internal audits, documentation of qualifications of investigators, and the use of central laboratory?

An assessment of the datasets and CRFs of Study FOR01C by this reviewer did not reveal miscoding or discrepancies between data recorded on CRFs and the datasets.

3.2 Compliance with Good Clinical Practices

According to the Applicant, all trials submitted to the NDA were conducted in accordance with Good Clinical Practice (GCP) and the Declaration of Helsinki. In support of this, the Applicant submitted samples of informed consent, documents of IRB approval, and required CRFs.

3.3 Financial Disclosures

Financial disclosures were made for all required studies submitted to the NDA. There is no evidence to suggest that a financial relationship had any impact on the study results.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

According to the CMC review:

1. This NDA has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product. The final recommendation from the Office of Compliance involving all facilities pertaining to the cGMP inspections of drug substance and drug product manufacturing and testing operations is acceptable.
2. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps: if Approvable As proposed and committed to by the sponsor in the Complete Response submission dated 17-Apr-2009, it is acceptable to establish a specification for in vitro release within 12 months following product approval.

Reviewer's comment: Compliance has determined that the inspections of the drug substance and drug product manufacturing and testing operations are acceptable. Although product labeling negotiations with the sponsor were substantially completed, a subsequent Division of Scientific

Investigation's inspection of (b) (4) revealed significant deficiencies which precluded approval of NDA 21-463. Labeling will be readdressed at the time of submission of a Complete Response.

4.2 Clinical Microbiology

The microbiology review was conducted for the original NDA submission dated May 31, 2002, and a recommendation of approval was determined from a microbiology perspective. No new microbiology data were submitted in or requested for the current Complete Response/NDA submission.

4.3 Preclinical Pharmacology/Toxicology

The Pharmacology/Toxicology review was conducted for the original NDA submission dated May 31, 2002 and a recommendation of approval was determined from a pharmacology / toxicology perspective. No new pharmacology/toxicology data were submitted to or requested for the current Complete Response/NDA submission.

4.4 Clinical Pharmacology

Clinical Pharmacology reviewer in his final review dated October 14th, 2009, wrote that based on the major deficiencies identified by the DSI, it was determined that the data generated from the trial FOR01C were not reliable to determine efficacy and safety of Fortesta for approval. The clinical pharmacology reviewer concluded that "The Division of Clinical Pharmacology 3, Office of Clinical Pharmacology, finds the clinical pharmacology information submitted in NDA 21-463 not acceptable based on the major deficiencies identified in the DSI Report."

The clinical pharmacology reviewer also believes that T transfer potential after the washing of primary user's application site has not been assessed in the current resubmission. Therefore, this needs to be addressed in the subsequent submission.

Reviewer's Comment: Following a teleconference on October 1, 2009, the sponsor agreed to perform a hand "wash-off" study as a Post Marketing Requirement. The sponsor's proposed timeline for completing this study is:

- *Date for submission of the study protocol – April 16, 2010*
- *Study projected to end – October 16, 2010*
- *Study report submission date – December 16, 2010*

Although product labeling negotiations with the sponsor were substantially completed, a subsequent Division of Scientific Investigation's inspection of (b) (4) *revealed significant deficiencies which precluded approval of NDA 21-463. The clinical-pharmacology review team concluded that the clinical pharmacology data as not acceptable and that NDA 21-463 should not be approved.*

Labeling will be readdressed at the time of submission of a Complete Response.

Because of the decision to issue a complete response action, the previously agreed upon Post-Marketing Requirement that included a "wash-off" study will be converted to a pre-approval requirement.

4.5 Biostatistics

From a statistical perspective, the Statistical Review Team recommends approval of the current Complete Response/NDA. The statistical reviewer's addendum updates the statistical review of this NDA for Fortesta (testosterone) 2% Gel to include information about the validity of the primary and important efficacy data used to claim efficacy. A DSI investigation of the laboratory used to assay total testosterone levels from blood samples drawn during the study resulted in the issuance of an FDA Form 483 citing deficiencies. The deficiencies were that the laboratory: (1) Did not meet quality control guidelines; (2) Failed to meet calibration criteria; (3) did not follow standard operating procedures. The total testosterone levels were used to calculate the primary efficacy endpoint (C_{avg} 0-24 hr on Day 90 ± 3) and secondary efficacy endpoint (C_{max} on Day 90 ± 3). Because of these deficiencies, the total testosterone data are not reliable and, therefore, efficacy has not been demonstrated for this product based on these data.

4.6 Consults from Other Divisions

4.6.1 Division of Medication Errors Prevention and Analysis (DMEPA)

DMEPA has determined that the proposed trade name "Fortesta" is not vulnerable to name confusion that could lead to medication errors and does not object to use of the proposed trade name.

Reviewer's Comment: The trade name Fortesta will be re-assessed at the time of submission of a Complete Response.

4.6.2 Division of Risk Management (DRISK)

DRISK reviewed the Prescribing Information and the Medication Guide.

Reviewer's Comment: The label and the Medication Guide will be re-assessed at the time of submission of a Complete Response.

4.6.3 Division of Drug Marketing, Advertising and Communications (DDMAC)

DDMAC reviewed the proposed product labeling (PI), carton labeling and container labeling for Fortesta submitted on April 17, 2009. The labeling comments were based on the revised version of the draft label sent to DDMAC on September 24, 2009. The DDMAC recommendations were considered during label negotiations with the sponsor. DDMAC had no comments concerning the container and carton labeling.

Reviewer's Comment: The label, carton labeling, and container labeling will be reassessed at the time of submission of a Complete Response.

4.6.4 Division of Pharmacovigilance (DPV)

The DPV agreed with the Division that REMS (including a Medication Guide) and labeling (that includes a black box warning for secondary exposure to testosterone) will be required for approval of Fortesta. Transfer of testosterone from patients using testosterone gel products to others (including children) was the subject of a June 23, 2009, Advisory Committee Meeting. A Medication Guide and a black box warning have been instituted for the two currently approved testosterone gel products.

Risk Evaluation and Mitigation Strategy (REMS): The sponsor submitted a REMS consisting of a Medication Guide and Timetable for Assessments. The REMS (including the Medication Guide) will be re-assessed following submission of a Complete Response.

4.6.5 Division of Scientific Investigation (DSI)

The DSI forwarded (on October 1, 2009) copies of 482 forms issued to(1) Mark R. Akerson, MD, and (2) (b) (4)

Dr. Akerson's form 483 contained: a) four instances in which adverse conditions were identified within the subjects' medical charts and not reported in the CRF's per the protocol; b) four instances in which the subjects full medical history was not captured during screening and not reported on the CRF's per the protocol; c) three instances in which subject inclusion/exclusion criteria were not met to enroll subjects per the protocol; d) failure to report promptly to the IRB all unanticipated problems involving risk to human subjects or others (a patient who was hospitalized was not reported); and e) failure to report to the sponsor adverse effects that may reasonably be regarded as caused by, or probably caused by, an investigational drug (this adverse event involved a subject being hospitalized).

(b) (4) form 483 contained multiple deficiencies including:

1) Failure to demonstrate accuracy of the DHT RIA assay. Specifically, calibration standards were prepared in solvent and did not undergo the extraction from serum matrix and subsequent oxidation as did for the quality control (QC) and subject serum samples. The concentrations extrapolated from the solvent based standard curve have not been shown to accurately represent the concentrations of DHT extracted from serum matrix.

2) Failure to fully validate the assays for LH and PSA in that (1)Study sample values were reported above 0.01 ng/ml for PSA and 0.07 mIU/ml for LH. However, precision and accuracy was only demonstrated above 0.5 ng/mL for PSA and above 0.59 mIU/mL for LH. (2) The PSA assay was not evaluated for freeze/thaw stability or matrix effects. (3) Commercial products were used for the preparation of the calibrators and QCs for the LH and PSA assays. The firm did not obtain certification of all these reagents' nominal concentrations.
3) Failure to accurately demonstrate the freeze/thaw (F/T) and frozen storage stability of all analytes at −20°C. Specifically, standard curves used in the stability experiments were not freshly prepared but generated from frozen calibration standards prepared previously and stored at −20°C. The F/T test stability samples were compared to frozen reference samples stored at −70°C.
4) Audit trail of the 'Analyst' software version 1.41 was not turned on for all the validation and analytical runs. There are no audit trail records available for inspection.
5) Many analytical runs had > 33.3% of the total QCs and/or > 50% at the same concentration with deviations > 15% (for MS-based assays) or 20% (for ligand-based assays) from the nominal concentrations or mean pooled QC concentrations for TT, DHT, free T, E2, FSH.
6) Failure to reject analytical runs when < 75% of calibration standards in a standard curve failed to meet the acceptance criteria (< 15% or < 20% (LLOQ) deviation from nominal values or mean pooled QC concentrations). In many of these runs listed below, majority of the calibration standards either failed near the beginning or near the end of the runs suggesting possible drift in the system during the run. These runs were accepted by deleting the failed standard curve.
7) The incurred sample reproducibility (ISR) of the LC/MS/MS method for TT (total testosterone) was not evaluated. TT concentrations determined by this method were used to calculate the primary ($C_{avg\ 0\text{-}24\ hr}$ at Day 90) and secondary efficacy endpoints (C_{max} at Day 90) of the study.
8) Failure to adequately monitor SHBG assay performance in that human serum lots 424 and 440 (used as quality controls) were used past their expiration dates

A meeting involving DSI, clinical-pharmacology, and the clinical review team was held on October 7, 2009, and a draft report from DSI reviewed. The DSI review was finalized on October 8, 2009, and recommended the following:

1) Data from the subjects listed in Attachment 6 should be omitted from data evaluation. The review division should consider if subjects with high number of failed samples be entirely removed.
2) The DHT measurements are not acceptable at this time. The firm should provide data to demonstrate that solvent calibrators used in the DHT RIA are equivalent to serum based calibrators, and did not affect accuracy of data generated by this assay.
3) PSA measurements <0.5 ng/ml should be considered BLOQ. The remaining measurements can be accepted for review.
4) LH measurements <0.59 mIU/ml cannot be assured and should be considered BLOQ.

5) The accuracy of the F/T and long term frozen storage stability data is questionable, as freshly prepared standard curves were not used in these stability experiments. The response provided by the firm is not adequate. The firm should repeat the F/T and long term frozen storage stability studies of all the analytes using freshly prepared standard curves.
6) To confirm that the 'Analyst' software audit trails are available, the firm should provide the audit trail records of the analytical runs in Attachment 5 to DSI for review.
7) Panhandle Family Care Associates enrolled subjects that did not meet the study inclusion/exclusion criteria. DSI recommends that data from subjects 032-014, 032-051, and 032-050 be excluded from study evaluation.
8) Panhandle Family Care Associates failed to report all adverse conditions within four subjects' medical chart in the CRFs; failed to capture full medical history of four subjects during screening and not reported them on the CRFs; did not report the SAE (Subject # 032-042) to the sponsor and promptly to the IRB. The medical reviewer should evaluate any impact of these findings on the safety evaluation of Foresta™.

Additional material was forwarded from DSI on October 9, 2009, which stated:

The application is not acceptable based on the results of audits conducted and arranged by the Division of Scientific Investigations (DSI) for phase III study (FOR01C). The major deficiencies identified in this study can be summarized as follows:

An internal meeting which included participants from DSI and the clinical, chemistry, clinical pharmacology, pharmacology/toxicology, and statistical teams was held on October 8, 2009, and teleconferences were held with the sponsor on October 8 and 9, 2009. Representatives from (b) (4) were present on the October 9, 2009, teleconference after obtaining a letter of authorization from them to discuss the DSI findings with Endo.
Following all of these discussions concerning the deficiencies noted in the DSI inspection on (b) (4) the clinical and clinical-pharmacology reviewers concluded that the inability to rely on the laboratory values currently precludes the approval of Fortesta. The testosterone PK values are used to calculate the primary endpoint (C_{avg}) and the C_{max} of testosterone is an important secondary safety endpoint. The extent of the problems at (b) (4) is not entirely clear. However, after discounting only those patients whose testosterone levels enabled them to be classified as "responders" in the mITT population, the primary endpoint would not be met. In addition, the uncertainty concerning the audit trail complicates matters further. Furthermore, the results of the clinical site inspection require that three patients be removed from the analysis. The status of the other hormonal evaluations is also in question. In summary, the data submitted to support the efficacy and safety of this product can not be currently relied upon.

4.6.6 Pediatric Review Committee (PeRC)

PeRC granted a full pediatric waiver for Fortesta on August 20, 2009 based on the following:

1) Studies would be highly impracticable to conduct and,
2) The disease/condition does not exist in children and,
3) The product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.

The PeRC requested that the Division modify the pediatric page to indicate that the primary reason for waiver as being too few children with disease/condition to study. PeRC also reiterated that Fortesta did not need PREA.

4.6.7 Controlled Substance Staff (CSS)

As a testosterone product, Fortesta is in Schedule III of the Controlled Substances Act. Testosterone is specifically designated a Schedule III anabolic steroid under 21 U.S.C. 802(41)(A)(xlvii).

Currently, the proposed labeling under Section 9 "DRUG ABUSE AND DEPENDENCE" reads as follow:

> 9 DRUG ABUSE AND DEPENDENCE
> FORTESTA contains testosterone, a Schedule III controlled substance as defined by the Anabolic Steroids Control Act.

CSS recommends that the labeling under section 9 "DRUG ABUSE AND DEPENDENCE" be changed to read as follow:

> 9 DRUG ABUSE AND DEPENDENCE
> 9.1 Controlled Substance
>
> FORTESTA (testosterone) Gel 2% contains testosterone, a Schedule III controlled substance under the Controlled Substances Act.
>
> 9.2 Abuse (b) (4)
>
> Anabolic steroids, such as testosterone, are reported to be abused. Abuse is often associated with adverse physical and psychological effects.
>
> 9.3 Dependence
> Although drug dependence is documented in individuals using therapeutic doses of anabolic steroids for approved indications, dependence is observed in some individuals abusing high doses of anabolic steroids. In general, anabolic steroid dependence is characterized by any three of the following:
> 1) taking more drug than intended
> 2) continued drug use despite medical and social problems
> 3) significant time spent in obtaining adequate amounts of drug

4) desire for anabolic steroids when supplies of the drugs are interrupted
5) difficulty in discontinuing use of the drug despite desires and attempts to do so
6) experience of a withdrawal syndrome upon discontinuation of anabolic steroid use.

(b) (4)

Reviewer's comment: The CSS recommendations were consolidated into the Fortesta labeling.

5 Sources of Clinical Data

Tables of Studies/Clinical Trials

Clinical trials conducted in support of the safety and efficacy of Fortesta are shown in Table 5.1. The clinical program includes three Phase 3 efficacy studies, two long-term safety extension trials, and six Phase I/II trials performed to evaluate parameters such as appropriate dose, site of application, and potential for skin irritation.

Table 5.1 Clinical studies with protocol numbers and report numbers

Study Description	Phase	Protocol #	Report #	Date Submitted
Phase I/II Studies				
Dose ranging study	I/II	T 98-02-01	T 98-03-01	May 31 2002
Transfer of testosterone	I/II	T 01-02-02	T 01-03-02	Jan 30 2003
Effect of showering	II	T 00-02-03	T 00-03-03	May 31 2002
Application site area	II	T 00-02-07	T 00-03-07	May 31 2002
Application site selection	II	T 00-02-08	T 00-03-08	May 31 2002
Phase III Studies				
Pivotal study	III	FOR01C	FORO01C	NDA 21-463 (This submission)
6-month study	III	T 00-02-01	T 00-03-01	May 31 2002 (interim) Oct 03 2002 (final)
Extension to 6-month study	III	T 00-02E-01	T 00-03E-01	Oct 03 2002 (interim) Jan 17 2006 (final)
Rotation study Extension to rotation study	III III	T 02-02-01 T 02-02E-01	T 02-03-01 T 02-03E-01	Jan 12 2004 Jan 17 2006
Additional Supportive Studies[a]				
Surgically menopausal female subjects	Ib	TF 00-02-06	TF 00-03-06	– [b]
Postmenopausal female subjects	Ib	TF 99-02-01	TF 99-03-01	– [b]
Skin irritation	I/II	T 00-02-09	T 00-03-09	May 31 2002
Sexual dysfunction in surgically and naturally postmenopausal women	II	TF 02-02-01	TF 02-03-01	– [b]
Hypogonadal patients with metabolic syndrome and/or type 2 diabetes mellitus	IIIb/IV	TSX/01/C	TSX/01/C	NDA 21-463 (this submission)

[a] Safety results included for supportive purposes only.
[b] Study report not submitted.
Source: Module 5.3.5.3 Integrated Summary of Safety.

5.2 Review Strategy

This review is based on the following information:

- A newly submitted pivotal Phase 3 study (FOR01C) conducted in the US (efficacy and safety data)
- A newly submitted phase 3b/4 study TSX/01/C conducted in Europe (safety data only)
- An integrated summary of safety data from all Phase 3 trials.

5.3 Discussion of Individual Studies/Clinical Trials

The pivotal study was:

- Study FOR01C: a Phase 3, multicenter, open-label, dose-titration, single arm study evaluating the safety and efficacy of 3-month treatment with Fortesta in hypogonadal men.

Two Phase 3 studies provided supportive efficacy data:

- Study T 00-03-01evaluated the safety and efficacy of 6-month treatment with Fortesta in hypogonadal men
- Study T 02-03-01: An 8-week study to evaluate the effect of increasing the area of application and rotating the site of application on application site reactions (ASRs)

Two Phase 3 extension studies, which provided data on the persistence of efficacy:

- Study T 00-03E-01: 12- to 24-month extension of Study T 00-03-01
- Study T 02-03E-01: 12-month extension of Study T 02-03-01

One Phase IIIb/IV study provided supportive safety data:

- Study TSX/01/C: a 2-year European study to determine the effect of Fortesta on insulin resistance in hypogonadal subjects with metabolic syndrome and/or type 2 diabetes mellitus

Study evaluating the potential of skin transference:

- Study T 01-03-02: A study to evaluate the transferability of Fortesta (testosterone) Gel 2% from a male to a female (in original submission)

Additional studies that have been included to support factors affecting dose response of Fortesta included:

- Study T 98-03-01: a Phase II study to determine dose, dosing interval and site of application. This study was the basis for the recommended starting dose selected for the majority of the subsequent clinical studies (60 mg testosterone per day)

- Study T 00-03-08: a randomized crossover study to evaluate the effect of application site (inner thigh, abdomen and upper arm; on the 24-hour serum testosterone concentration profile in hypogonadal men
- Study T 00-03-07: a randomized crossover study to evaluate the effect of surface area of application site (1, 2 and 4 times the routine area of application; on the 24-hour serum testosterone concentration profile in hypogonadal men
- Study T 00-03-03: a randomized crossover study to evaluate the effect of showering on the 24-hour serum testosterone concentration profile in hypogonadal men

6 Review of Efficacy

Efficacy Summary

Fortesta is effective in restoring mean serum testosterone (T) level (C_{avg}) within the physiologic range in men with hypogonadism. Supra-physiologic T concentrations may be prevented by the proposed starting dose of Fortesta 40 mg once daily, titrating in 10 mg increments as needed, to a final dose ranging from 10 mg to 70 mg once daily.

6.1 Indication

The Applicant seeks the following indications:
Fortesta is indicated for testosterone replacement therapy in adult male with:

- Primary hypogonadism (congenital or acquired)
- Hypogonadotrophic or secondary hypogonadism (congenital or acquired)

6.1.1 Methods

The primary objective of the efficacy review was to assess whether Fortesta treatment restored mean T serum levels within eugonadal range with minimal risk of producing supraphysiologic maximum T levels. The efficacy assessment relied primarily on the newly submitted phase 3 study (FOR01C). A detailed review of study FOR01C is found in Appendix A. Efficacy findings from FOR01C were not integrated with those from previous phase 3 studies submitted to the original NDA or Complete Response #1 because of differences in dose and dose titration scheme.

Table 6.1 Description of Clinical Efficacy Studies

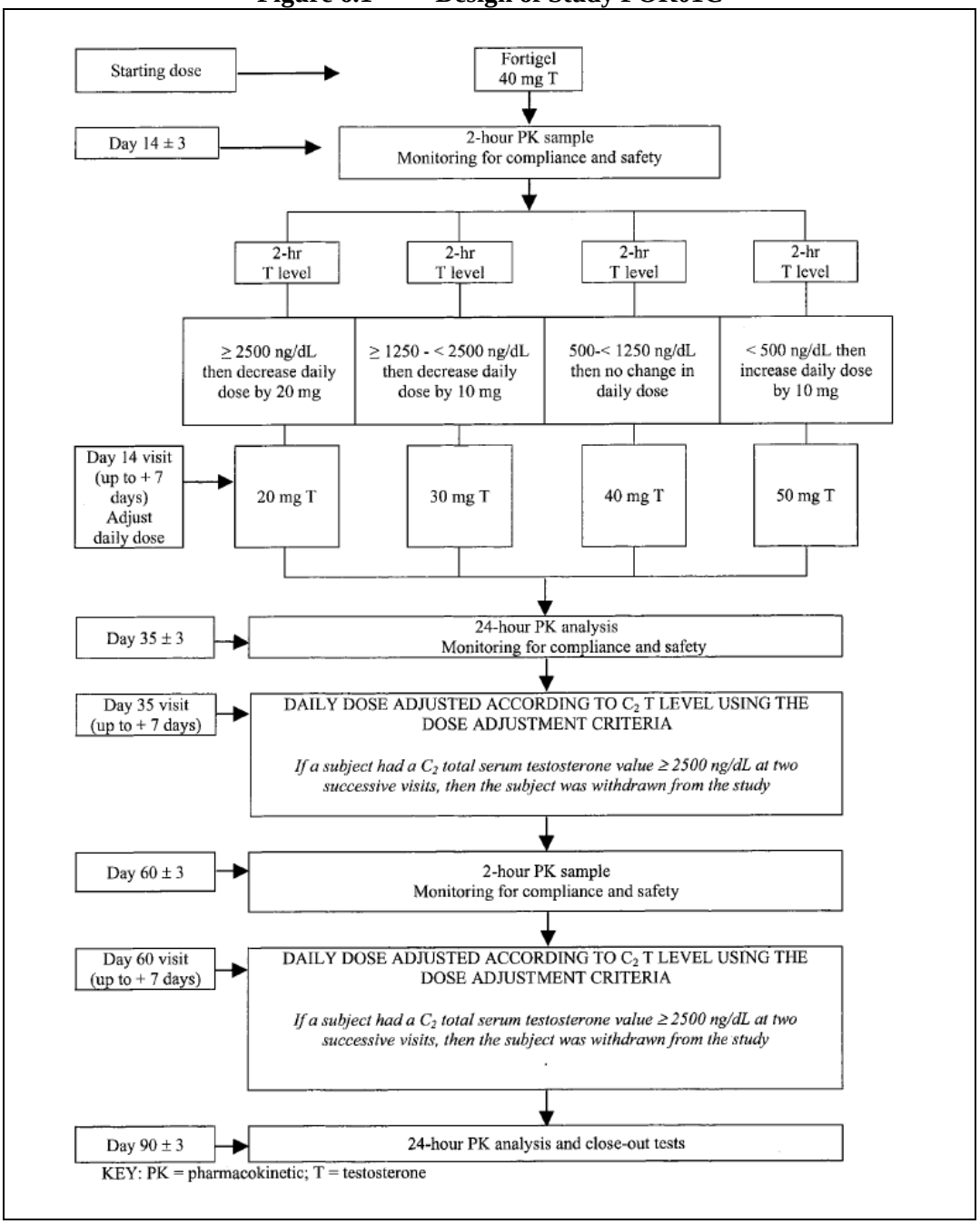
Study I.D.	Study Design	Study Drug Dose, Route, and Regimen	No. of patients enrolled / evaluated	Duration	Primary Endpoints
Pivotal Study					
FOR01C (Current submission)	Multicenter, open-label, non-vehicle-controlled	2 g (40 mg T) once daily on the thighs; dose was adjusted to between 10 and 70 mg based on C_2 on Day 14±3, Day 35 ± 3 and Day 60±3.	149	90 days	C_{avg} on Day 90
Supportive Studies					
T 00-03-01 10/03/2002	Open-label, non-vehicle-controlled	3 g (60 mg T) once daily on the thighs; dose modified at Day 28 based on C_{min} and C_{max} on Day 14; increased to 80 mg or decreased to 40 mg	204/201	6 months	The proportion of pts with C_{min} & C_{avg} within the PR (300–1140 ng/dL) on Day 42/56
T 02-03-01 01/12/2004	Open-label, non-placebo controlled; application site daily rotated between thighs and abdomen	3 g (60 mg T) once daily, dose modified based on C_{min} and C_{max} on Day 14; decreased to 2 g/day (2 g on abdomen or 1 g on each thigh) or increased to 4 g/day (4 g on abdomen or 2 g on each thigh)	68/65	56 days	The proportion of pts with C_{avg} within the PR (300 –1140 ng/dL) on Day 56

Source: Module 5.3.5.3 Integrated Summary of Efficacy.

6.1.1.1 Study Design for the Pivotal Phase 3 Study FOR01C (Current Submission)

The study design of Study FOR01C is shown in Figure 6.1.

Figure 6.1 Design of Study FOR01C



Reviewer's comment: The starting dose (40 mg T, 2 g gel) of Study FOR01C is lower than those of previous 2 supporting studies (60 mg T, 3 g gel), and the times of dose adjustments also increased from once to 3 times (Day 14, Day 35, and Day 60).

Study FOR01C was a multicenter, open-label, dose titration, single arm study to evaluate the safety and efficacy of Fortesta in the treatment of hypogonadal men after 3 months of treatment. The study was conducted at 32 study sites in the U.S. enrolling 149 subjects, All subjects started treatment using 40 mg testosterone (2 g Fortesta) applied to their thighs once daily. A 24-hour pharmacokinetic profile was obtained on Day 35 (± 3) and Day 90 (± 3), and a single serum testosterone sample was obtained 2 hours post-dose (C_2) on Day 14 (± 3) and Day 60 (± 3). The C_2 results obtained on Days 14, 35 and 60 were the basis for dosage adjustment, as shown in Table 6.2.

Table 6.2 Dose Adjustment Criteria for Study FOR01C

Total serum Testosterone Concentration (C2)	Dose Titration
C2 ≥ 2500 ng/dL	**Decrease daily dose by 20 mg T (1 g gel)**
1250 ≤ C2 < 2500 ng/dL	**Decrease daily dose by 10 mg T (0.5 g gel)**
500 ≤ C2 < 1250 ng/dL	**No change continue on current dose**
C2 < 500 ng/dL	**Increase daily dose by 10 mg T (0.5 g gel)**
If a patient had a C2 total serum T value > 2500 ng/dL at 2 successive visits, then the patient was withdrawn from the study.	

KEY: T = testosterone Source: Module 5.3.5.1 FOR01C Main Report.

The primary endpoint was the proportion of subjects with C_{avg} in the normal physiologic range at Day 90. The treatment duration was 90 days.

Reviewer's comment:
A starting dose of 40 mg/day with dose adjustment of 10-70 mg /day depending upon serum testosterone level was able to achieve the primary end point as pre-specified for this study.

6.1.1.1 Data Sets Analyzed

The analysis populations from study FOR01C are shown in Table 6.3. The intent-to-treat (ITT) population included all subjects who received a minimum of one dose of study drug. The modified ITT (mITT) population, which consisted of all subjects who received at least one dose of study drug and who also reached the dosage assessment period of the trial, was used for the primary and secondary efficacy analyses. All enrolled patients were included in the safety analysis and ITT population. Overall, 92.6% (138/149 patients) of patients contributed to the efficacy mITT analysis set, and 56.4% (84/149 patients) contributed to the mPP analysis set.

Table 6.3 Populations Analyzed for Study FOR01C

	Number (%) of Patients
Safety population (had at least one application of CTM	149 (100)
Intent-to- Treat (ITT) population (had at least 1 efficacy measurement subsequent to 1st application of study drug in the safety population)	149 (100)
Modified ITT (mITT) population (had > 1 PK sample on Day 90 in the ITT population)	138 (92.6)
Per-Protocol (PP) population	35 (23.5)
Modified Per-Protocol (mPP) population	84 (56.4)

Source: Module 5.3.5.1 FOR01C Main Report

6.1.2 Demographics

Study FOR01C enrolled 149 subjects from 32 study sites in the United States. A summary of subject demographic and baseline characteristics is presented in Table 6.4. The mean age of patients in this study was 54.5 years (range 29 to 77 years) and the majority of patients were white (87.9%).

Table 6.4 Demographic Characteristics (All enrolled patients): FOR01C

Demographic Variable	Patients (N=149)
Age (years)	
Mean (SD)	54.5 (10.1)
Median	55.0
Range	29-77
Ethnicity (n[%])	
Hispanic or Latino	11 (7.4)
Not Hispanic or Latino	138 (92.6)
Race, (n[%])	
White	131 (87.9)
Black or African American	15 (10.1)
American Indian	0
Asian	0
Native Hawaiian or Other Pacific Islander	0
Other[a]	3 (2.0)
Weight (kg)	
Mean (SD)	97.65 (14.73)
Median	97.10
Range	65.3 – 147.6
Height (cm)	
Mean (SD)	178.08 (6.53)
Median	177.80
Range	162.6 - 198.1
Body Mass Index (kg/m2)	
Mean (SD)	30.61 (3.50)
Median	30.80
Range	22.1 -41.

Source: Module 5.3.5.1 FOR01C Main Report
a = "Other" reported races included Mixed, Asian Indian, and Middle Eastern Arabic.

For the pivotal Study FOR01C, patient type (primary or secondary) and duration of hypogonadism diagnosis, as well as history of prior hormone replacement therapy, are presented in Table 6.5.

Table 6.5 Diagnosis and history of testosterone deficiency and prior hormone replacement therapy (All Enrolled patients), study FOR01C

	Patients (N=149)
Time since Diagnosis (years)	
Mean (SD)	2.2 (3.3)
Median	1.0
Range	0-22
Type of Hypogonadism (n[%])	
Primary	105 (70.5)
Secondary	44 (29.5)
Was Replacement Therapy Ever Taken?(n[%])	
Yes	98 (65.8)
No	51 (34.2)

Source: Module 5.3.5.1 FOR01C Main Report.

6.1.3 Subject Disposition

Study FOR01C enrolled 149 subjects from 32 study sites in the United States. Overall, 138 (92.6%) patients completed the study. The most common reason for discontinuation was because of an adverse event (3.4%) followed by protocol violation and patient's choice (1% each). See Table 6.6.

Table 6.6 Patient Disposition for Study FOR01C

	Number (%) of Patients[1]
Patients screened	406
Screen failures	257 (63.3)
Patients entering the study	149
Patients completing the study	138 (92.6)
Patients discontinuing the study	11 (7.4)
Primary reason for discontinuation:	
Adverse event	5 (3.4)
Protocol violation	2 (1.)
Patient non-compliance	1 (0.7)
Patient choice	2 (1.)
Lost to follow-up	0
Other	1 (0.7)

1. Percentage for number of screen failure is based on the number of patients screened. All over percentages are based on the number of patients entering the study.

Source: Module 5.3.5.1 FOR01C Main Report

6.1.3.1 Adverse Events Leading to Discontinuation

Adverse events leading to permanent discontinuation of study drug were reported in five patients (3.4%) and are shown in Table 6.7.

Table 6.7 Adverse Events Leading to Premature Discontinuation from Study FORC01

System Organ Class (SOC) MedDRA Preferred Term	Number (%) of Patients N=149
Patients with Any AE Leading to Discontinuation	5 (3.4)
Skin and Subcutaneous Tissue Disorders	2 (1.3)
Dermatitis contact	1 (0.7)
Skin reaction	1 (0.7)
Gastrointestinal Disorders	1 (0.7)
Gastric hypomotility	1 (0.7)
Injury, Poisoning and Procedural Complications	1 (0.7)
Contusion	1 (0.7)
Respiratory, Thoracic and Mediastinal Disorders	1 (0.7)
Dyspnoea	1 (0.7)

Source: Module 5.3.5.1 FOR01C Main Report

Reviewer's comment: There were five patients that discontinued due to adverse events. These included two with moderate application site reaction (contact dermatitis and skin reaction) determined to be probably related to the study medication. There was also one with gastro-intestinal hypomotility that was determined to be possibly related to the study medication. The rest of two patients: one with dyspnea and the other with a contusion were determined not to be related to the study medication. However, there is no trend among adverse events leading to discontinuation that raise a concern regarding the tolerability of Fortesta at this time.

6.1.3.2 Protocol Deviations

Major protocol deviations and violations are summarized in Table 6.8. Overall, 69.1 % (103/149) of patients had at least one major protocol deviation. The most common protocol deviation was study medication non-compliance (63.1%, 94 patients)

Table 6.8 Major Protocol Deviations and Violations (mITT population)

Type of Deviation	Number (%) of Patients (N=138)
Any protocol deviation	103 (74.6)
Trial medication non-compliance (% compliance < 85% or > 115%) Days 14, 35, and 60 Day 90	 94 (68.1) 51 (37.0) 43 (31.2)
Non-compliant with trial visit schedule Days 14, 35, and 60 Day 90	13 (9.4) 12 (8.7) 1 (0.7)
Incorrect dose titration Days 14, 35, and 60 Day 90	7 (5.1) 7 (5.1) 0 (0)
Prohibited concomitant medications Saw Palmetto Dutasteride	5 (3.6) 4 (2.9) 1 (0.7)
Inclusion/exclusion criteria violation BMI higher than 35 Patient with eczema Age higher than 75	5 (3.6) 3 (2.2) 1 (0.7) 1 (0.7)

Source: Module 5.3.5.1 FOR01C Main Report

Reviewer's comment: The most common protocol violation was study medication non-compliance. It is the impression of this reviewer that the patients might have missed one or a few doses of Fortesta or have applied lesser quantity of the gel as obtained from the canister. It is also possible that a few patients could have used more of the gel by obtaining more as they might have over-pressed the canister. Additionally, there were three patients whose BMI > 35 kg/m^2, and only one patient with age > 75 years old, that also accounted for protocol violation. None of these are of any concern at this time.

6.1.4 Analysis of Primary Endpoint

The primary endpoint was the proportion of subjects with mean serum T levels in the physiologic range (300-1140 ng/dL) on Day 90. This PK endpoint is currently used as the primary endpoint in phase 3 clinical trials evaluating testosterone therapy in hypogonadal men. Currently, the Division considers a point estimate of at least 75% of subjects having a testosterone C_{avg} within physiologic range with a lower bound of a 95% CI of ≥ 65% to be evidence of effectiveness. At Day 90, 76% of subjects treated with Fortesta, with a lower bound of a 95% CI of 69%, had a serum testosterone C_{avg} within the physiologic range (see Table 6.9).

Table 6.9 Primary efficacy endpoint

Efficacy	Target	N=138
Primary endpoint C_{avg}		
on Day 90 (ng/dL)		442.41±177.73 (Mean±SD)
% patients $300 \leq C_{avg} \leq 1140$	≥ 75	76.1
95% CI limit	lower bound at 65%	(69.0, 83.2)

Source: Module 5.3.5.1 FOR01C Main Report

6.1.5 Analysis of Secondary Endpoints

The secondary endpoint for each subject was C_{max} on Day 90 ± 3 days, and the secondary objectives were to achieve the following C_{max} levels:

- ≤ 1500 ng/dL in ≥ 85% of subjects
- ≥ 1800 to ≤ 2500 ng/dL in < 5% of subjects
- ≥ 2500 ng/dL in no subjects

The secondary objectives were achieved, as shown in Table 6.10.

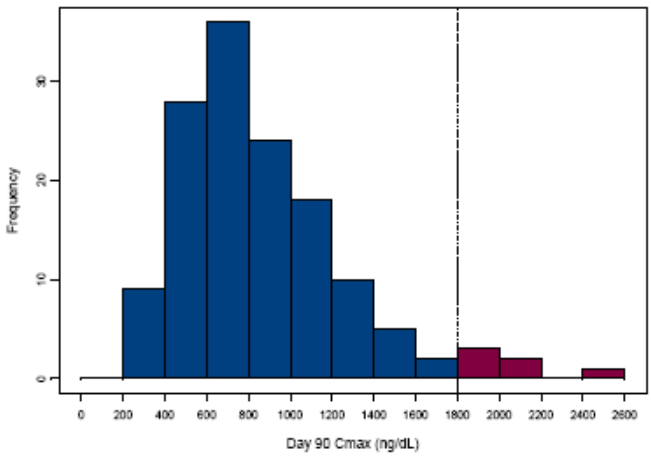
Table 6.10 Secondary Efficacy Endpoint Study FOR01C

Secondary endpoint C_{max}		
	Target	**Results**
Cmax on Day 90 (ng/dL)		863.92±408.01 (Mean±SD)
% patients $C_{max} \leq 1500$	≥ 85	93.1
% patients $1800 \leq C_{max} \leq 2500$	< 5	4.3
$C_{max} > 2500$	none	0

All with mITT population (N=138) for efficacy analyses; Source: Module 5.3.5.1 FOR01C Main Report.

The distribution of C_{max} on Day 90 is shown below:

Figure 6.2 Serum testosterone C_{max} at Day 90



Source: Sponsor's submission on July 22, 2009: Response to clinical information request

6.1.6 Other Endpoints

6.1.6.1 Testosterone C_{avg} according to final testosterone dose at Day 90

The C_{avg} for T according to final Fortesta dose (on Day 90) is shown in Table 6.11.

Table 6.11 Day 90 $C_{avg0\text{-}24hr}$ by final dose (mITT population)

	Tesosterone dose in mg (Fortesta dose in g)						
$C_{avg\ 0\text{-}24hr}$ (ng/dL)	10mg (0.5 g)	20mg (1.0 g)	30mg (l.5 g)	40mg (2.0 g)	50mg (2.5 g)	60mg (3.0 g)	70mg (3.5 g)
N	1	7	17	30	27	31	25
Mean	230.76	410.94	403.22	442.31	497.01	453.49	413.77
SD	0.00	220.10	141.99	182.55	162.75	215.75	141.45
Median	230.76	414.79	396.80	387.09	484.24	394.63	362.51
Range	230.8	107.2–810.3	170.7–729.6	171.0–958.0	243.1–782.5	199.7–1132.3	224.4–774.2

Source: Module 5.3.5.1 FOR01C: Main Report.

Reviewer's comment: The mean and median C_{avg} testosterone concentrations for each final dose level, with the exception of the 10 mg dose group, were within the physiological range. There was no clear dose-exposure (by C_{avg}) relationship in the testosterone dose range of 20-70 mg.

6.1.6.2 Testosterone C_{max} values according to final testosterone dose at Day 90

Mean and median Day 90 C_{max} values according to final T dose were similar for each group (see Table 6.12). Higher supraphysiologic Cmax values were associated with testosterone doses ≥ 30 mg compared to lower doses.

Table 6.12 Day 90 C_{max} by final dose (mITT population)

	Testosterone dose in mg (Fortesta dose in g)						
C_{max} (ng/dL)	10mg (0.5 g)	20mg (1.0 g)	30mg (l.5 g)	40mg (2.0 g)	50mg (2.5 g)	60mg (3.0 g)	70mg (3.5 g)
N	1	7	17	30	27	31	25
Mean	587.00	869.71	905.94	874.60	998.56	815.42	746.72
SD	0.00	412.12	488.99	434.43	400.79	393.48	332.39
Median	587.00	930.00	781.00	780.50	996.00	763.00	623.00
Range	587.0	250.0–1310.0	430.0–2460.0	284.0–2010.0	370.0–2100.0	305.0–1930.0	388.0–1800.0

Source: Module 5.3.5.1 FOR01C: Main Report.

6.1.6.3Dose adjustment using total serum T measured 2-hours post dose (C_2)

An analysis of the distribution of T_{max} by post-dose time point was performed, and data are summarized for Days 35 and 90 in Table 6.13. In a majority of subjects, Tmax occurred at 2 or 4 hours post-dose. On both Days 35 and 90, serum testosterone concentrations obtained 2 hours (C_2) or 4 hours (C_4) post-dose correlated well with C_{max} levels. The correlation appeared to be slightly better for C2 (correlation coefficient of 0.835) than C4 (correlation coefficient 0.822) , indicating that it is appropriate to titrate testosterone dose based on a single serum testosterone level obtained at 2 hours post-dose.

Table 6.13 Distribution of T_{max} by post-dose timepoint: mITT population for Study FOR01C

	Day 35	Day 90	Total
Total number of subjects	**138**	**138**	**276**
Number of subjects with T_{max} at post-dose time point			
0:00 hour	4	4	8
0:30 hour	3	4	7
1:00 hour	6	10	16
2:00 hour	54	35	89
4:00 hour	44	56	100
6:00 hour	13	18	31
8:00 hour	7	1	8
10:00 hour	0	0	9
12:00 hour	4	1	5
24:00 hour	3	0	3
Correlation[a] C_2:C_{max}	**0.854**	**0.813**	**0.835**
Correlation[a] C_4:C_{max}	**0.836**	**0.806**	**0.822**

[a] Spearman correlation coefficient. Source: Module 5.3.5.1 FOR01C : Main Report.
KEY: C_2= 2-hour post-dose total serum testosterone concentration.
C_4= 4-hour post-dose total serum testosterone concentration.

6.1.6.4 Outlier Day 90 $C_{max} \geq 1800$ ng/dL

On Day 90, 6 subjects had $C_{max} \geq 1800$ ng/dL (Table 6.18). Such threshold levels of C_{max} were not observed at Day 35 for any of the 6 subjects. The median Day 90 daily dose was 40mg (range 30–70 mg) for these 6 patients.

Table 6.14 Dose adjustments for 6 patients with outlier C_{max} at Day 90

Patient ID	Baseline		Day 14		Day 35				Day 60		Day 90			
	Dose	C_{avg}	Dose	C_2	Dose	C_{avg}	C_{max}	T_{max}	Dose	C_2	Dose	C_{avg}	C_{max}	T_{max}
005-001	40	272	40	246	50	415	757	360	60	245	70	774	1800	240
032-042	40	370	40	241	50	592	1410	240	50	384	60	1132	1930	360
016-006	40	479	40	873	40	512	1360	240	40	994	40	759	1944	240
016-003	40	176	40	1170	40	491	1160	240	50	1790	40	607	2010	60
018-002	40	313	40	334	50	476	1260	240	50	980	50	702	2100	240
018-001	40	174	40	364	50	426	1740	120	40	1360	30	477	2460	120

Source: Division's Clinical Analysis.

Reviewer's comment: This reviewer further analyzed for any key differences in these 6 subjects from the overall study population that may explain the outlying values of Cmax.
1. Patient Demographics: The mean age, ethnicity, and BMI of the 6 subjects were similar to the study population.
2. The Tmax of the subjects ranged from 1 to 6 hours with most subjects (3-4 out of 6) having Tmax at 4 hours on Days 35 (4 subjects) on 90 (3 subjects). The distribution of Tmax appeared to be similar to that to the study population.
3. Titration steps: Each patient in the study had 3 separate dose titration steps. Among the 6 subjects, there was no consistent pattern of up or down titration (Table 6.15).

Table 6.15 Dose titrations performed at Days 14, 35, 60 for the 6 patients

Subject	Day 14	Day 35	Day 60	Day 90
005-001	↑	↑	↑	→
016-003	→	↑	↓	→
016-006	→	→	→	→
018-001	↑	↓	↓	→
018-002	↑	→	→	→
032-042	↑	→	↑	→

Key: → =no change; ↑ =up titrate; ↓ =down titrate
Source: Sponsor's submission on July 22, 2009: Response to clinical information request.

4. Compliance with study treatment: Treatment compliance among the 6 subjects were within the variability of compliance seen in the overall study population.

In summary, there are no clear unique factors among the 6 subjects which may explain their outlier C_{max} values at Day 90.

6.1.6.5 Additional Endpoints

Laboratory parameters such as SHBG, LH, FSH, E2, free testosterone, total testosterone and ratio of DHT to total testosterone, were evaluated to demonstrate the pharmacodynamic of testosterone replacement therapy. The results are summarized in Table 6.16.

Table 6.16 Other Measures of Interest – Change from Baseline in Study FOR01C (mITT Population)

	Baseline Mean (SD)	Mean change from baseline (SD)			
		Visit 3 (Day 14)	Visit 4 (Day 35)	Visit 5 (Day 60)	Visit 6 (Day 90)
SHBG (nmol/L)	37.1 (20.3)	–	0.6 (12.4)	–	–1.0 (11.0)
LH (mIU/mL)	5.50 (7.33)	–	–3.55 (6.31)	–	–4.41 (7.38)
FSH (mIU/mL)	10.51 (15.94)	–	–5.34 (8.68)	–	–6.52 (12.45)
E2 (ng/dL)	1.69 (0.79)	–	1.09 (1.3) -	–	1.2 (1.5)
Mean (SD)					
Ratio DHT/Total testosterone	0.13 (0.07)	0.02 (0.10)	0.04 (0.08)	0.01 (0.12)	0.04 (0.09)

Source: Module 5.3.5.1 FOR01C: Main Report.

The SHBG level declined slightly on Day 90, suggesting an androgen effect; testosterone decreases liver production of SHBG. Both serum gonadotropins were declined at Day 35 and 90, consistent with increased circulating testosterone suppressing LH and FSH secretion. Estradiol concentrations increased over time, consistent with aromatization of the exogenous testosterone to estradiol. The ratio of DHT/Total testosterone declined from baseline indicating that the testosterone levels were rising without an excessive amount of metabolism to DHT via skin 5α-reductase.

6.1.7 Subpopulations

6.1.7.1 Body Mass Index (BMI)

No notable differences in C_{avg} and C_{max} on Day 90 were reported across 4 BMI subgroups (22 to < 25; 25 to < 30; 30 to < 35 and > 35 kg/m^2). The proportion of subjects achieving C_{avg} within the physiologic range on Day 90 was comparable across the BMI subgroups 22 - 35 kg/m^2 (74.0–77.1%), and BMI subgroup > 35 kg/m^2 (100.0%). The proportion of subjects with $C_{max} \leq$ 1500 ng/dL was comparable across the 4 subgroups (80.0–92.2%). A comparable proportion of subjects had C_{max} testosterone levels between 1800–2500 ng/dL in the BMI subgroup 25 to < 30 kg/m^2 and subgroup 30 to < 35 kg/m^2 s (4.2% and 3.9%, respectively). However, a higher proportion (20.0%) of subjects with a BMI > 35 kg/m^2 and no subjects with a BMI of 22 to < 25 kg/m^2 had C_{max} testosterone levels within the 1800–2500 ng/dL range.

Reviewer's comment: Only 5 subjects were in the BMI > 35 kg/m^2 subgroup, all of whom were protocol violators because the BMI inclusion criterion was < 35 kg/m^2.

6.1.7.2 Effect of Age

No subgroup analysis based on age was performed in study FOR01C.

Reviewer's comment: In the Phase 3 study T 00-03-01 previously submitted to the original NDA (May 31, 2002), the proportion of subjects with C_{avg} values within the PR was similar for both age subgroups (94.4% [≥55 years] and 90.2% [<55 years]).

In the second Phase 3 study conducted in support of the original NDA submission (T 02-03-01), analysis of the pharmacokinetic parameters by age < 55 years (N=29) and ≥ 55 years (N=36) showed that the mean total serum testosterone C_{avg} on Day 14 was higher in younger subjects (525.6± 226.2 ng/dL) than in the older subjects (385.9± 143.2 ng/dL). A higher percentage of younger subjects (89.7%) had testosterone concentrations in the PR on Day 14 compared to subjects aged ≥ 55 years (66.7%). Only 28% of those < 55 years required a dose increase to 4 g of testosterone gel compared to 64% of those aged ≥ 55 years. These data suggest that older subjects may require larger doses of testosterone gel to achieve serum T concentration in the PR.

This reviewer considers the data on subgroup analysis based on age to be exploratory and does not recommend any specific dose adjustment based on age.

6.1.7.3 Effect of Race and Ethnicity

In Study FOR01C, no notable differences in C_{avg} and C_{max} on Day 90 were reported across race or ethnicity subgroups.

Reviewer's comment:
The number of minority subjects was too small to draw meaningful conclusions.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendation

The efficacy results of FOR01C support the sponsor's regimen of a starting dose of 40 mg of testosterone, titrating up or down in increments of 10 mg based on a total serum testosterone level 2 hours post-dose. Titration may occur on Day 14, 35, and 90 with the final testosterone dose ranging between 10 and 70 mg once daily.

When data from Study FOR01C were analyzed by final dose received (10, 20, 30, 40, 50, 60, and 70 mg testosterone), mean and median C_{avg} testosterone levels were within the PR in all dose groups except the 10 mg dose group, where the C_{avg} levels were slightly below the PR for the single subject in this group (C_{avg} of 230.76 ng/dL). The highest mean C_{avg} levels were reported in the 50 mg final dose group. However, mean C_{avg} testosterone concentrations were similar across the 20 mg to 70 mg final dose groups (range, 403.22 to 497.01 ng/dL) and similar numbers of subjects received final doses of 30, 40, 50, 60, and 70 mg. Analyses of C_{max} data by final dose demonstrated that the highest mean C_{max} testosterone level was in the 50 mg dose group. A majority of subjects (91.3%) had C_{max} values' < 1500 ng/dL, with only a small percentage of subjects (4.3%) having values within the 1800 to 2500 ng/dL range on Day 90. No subjects had C_{max} values > 2500 ng/dL at this timepoint.

6.1.8.1 Dosing Recommendation

The recommended dosing should be the same as that outlined in study FOR01C:

1) Start dose of 40 mg testosterone
2) Morning total serum testosterone levels should be obtained 2-hours post-applications on Days 14. Fortesta should be titrated according to clinical symptoms and results of total testosterone levels outlined in Table 6.18. This process should be repeated on Days 35 and 60.
3) The final testosterone dose should be established after 3 dose titrations and should range between 10 and 70 mg once daily. Based on the results of Study FOR01C that demonstrated the effectiveness of Fortesta.

Table 6.18 Recommendation for dose adjustment criteria

Total Serum T Concentration (ng/dL) (C_2)	Dose Titration
≥ 2500	Decrease daily dose by 20 mg T (1.0 g gel)
1250 to < 2500	Decrease daily dose by 10 mg T (0.5 g gel)
500 to < 1250	No change: continue on current dose
< 500	Increase daily dose by 10 mg T (0.5 g gel)

Source: Module 5.3.5.3 Integrated Summary of Efficacy

6.1.9.1 Dose Titration

Each patient in Study FOR01C was evaluated for the need for dose titration on Days 14, 35 and 60. The results of dose titration are shown in Table 6.19.

Table 6.19 Summary of titration steps for the mITT population

Titration		Number of Patients	% mITT
Up titration	3 up titrations	25	18.1
	2 up titrations, no down titrations	31	22.5
	1 up titration, no down titrations	23	16.7
Mixed up and down titrations		21	15.2
Down titration	1 down titration, no up titrations	15	10.9
	2 down titrations, no up titrations	4	2.9
	3 down titrations	1	0.7
No dose adjustments		18	13.0
Total		138	100.0

Source: Division's Clinical Analysis.

Reviewer's comment: A majority of subjects (~85%) needed some dose adjustment from the starting dose. The distribution of up titration, down titration, or both, were variable across the study population, with more subjects needing up titration than down titration. The proposed titration scheme appears to be prudent and flexible.

6.1.9.1 Long-term Efficacy

Data to support the long-term efficacy (up to 12 months) of Fortesta in maintaining physiologic serum testosterone concentration came from the Phase 3 safety extension studies, T 00-03E-01 and T 02-03E-01. There was no long-term efficacy evaluation for the pivotal study FOR01C.

6.1.9.3 Tolerance

There was no evidence of the development of tolerance to Fortesta over time in the safety extension studies (T 00-03E-01 and T 02-03E-01).

6.1.9.4 Withdrawal Effects

No specific studies were conducted to assess the effects of withdrawal.

7 Review of Safety

Safety Summary

The safety and tolerability of Fortesta are overall acceptable. Significant adverse reactions were related to hematologic events described with testosterone products. The most common adverse reactions were application site reactions and the most common systemic adverse reactions included increased hematocrit and increase in PSA and slight decrease in HDL cholesterol levels. The safety findings are consistent with other approved transdermal testosterone products and can be adequately addressed through labeling.

7.1 Methods

7.1.1 Studies Used to Evaluate Safety

The Phase 3 and Phase 1/2 studies used to evaluate safety of Fortesta are shown in Table 7.1. This safety review focuses primarily on Study FOR01C, as well as a Phase 3 European study TSX/01/C. Supporting safety information were based on findings of previously submitted phase 3 studies (T 00-03-01 and T 02-03-01) and 2 extension safety studies (T 00-03E-01 and T 02-03E-01).

Table 7.1 Studies included in the ISS

Study	Study design	No. of Subjects Enrolled/Safety	Subjects	Length of Study
Phase III Studies				
FOR01C	Open-label, non-vehicle controlled	149/149	Hypogonadal men	3 months
T 00-03-01	Open-label, non-vehicle controlled	204/204[c]	Hypogonadal men	6 months
T 00-03E 01[a] Extension	Open-label, non-vehicle controlled 12-mo. (to 24-mo.) extension study	83/83[d] (11/11)[e]	Hypogonadal men	12-24 months
T 02-03-01	Open-label, non-vehicle controlled	68/68	Hypogonadal men	8 weeks
T 02-03E-01[b] Extension	Open-label, non-vehicle controlled l2-mo. extension study	55/55	Hypogonadal men	12 months
TSX/01/C	Double-blind placebo-controlled, randomized, Phase IIIb/IV study	108/108[f]	Hypogonadal men of meta-bolic synd. or type 2 diabetes	2 years

a. 83 of the 204 subjects in Study T 00-03-01 continued treatment for a further 12 months; 11 of these continued for a further 12 months (30 months total).
b. 55 of the 68 subjects in Study T 02-03-01 continued for a further 12 months (T 02-03E-01).
c. Three subjects in Study T 00-03-01 were enrolled twice (one as 014-130 and 014-143; another as 002-106 and 002-206, and the third as 002-107 and 002-207) and were counted for each enrollment.
d. One subject (012-100) discontinued the extension study T 00-03E-01 due to the adverse event of testosterone elevated, which started during the main phase of the 6-month study (T 00-03-01). This subject was not included in the dataset for the main phase study or in the study report for the extension phase, but has been included in the extension phase dataset for the integrated summaries. Therefore the total number of subjects reported in the integrated summaries for the extension study T 00-03E-01 is 83, whereas 82 subjects were reported in the study report.
e. Subject 012-110 was excluded from the 24 month data for extension study T 00-03E-01, but has been included in tables of this ISS. Therefore, there are 11 subjects reported for the 24 months extension study T 00-03E-01, but 10 subjects reported in the study report.
f. Placebo subjects in Study TSX/01/C excluded from integrated summaries

Source: Module 5.3.5.3: Integrated Summary of Safety.

Table 7.2 Summary of studies included in the ISS (Cont.)

Study	Study design	No. of Subjects Enrolled/Safety	Subjects	Length of Study
Phase I/II Studies				
T 98-03-01	Open-label, non-vehicle-controlled, randomized, 7 treatment regimen, 3-way, 3-period, matrix-type crossover (Treatment G added by amendment)	18/18	Hypogonadal men	21 days (28 days)
T 00-03-03	Open-label, non-vehicle-controlled, randomized, 2-treatment, 2-period crossover	7/7	Hypogonadal men	14 days
T 00-03-07	Open-label, non-vehicle-controlled, randomized, 3-treatment, 3-period crossover	12/12	Hypogonadal men	24 days
T 00-03-08	Open-label, non-vehicle-controlled, randomized, 3-treatment, 3-period crossover	15/15	Hypogonadal men	24 days
T 00-03-09[a]	Open-label, randomized, 3-treatment, parallel groups	72/72	Healthy volunteers	56 days
T 01-03-02[b]	Open-label, vehicle-controlled, randomized, 3-period crossover	8/8 males	Healthy volunteers	3 months[C]

a. Study T 00-03-09: not included in any tabulations, vehicle only

b. Study T 01-03-02: only male subjects included in integrated tabulations. There were 8 treatment-emergent AEs in 5 of the 8 female subjects in this study; none were considered treatment related
c. Study was 3 months in duration; dosing on 1 day for up to 3 days
Source: Module 5.3.5.3: Integrated Summary of Safety.

In addition, Phase 1/2 studies conducted in female patients were also included in safety evaluation for Fortesta:

Table 7.3 Summary of Studies included in the ISS (Cont.)

Study	Study design	No. of Subjects Enrolled/Safety	Subjects	Length of Study
Phase I/II Studies in Female Subjects[a]				
TF 99-03-01	Open label randomized, 3-treatment, 3- period, crossover, matrix-type study	22/21	Healthy, postmenopausal women	24 days
TF 00-03-06	Open-label, randomized, 6 treatment, 3 period, crossover, matrix-type study	40/36	Healthy, surgically-menopausal women	24 days
TF 02-03-01	Randomized, double-blind, parallel group, placebo-controlled	103/96	Healthy, postmenopausal women with sexual dysfunction	20 weeks

[a] Included in this submission as supportive for skin data only
Source: Module 5.3.5.3: Integrated Summary of Safety.

7.1.2 Categorization of Adverse Events

All adverse events were coded to MedDRA coding dictionary by Preferred Terms and System Organ Class, version. This reviewer assessed the mapping of verbatim terms to MedDRA terms and found the mapping of terms to be acceptable.

7.1.3 Pooling of Data Across Studies to Estimate and Compare Incidence

The integrated safety review is based on safety data from the individual studies, together with the summaries of demographic data, application site, and clinical laboratory data pooled separately for the Phase 3 studies (FOR01C, T 00-03-01, T 00-03E-01, T 02-03-01, T 02-03E-01, and TSX/01/C), and for Phase 1 / 2 studies (T 00-03-03, T 00-03-07, T 00-03-08, and T 01-03-02). The data from vehicle only study T 00-03-09 have not been included in the integrated summaries. Subjects on placebo in Phase 3 Study TSX/01/C were excluded from the integrated summaries; however, a separate summary was produced to present adverse event data in the placebo and Fortesta treatment groups. Only male subjects from the transference Study T 01-03-02 are included in the Phase 1/2 integrated summaries. Female subjects are reported by referring to the clinical study report (and therefore are not tabulated specifically for the integrated safety review). Skin data for female subjects in Studies TF 99-03-01, TF 00-03-06 and TF 02-03-01 are reviewed separately.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

7.2.1.1 Overall Exposure at Appropriate Doses/Durations

Overall exposure to Fortesta is summarized by dose (Table 7.4) and by duration (Table 7.5). In crossover studies where different sites were exposed in different study periods, it was assumed that adequate wash-out occurred; however, subjects were counted for each study period that they undertook. Table 7.9 shows the exposure for the pivotal study FOR01C alone.

Table 7.4 Extent of exposure to testosterone by final daily dose level (ISS population)

	Phase III								Phase I/II				
Daily dose level (mg)	10	20	30	40	50	60	70	80	10	20	30	40	60
Person weeks at this dose level	3	114	138	3000	568	8616	194	5345	16	25	2	50	63
Number of subjects with this final daily dose level	1	9	17	85	31	228	27	131	4	6	8	14	28

Studies included: FOR01C, T 00-03-01, T 00-03E-01, T 02-03-01, T 02-03E-01, TSX/01/C, T 98-03-01, T 00-03-03, T 00-03-07, T 00-03-08 and
T 01-03-02 (male subjects only)
Source: Module 5.3.5.3 Integrated Summary of Safety

Table 7.5: Duration of Therapy (ISS Population)

	Phase III	Phase I/II
Study Days Of Therapy [a]	n	n
1 –14 (Weeks 1–2)	16	18
15–35 (Weeks 3–5)	27	40
36–60 (Month 2)	30	–
61–90 (Month 3)	35	–
91–120 (Month 4)	128	–
121–150 (Month 5)	19	–
151–180 (Month 6)	8	–
181 + (Month 7+)	268	–

[a] Days on therapy excludes washout periods (if applicable).
n is the number of subjects
Studies included: FOR01C, T 00-03-01, T 00-03E-01, T 02-03-01, T 02-03E-01, TSX/01/C, T 98-03-01, T 00-03-03, T 00-03-07, T 00-03-08 and T 01-03-02 (male subjects only)
Source: Module 5.3.5.3 Integrated Summary of Safety

Table 7.6 Duration of Exposure to Study Drug (FOR01C)

Duration of Exposure[a]	Patients (N=149)
Duration of Exposure (days)	
n	149
Mean (SD)	93.0 (18.7)
Median	93.0
Range	15 – 177[b]
Numbers of patients by days exposed to drug, N (%)	
1-14 days	0
15-35 days	5 (3.4)
36-60 days	2 (1.)
61-90 days	21 (14.1)
> 90 days	121 (81.2)

a= Duration of exposure is calculated as the integer value of (date of last application minus date of first application plus one)/365.25.
b= The date of completion or discontinuation from the study was used as a proxy for the date of last application, since last application date was not explicitly collected on the CRF. In at least one case, this resulted in an over-estimate of exposure to study medication. Patient 032-003 was followed beyond Day 90 for an AE of elevated PSA. In this case, the date of study completion reflected the resolution of the AE.
Source: Module 5.3.5.1 FOR01C: Main Report.

Reviewer's comment: The overall exposure of Fortesta is adequate per ICH guideline.

7.2.1.2 Demographics of Target Populations

Demographic and baseline characteristics are shown in Table 7.7, Overall, the majority of subjects (70%) were Caucasian and approximately half of the subjects were 55 years or older with a mean age of 55 years. The average weight was 100 kg with an average BMI of 32 kg/m2. Demographic and baseline characteristics of the patient population in study FOR01C are similar to those of the integrated phase 3 population. The mean baseline total testosterone levels were approximately 180-190 ng/dL. The demographics and baseline characteristics of subjects in study FOR01C were similar to those of the integrated phase 3 studies. The safety population appears to be similar to the target population of Fortesta.

Table 7.7 Demographic and Baseline Characteristics by Phase of Study (ISS)

Characteristics	Phase III [a,b]		Phase I/II		Total	
N (Safety population)	526		60		586	
Age (years) (n, %)						
< 55	246	36.4	39	65.0	285	38.8
≥ 55	280	41.5	21	35.0	301	41.0
Mean±SD	55.0±11.2		49.5±12.5		54.5±11.4	
Race (n, %)						
Caucasian	461	68.3	57	95.0	518	70.5
Black	53	7.9	0		53	7.2
Asian	1	0.1	0		1	0.1
Hispanic	8	1.2	3	5.0	11	1.5
Other	3	0.4	0		3	0.4
Weight (kg)						
Mean±SD	100.25±18.73		101.77±22.40		100.40±19.12	
BMI (kg/m2)						
Mean±SD	32.16±5.72		32.89±6.49		32.22±5.79	
Serum Testosterone Level (ng/dL)[c]						
Mean±SD	197.90±82.75		177.85±78.32		196.10±82.49	

[a] In T 00-03-01, 3 subjects were randomized twice; first set of data are presented
[b] On1y includes male subjects from Study T 01-03-02
[c] Not recorded in the male subjects in T 01-03-02
Studies included: FOR01C, T 00-03-01, T 02-03-01, TSX/01/C, T 98-03-01, T 00-03-03, T 00-03-07, T 00-03-08 and T 01-03-02
Source: Module 5.3.5.3 Integrated Summary of Safety

7.2.1.3 Compliance with Study Medication

Compliance with study medication in phase 3 studies was summarized in Table 7.8. Compliance with study medication 70% to 130% were reported in approximately 80-90% of subjects in phase 3 studies; compliance in this range was lower in the 2 extension studies (33% to 68%).

Table 7.8 Compliance with Study Medication by Study: Phase III Studies

	T 00-03-01		T 00-03E-01 (12)		T 00-03E-01 (24)		T 02-03-01		T 02-03E-01		FOR01C	
N (Safety Population)	201[b]		83[d]		11		68		55		149	
Percent Compliance[a] Mean±SD Range	81.3±18.4 13-135		81.0±30.2 9-185		70.8±21.6 47-114		89.3±39.1 34-282		74.9±24.2 5-149		85.9±12.7 19-129	
Total with compliance recorded	172		63		9		62		40		134	
	n	%[c]	n	%	n	%	n	%	n	%	n	%
<70%	31	18.0	17	27.0	6	66.7	9	14.5	13	32.5	8	6.0
≥70% to 130%	138	80.2	43	68.3	3	33.3	49	79.0	26	65.0	126	94.0
>130%	3	1.7	3	4.8	0	-	4	6.5	1	2.5	0	-

a Compliance calculated as 100*(total gel used/total gel prescribed)
b In T 00-03-01, 3 subjects were randomized twice; these subjects are presented once.
c Percentage of those with compliance recorded
d An evident outlier, Subject 012-100, value 2880%, was not included in the analysis
e Compliance data not recorded for Study TSXl/01/C
Source: Module 5.3.5.3 Integrated Summary of Safety.

Reviewer's comment: The overall compliance to the study medication is acceptable.

7.2.2 Explorations for Dose Response

In study FOR01C, only a single starting dose and a single titration scheme with dose adjustment of 10 mg with each titration event were evaluated.

The two phase 3 studies submitted to the original NDA and Complete Response #1 evaluated a higher starting dose of 2% testosterone gel (60 mg) than that used in study FOR01C (40 mg). The lower dose in FOR01C resulted in a significantly lower proportion of subjects with high supraphysiologic testosterone C_{max}.

7.3 Major Safety Results

7.3.1 Deaths

No deaths were reported in Fortesta-treated subjects in the entire safety database.

7.3.2 Nonfatal Serious Adverse Events

In the integrated phase 3 studies database, 32 of 526 subjects (6%) experienced a total of 47 serious adverse events (SAEs), which are detailed in Table 7.9. Of these 32 subjects, the majority (21 of 32) were > 55 years old. The most common SAEs were polycythemia (3 subjects) and dyspnea (2 subjects). Most SAEs occurred at testosterone doses higher than 40 mg. Five subjects had SAEs considered to be drug-related. These included: severe congestive cardiac failure (Subject 010-103), polycythemia (Subjects 022-103, 014-118, and 014-137) in Study T 00-03-01; and deep vein thrombosis (DVT, [Subject 002-105]) in Study T 00-03E-01.

Five subjects (022-103 in Study T 00-03-01; 002-105 and 014-118 in Study T 00-03E-01; 23-0166 and 52-0257 in Study TSX/01/C) withdrew from the study due to an SAE.
.
There were no SAEs reported in the Phase 1 or 2 studies.

Table 7.9 Subjects with Serious Adverse Events: Phase 3 Studies[a]

Study	Subject ID	Dose (mg) at onset of SAE	Preferred Term (PT)	Severity	Relationship to CTM	Action taken	Outcome
FOR01C	FOR01C014-034	30 30	Colon cancer Rectal hemorrhage	Severe Severe	Not related Not related	None Study drug interrupted	Resolved Resolved
	FOR01C014-058	50	Dyspnea	Severe	Not relatedq	Study drug discontinued	Resolved
	FOR01C026-007	40	Intestinal obstruction	Moderate	Not related	None	Resolved
	FOR01C027-004	50	Cellulitis	Moderate	Not related	None	Resolved
	FOR01C028-007	40	Intestinal obstruction	Severe	Not related	Study drug interrupted	Resolved
T 00-03-01	010-103	60 60 60 60	Cardiac failure congestive Chest pain Orthopnoea Sinus arrhythmia	severe mild moderate moderate	Related Not related Not related Not related	Other None None None	Resolved Resolved Resolved Resolved
	011-109	40 40 60	Dehydration Procedural pain Sleep apnea syndrome	Severe Moderate Moderate	Not related Not related Not related	Other Other Other	Resolved Resolved Resolved
	014-106	60 60	Abdominal pain Diverticulitis	Severe Severe	Not related Not related	None Prescribed therapy	Resolved Resolved
	014-114	60	Coronary artery occlusion	Moderate	Not likely	Other	Resolved
	014-118	60	Polycythemia	Moderate	Related	None	Unchanged
	014-137	80	Polycythemia	Moderate	Related	Other	Lost-to-follow-up
	014-141	60	Dyspnea	Severe	Not related	Other	Resolved
	020-110	40	Renal artery stenosis	Severe	Not related	Other	Resolved
	022-103	80	Polycythemia	Severe	Related	Discontinued study	resolved
T 00-03E-01	001-131	60	Intestinal obstruction	Severe	Not related	Prescribed therapy	Resolved
	002-105	40	Deep vein thrombosis	Severe	Related	Discontinued study	Unchanged
	006116	60	Myocardial infarction	Mild	Not related	Prescribed therapy	Resolved
	014-100[b]	80	Chest pain	Severe	Not related	Prescribed therapy	Resolved
	014-133	60	Intervertebral disc	Severe	Not related	Other	Resolved
	020-110[c]	40	Basal cell carcinoma	Moderate	Not related	Other	Resolved
	021-105	60	Wound infect. Staphylococcal	Severe	Not related	Other	resolved

Source: Module 5.3.5.3: Integrated Summary of Safety.

Table 7.9 Subjects with Serious Adverse Events: Phase 3 Studies[a] (Cont.)

Study	Subject ID	Dose (mg) at onset of SAE	Preferred Term (PT)	Severity	Relationship to CTM	Action taken	Outcome
T 02-03-01	009-109	80	Non-cardiac chest pain	Moderate	Not related	None	resolved
T 02-03E-01	008-107	60	Bipolar disorder	Severe	Not related	None	Worsened
		60	Overdose	Severe	Not related	None	Improved
	009-104	80	Atrial fibrillation	Moderate	Not related	Dose discontinued	Resolved
		80	Pneumonia	Moderate	Not related	Dose discontinued	Resolved
		80	Renal failure acute	Moderate	Not related	Dose discontinued	Resolved
		80	Urinary tract infection	Mild	Not related	Dose discontinued	Resolved
	011-103	80	Chest pain	Severe	Not related	None	Hospitalized
	012-102	80	Skin laceration	Severe	Not related	Dose suspended	Resolved
	015-108	40	Myocardial infarction	Severe	Not related	Dose suspended	Hospitalized
	015-119	60	Coronary artery bypass	Severe	Not related	Dose suspended	improved
TSX/01/C	11 0004	80	Pneumonia	Severe	Not related	Hospitalized + therapy	Resolved
		80	Renal failure acute	Severe	Not related	Hospitalized + medication	Resolved
		80	Respiratory failure	Severe	Not related	Study therapy interrupted Hospitalized + medication	Resolved
		80	Sepsis	Severe	Not related	Hospitalized + medication	resolved
	16 0018	80	Skin neoplasm excision	Mild	Not related	Hospitalized + medication	Resolved
	23 0166	60	Myocardial infarction	Severe	Not related	Subject withdrawn; Concomitant medication	Resolved
	24 0148	60	Diabetes mellitus	Severe	Not related	Hospitalized + medication	Resolved
	52 0257	80	Squamous cell carcinoma	Severe	Not related	Hospitalized Subject withdrawn	resolved

a No treatment-emergent serious adverse events were reported in Phase I/II studies
b SAE of chest pain in Subject 014-100 present in dataset for Study T 00-03E-01 but not included in study report or original submission
c SAE of basal cell carcinoma in Subject 020-110 present in dataset for Study T 00-03E-01 but not included in study report or original submission
KEY: CTM = clinical trial material; ID = identification; SAE = serious adverse event
Source: Module 5.3.5.3: Integrated Summary of Safety.

Reviewer's comment: This clinical reviewer reviewed the case narratives of SAEs from study FOR01C and TSX/01/C and did not consider any of the SAEs in these 2 studies to be drug-related. The narratives of SAEs in the other studies were reviewed with previous submissions and are found in the appendices under each respective study.

7.3.3 Dropouts and/or Discontinuations

In the six Phase 3 studies (FOR01C, T 00-03-01, T 00-03E-01, T 02-03-01, T 02-03E-01 and TSX/01/C), 73 of the 526 subjects (13.9%) discontinued the study due to an adverse event. Adverse events leading to drug discontinuation are showed in Table 7.10. The most common AEs which were considered to be treatment leading to discontinuation were application site reactions (ASRs), followed by polycythemia (n=14, all from previous supporting phase 3 studies), and increase in PSA (n=5). One single patient from previous supporting phase 3 study (T 00-03-01) who developed prostate cancer was also discontinued from the study. Other significant AEs that were considered to be drug-related included: congestive heart failure (1), liver disorder (1), etc. Most AEs that led to drug discontinuation occurred at doses ≥ 60 mg.

Table 7.10 Subjects with TEAEs leading to Discontinuation: All Studies (ISS Population)

Study	Subject ID	Dose at AE Onset (mg)	TEAE (Preferred Term)	Severity	Relationship to CTM	Day of Onset a	Duration of Therapy (days)b
FOR01C	006-004	40	Application site reaction	Moderate	Related	8	17
	014-058	50	Dyspnea	Severe	Not related	30	122
	027-004	60	Application site reaction	Moderate	Related	84	92
	032-024	50	Contusion	Moderate	Not related	37	38
	032-052	40	Gastrc hypomotility	Moderate	Related	9	94
T 00-03-01	001-129	60	Application site erythema	Moderate	Related	2	7
	002-106	60	Chest pain	Moderate	Not related	23	37
		60	Dyspnea	Moderate	Not related	23	37
	002-109	60	Application site rash	Mild	Related	4	12
	002-115	60	Po1ycythemia	Moderate	Related	36	28
	002-116	60	Prostate cancer	Severe	Related	150	149
	005-102	60	Application site dryness	Moderate	Related	2	15
	006-102	60	Application site erythema	Moderate	Related	17	70
		60	Application site pruritus	Moderate	Related	17	70
		60	Application site dryness	Moderate	Related	21	70
		60	Application site exfoliation	Moderate	Related	21	70
	006-108	60	Application site erythema	Moderate	Related	1	23
		60	Application site irritation	Moderate	Related	8	23
		60	Application site discomfort	Moderate	Related	8	23
		60	Application site pruritus	Moderate	Related	8	23
		60	Application site erythema	Moderate	Related	8	23
	006-110	60	Headache	Moderate	Related	1	15
	006-112	60	Application site erythema	Moderate	Related	20	35
		60	Application site pruritus	Mild	Related	20	35
		60	Application site exfoliation	Mild	Related	20	35
	006-115	60	Application site pruritus	Mild	Related	10	29
		60	Application site exfoliation	Mild	Related	10	29
	006-121	80	Application site irritation	Moderate	Related	55	69
		80	Application site erythema	Moderate	Related	55	69
	007-101	60	Application site erythema	Moderate	Related	7	12
		60	Application site paraesthesia	Moderate	Related	7	12
		60	Application site irritation	Moderate	Related	8	12
		60	Application site erythema	Moderate	Related	9	12
		60	Application site dryness	Moderate	Related	9	12
		60	Application site exfoliation	Moderate	Related	9	12
		60	Application site pruritus	Moderate	Related	11	12
	007-107	80	Application site pruritus	Moderate	Related	37	50
	007-110	60	Application site irritation	Moderate	Related	17	18
		60	Application site erythema	Moderate	Related	17	18
		60	Application site exfoliation	Mild	Related	19	18
	010-103	60	Cardiac failure congestive	Severe	Related	48	84
	010-106	60	Application site rash	Moderate	Related	24	28
	010-107	60	Application site rash	Moderate	Related	45	38

Source: Module 5.3.5.3: Integrated Summary of Safety.

Table 7.10 Subjects with TEAEs leading to Discontinuation: All Studies (Safety Population) (Cont.)

Study	Subject ID	Dose at AE Onset (mg)	TEAE (Preferred Term)	Severity	Relationship to CTM	Day of Onset a	Duration of Therapy (days)b
Phase III Studies (cont.)							
T 00-03-01	014-114	60	Coronary artery occlusion	Moderate	Not related	137	139
	014-137	80	Po1ycythemia	Moderate	Related	96	102
	014-141	60	Dyspnea	Severe	Not related	27	31
	015-101	60	Application site irritation	Moderate	Related	3	5
		60	Application site warmth	Moderate	Related	3	5
		60	Application site pruritus	Moderate	Related	3	5
		60	Application site erythema	Moderate	Related	3	5
	015-108	80	Application site pruritus	Moderate	Related	39	46
		80	Application site erythema	Moderate	Related	40	46
		80	Application site swelling	Moderate	Related	40	46
	017-101	60	Application site erythema	Moderate	Related	28	30
		60	Application site pruritus	Severe	Related	28	30
		60	Application site dryness	Severe	Related	28	30
	017-110	60	Application site erythema	Moderate	Related	30	43
	017-117	60	Anxiety	Moderate	Not related	26	24
	017-127	60	Application site irritation	Moderate	Related	3	16
	018-101	60	Osteoarthritis	Moderate	Not related	60	52
	018-102	80	Liver disorder	Mild	Related	45	52
	018-115	60	Po1ycythemia	Moderate	Related	99	120
	018-117	60	Application site pruritus	Mild	Related	4	30
	019-101	60	Application site erythema	Moderate	Related	1	7
		60	Application site pruritus	Moderate	Related	1	7
	019-110	60	Application site erythema	Mild	Related	18	34
		60	Application site rash	Moderate	Related	33	34
	022-103a	80	Po1ycythemia	Severe	Related	109	194
T 00-03E-01	001-120	40	Pigmentation disorder	Moderate	Related	470	324
(12 mo)		40	Application site exfoliation	Mild	Related	470	324
		40	Application site pruritus	Moderate	Related	470	324
		40	Application site rash	Moderate	Related	470	324
	002-105	40	Deep vein thrombosis	Severe	Related	405	175
	010-112	80	Application site pruritus	Severe	Related	435	302
	012-100	40	Hyperandrogenism	Mild	Not related	187	1
	014-118	60	Po1ycythemia	Moderate	Related	186	59
T 00-03E-01	012-110	60	Po1ycythemia	Mild	Related	606	20
(24 mo)	012-130	80	Po1ycythemia	Mild	Related	556	13
	017-129	80	Pain in extremity	Moderate	Related	630	98
		80	Edema peripheral	Moderate	Related	630	98
	022-105	80	Po1ycythemia	Severe	Related	586	68
		80	Po1ycythemia	Severe	Related	586	68
	022-112	60	Po1ycythemia	Severe	Related	522	8
	022-114	80	Po1ycythemia	Severe	Related	522	8

Source: Module 5.3.5.3: Integrated Summary of Safety.

Table 7.10 Subjects with TEAEs leading to Discontinuation: All Studies (Safety Population) (Cont.)

Study	Subject ID	Dose at AE Onset (mg)	TEAE (Preferred Term)	Severity	Relationship to CTM	Day of Onset a	Duration of Therapy (days)b
Phase III studies (cont.)							
T 02-03E-01	009-104	80	Rash pruritic	Moderate	Not related	92	32
		80	Renal failure acute	Moderate	Not related	94	32
		80	Atrial fibrillation	Moderate	Not related	94	32
		80	Pneumonia	Moderate	Not related	94	32
		80	Urinary tract infection	Mild	Not related	94	32
	010-104	80	Po1ycythemia	Mild	Related	176	173
		80	PSA increased	Mild	Related	176	173
	011-103	80	Po1ycythemia	Mild	Related	58	13
	011-104	60	Po1ycythemia	Mild	Related	57	14
TSX/01/C	16 0021	60	Acne	Mild	Related	115	259
	16 1131	60	Myalgia	Mild	Related	12	57
		60	Dyspnea exertional	Mild	Related	15	57
		60	Dizziness	Mild	Related	17	57
	16 1132	60	Rash erythematous	Mild	Related	13	94
		60	Rash	Mild	Related	13	94
	17 1169	60	Rash pruritic	Moderate	Related	92	113
	20 0133	60	Flushing	Moderate	Not related	129	206
		60	asthenia	Moderate	Not related	129	206
	23 0166	60	Myocardial infarction	Severe	Not related	358	421
	37 0187	60	Palpitations	Moderate	Related	17	84
		60	Tremor	Moderate	Related	17	84
		60	Nervousness	Moderate	Related	17	84
		60	Angina pectoris	Moderate	Related	83	84
	51 0226	60	PSA increased	Mild	Related	84	92
	52 0257	80	Squamous cell carcinoma	Severe	Not related	85	85
	52 1261	40	Hyperhidrosis	Moderate	Related	174	365
	61 0242	60	PSA increased	Mild	Related	99	118
		60	Prostatomegaly	Mild	Related	118	118
	64 0233	60	Diabetes inadequate control	Moderate	Not related	194	194
	66 1268	60	Pruritus	Moderate	Related	13	26
		60	Erythema	Moderate	Related	13	26
	71 0057	60	PSA increased	Moderate	Related	92	127
	71 1058	60	Dermatitis allergic	Moderate	Related	37	51
	71 1059	80	Pruritus, erythema	Moderate	Related	183	203
	72 1091	80	Sleep apnea syndrome	Moderate	Related	371	398
	73 1066	80	PSA increased	Mild	Related	197	197
	81 0302	60	Urticaria	Severe	Related	2	6
Phase I/II studies							
T 00-03-08	002-112	60	Edema peripheral	Mild	Related	9	8
		60	Pain in extremity	Mild	Not related	12	8

[a]Day of onset is relative to start of CTM
[b]Duration of therapy is total days of application of CTM
Source: Module 5.3.5.3: Integrated Summary of Safety.

In study FORO1C, 5 of 149 subjects (3.4%) discontinued due to an AE (one each of gastric hypomobility, contusion, dyspnea, skin reaction, and contact dermatitis). The two application site reactions were most likely drug-related and the gastric hypomobility was considered by the investigator to possibly be related to drug.

7.3.4 Significant Adverse Events

No significant adverse events were reported for study FOR01C in the current submission

7.3.5 Submission Specific Primary Safety Concerns

Specific safety concerns for testosterone replacement therapy include increased hematocrit levels, decreased HDL cholesterol, and increased PSA levels that may result in adverse clinical outcomes that have been associated with adverse clinical outcomes (e.g., thromboembolic events, prostate cancer). Further, concerns which led to the Non-Approval action for the original NDA 21-463 included a decrease in HDL and an increase in hematocrit that was statistically significantly correlated with elevated serum testosterone C_{max} levels.

7.3.5.1 Changes in hematocrits, HDL, and PSA

This clinical reviewer and the statistical reviewer for the current NDA submission conducted an analysis for the changes in hematocrit (HCT), HDL, and PSA for the pivotal study FOR01C (see Table 7.11). The mean changes from baseline in these 3 laboratory measures were of small absolute magnitude. The changes from baseline in hematocrit, HDL levels and PSA were not statistically significant.

Table 7.11 Descriptive Statistics of Changes of Day 90 from Baseline for HCT, HDL, and PSA

	N	Mean	SD	Minimum	Maximum	Median	Lower 95%	Upper 95%
Δ HCT (%)	131	0.01	3.15	–8.2	10.70	–0.10	–0.53	0.56
Δ HDL (mg/dL)	137	–0.55	7.48	–20.00	38.00	–1.00	–1.82	0.71
Δ PSA (ng/mL)	135	0.24	0.62	–1.00	3.60	0.10	0.14	0.35

Source: Division's Clinical Analysis.

***Reviewer's comment**: There were five patients with an increase in Hct and 2 patients with an increase in PSA. However, none of these were clinically significant.*

7.3.5.2 Correlation of changes in hematocrit, HDL, and PSA with serum testosterone levels

This reviewer and the statistical reviewer assessed the correlation of serum testosterone C_{max}, C_{avg} with changes from baseline for hematocrit, HDL, and PSA at Day 90. The analysis did not

indicate that any statistically significant correlation between testosterone PK parameters and the changes in these 3 laboratory values (see Table 7.12)

Table 7.12 Correlation of D90 serum testosterone C_{max}, C_{avg} with Day 90 changes from baseline for hematocrits (HCT), HDL, and PSA

Correlation with serum T C_{max} or C_{avg} on Day 90		Δ Hematocrit (%)	Δ HDL (mg/dL)	Δ PSA (ng/mL)
with C_{max}	**Pearson coefficients**	0.00802	–0.10390	–0.14863
	p for correlation	0.9276	0.2269	0.08
with C_{avg}	**Pearson coefficients**	0.07025	–0.10390	–0.11334
	p for correlation	0.4258	0.2043	0.1904

Source: Division's Clinical Analysis.

Reviewer's comment: In contrast to previous results (from the original submission) for the correlation between the supra-physiological Cmax and the changes in hematocrit and HDL, the results of the pivotal study FOR01C showed that the Day 90 serum testosterone C_{max} or C_{avg} did not correlate with the changes on Day 90 from the baseline for the hematocrit, HDL, and PSA.

As an exploratory analysis, this reviewer evaluated the changes in hematocrit, HDL, and PSA levels for the 6 subjects in study FOR01C with Cmax ≥ 1800 ng/dL. The results are presented on Table 7.13. No consistent trend was observed for hematocrit or PSA changes and a trend was observed for small changes in HDL levels.

Table 7.13 Safety PD of Patients with Day 90 Cmax ≥ 1800 ng/dL (Study FOR01C)

Patient I.D.	Dose	C_{avg}	C_{max}	Δ HDL (mg/dL)	Δ Hematocrit (%)	Δ PSA (ng/mL)
005-001	**70**	**774**	**1800**	**0**	**6.7**	**0.1**
032-042	**60**	**1132**	**1930**	**–2**	**1.5**	**–0.2**
016-006	**40**	**759**	**1944**	**–7**	**–3.8**	**–0.1**
016-003	**40**	**607**	**2010**	**–11**	**-3**	**–0.2**
018-002	**50**	**702**	**2100**	**2**	**–2.2**	**0**
018-001	**30**	**477**	**2460**	**–3**	**0.1**	**–0.1**

Source: Division's Clinical Analysis.

The results showed that a significant increase of hematocrits (> 5 %) in 1 patient (#005-001), a decrease of > –5 mg/dL for HDL that was seen in 2 patients (#016-006 and #016-003), and no significant increase in PSA was seen.

***Reviewer's comment**: The results of FOR01C were reassuring for adverse changes in hematocrit, HDL, and PSA levels. However, changes in hematocrit, HDL and PSA levels will be included in the Fortesta product label, as in all other testosterone drug labels.*

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

7.4.1.1 Overall Incidence of Adverse Events

In the integrated phase 3 database, 361 of 526 subjects (68.6%) reported at least one adverse event. A summary of the overall AE experience is shown in Table 7.14.

Table 7.14 Overall Summary of Treatment-Emergent Adverse Events: Phase III Studies (ISS Population)

	Phase III Studies (N=526)	
	n	%
Number (%) of subjects with:		
At least one TEAE	361	68.6
At least one related" TEAE	246	46.8
At least one severe TEAE	42	8.0
At least one SAE	32	6.1
At least one TEAE leading to discontinuation	73	13.9
At least one treatment-related TEAE leading to discontinuation	60	11.4

[a] Possibly related, related or relationship unknown; Percentages are of N
Studies included: FOR01C, T 00-03-01, T 00-03E-01, T 02-03-01, T 02-03E-01, TSX/01/C, (male subjects only)
Source: Module 5.3.5.3: Integrated Summary of safety (ISS); modified by this reviewer.

7.4.1.2 Common Treatment-Emergent Adverse Events

Table 7.15 summarizes the most common AEs (>2% in a System Organ Class) in the integrated phase 3 database. The most frequently reported AEs were in the following MedDRA System Organ Class: general disorders and administration site conditions (37%); infections and infestations (24%) and; Skin and cutaneous disorders (13%). The most common adverse events were application site reactions.

Table 7.15 Incidence of TEAEs Reported in ≥ 2%[a] of Subjects Summarized by System Organ Class and PT: Phase 3 Studies (Safety Population)

MedDRA SOC / PT	Phase III Studies (N=526)	
	n	%
Subjects With TEAEs	361	68.6
General disorders and administration site conditions	192	36.5
Application site erythema	81	15.4
Application site dryness	48	9.1
Application site pruritus	40	7.6
Application site exfoliation	22	4.2
Application site reaction	25	4.8
Application site rash	22	4.2
Application site irritation	20	3.8
Edema peripheral	17	3.2
Application site pain	0	-
Swelling	0	-
Infections and infestations	124	23.6
Upper respiratory tract infection	34	6.5
Nasopharyngitis	28	5.3
Sinusitis	22	4.2
Influenza	16	3.0
Skin and subcutaneous tissue disorders	68	12.9
Eryhema	15	2.9
Pruitus	11	2.1
Musculoskeletal and connective tissue disorders	65	12.4
Arthralgia	15	2.9
Back pain	13	2.5
Gastrointestinal disorders	56	10.6
Diarrhea	13	2.5
Nervous system disorders	49	9.3
Headache	21	4.0
Migraine	1	0.2
Metabolism and nutrition disorders	53	10.1
Hyperglycemia	11	2.1
Respiratory, thoracic and mediastinal disorders	43	8.2
Vascular disorders	41	7.8
Hypertension	25	4.8
Injury, poisoning and procedural complications	38	7.2
Reproductive system and breast disorders	32	6.1
Blood and lymphatic system disorders	28	5.3
Polycythaemia	21	4.0
Eosinophilia	3	0.6
Psychiatric disorders	27	5.1
Investigations	26	4.9
Prostate specific antigen increased	15	2.9
Renal and urinary disorders	26	4.9
Cardiac disorders	16	3.0

[a] SOC and/or PT reported in ≥ 2% of subjects in Phase III studies; since subjects may be counted more than once in a column, the sum column counts may exceed the total subjects. Percentages are of N
ASRs in 25 subjects in Study FOR01C were coded to the PT 'skin reaction' in the study report, and coded to the PT 'application site reaction' in the integrated summaries
Studies included: FOR01C, T 00-03-01, T 00-03E-01, T 02-03-01, T 02-03E-01, TSX/01/C, (male subjects only)
Source: Module 5.3.5.3: ISS; modified by this reviewer.

Adverse events were also analyzed for 3 different periods to evaluate for possible association of certain AEs and duration of drug use. The most 3 common AEs by SOC for the AEs reported during the following time period included:

Table 7.16 Most Common AEs Reported During different periods

	Days 1-120 (N= 526) n (%)	**Days 121-180 (N= 364) n (%)**	**Days > 180 (N= 246) n (%)**
Any AE	309 (59)	71 (20)	129 (52)
SOC: N (%)	• General disorders and administration site conditions: 177 (34) • Infections and infestions: 88 (17) • Skin and cutaneous tissue disorder: 42 (8)	• Infections and infestations: 24 (7) • General disorders and administration site conditions: 10 (3) • Skin and cutaneous tissue disorders: 10 (3)	• Infections and infestations: 36 (15) • General disorders and administration site conditions: 21 (9) • Gastrointestinal disorders: 19 (8)

Reviewer's comment:
The common AE profile of study FOR01C is similar to that of the integrated phase 3 database. Most common AEs by PTs (> 2%) in study FOR01C were skin reaction (17%), upper respiratory infection (7%), sinusitis (4%), and hypertension (3%).

7.4.1.3 Treatment-Related Treatment-Emergent Adverse Events

In the integrated phase 3 safety database, 246 of 526 subjects (47%) experienced at least one AE that was considered by the investigator to be treatment-related (adverse reactions). The most frequently reported adverse reactions were those related to application site reactions, which included application site erythema, dryness, pruritus, exfoliation, rash, irriation, and pain. The most common reactions by PT not related to the application site were polycythemia (4%) and increased PSA (3%), With the exception of eosinophilia, all of the adverse reactions associated with Fortesta have been reported with other testosterone replacement therapy.

Table 7.17 Incidence of Adverse Events Reported in ≥ 2%[a] of Subjects and Assessed as Causally Related[b] or Unrelated to Testosterone for the Integrated Phase 3 (ISS Population)

	Phase III Studies (N= 526)			
MedDRA SOC / PT	**Unrelated**		**Related**	
	n	**%**	**n**	**%**
Subjects With TEAEs	115	21.9	246	46.8
General disorders and application site conditions	24	4.6	168	31.9
Application site erythema	0	-	81	15.4
Application site dryness	0	-	48	9.1
Application site pruritus	0	-	40	7.6
Application site reaction	1	.02	24	4.6
Application site exfoliation	0	-	22	4.2
Application site rash	0	-	22	4.2
Application site irritation	0	-	20	3.8
Edema peripheral	9	1.7	8	1.5
Application site pain	0	-	0	-
Swelling	0	-	0	-
Skin and subcutaneous tissue disorders	33	6.3	35	6.7
Blood and lymphatic system disorders	5	1.0	23	4.4
Polycythaemia	1	0.2	20	3.8
Eosinophilia	0	-	3	0.6
Investigations	6	1.1	20	3.8
PSA increased	0	-	15	2.9
Reproductive system and breast disorders	13	2.5	19	3.6
Nervous system disorders	32	6.1	17	3.2
Metabolism and nutrition disorders	38	7.2	15	2.9
Vascular disorders	27	5.1	14	2.7
Musculoskeletal and connective tissue disorders	52	9.9	13	2.5

[a] SOC and/or PT reported by ≥ 2% of subjects in Phase III studies; Percentages are of N

[b] PT reported as possibly related, related or relationship unknown by ≥ 2% of subjects

NOTE: Subjects who reported multiple events at any level (event, SOC, PT) are categorized according to the causality relationship at that level.

Studies included: FOR01C, T 00-03-01, T 00-03E-01, T 02-03-01, T 02-03E-01, TSX/01/C, (male subjects only)

Source: Module 5.3.5.3:ISS, modified by this review.

***Reviewer's comment**: In study FOR01C, the most common adverse reactions was application site reactions (16%), but increased PSA was reported in only 2 subjects (1.3%) and no subject had polycythemia.*

7.4.1.4 Severity of Treatment-Emergent Adverse Events

In the integrated Phase 3 study data, 42 of 526 subjects (8%) experienced at least one severe AE. The most common severe AEs were in the SOC general disorders and administration site conditions (7 subjects) and gastrointestinal disorders (7 subjects). The most common severe AEs by PT's (reported ≥ 2 subjects) were those related to application site reactions (4 subjects).

7.4.1.5 Application Site Reactions (ASRs)

Application site reactions were assessed by various scales in the studies FOR01C, T 00-03-01, TSX/01/C, and T 02-03-01, as well as T 98-03-01, T 00-03-03, T 00-03-07, and T 00-03-08. However, study FOR01C was designed to evaluate application site reactions (ASRs) consistent with the Division's recommendations. As such, the primary support for ASR safety of Fortesta is based on the findings of study FOR01C with supportive evidence from the integrated safety database.

Study FOR01C: In addition to conventional soliciting of adverse event related to application site reactions, trained investigators conducted a visual assessment of the application site at each study visit using the Berger/Bowman scoring scale recommended by the Division (see Table 7.40 for dermal response and dermal effects components of this scale). All the dermal responses and other dermal effects and application site adverse events were reviewed by the medical monitor and reconciled into a single clinical ASR. For example, if there were dermal responses at Visit 4 and Visit 5, and an AE related to the application site was reported between visits, those responses and AEs would be considered to be one clinical ASR.

The results of study FOR01C are presented in Table 7.18. With regards to dermal response, 3 subjects of 140 (2%) at Day 60 and 3 subjects of 146 (2%) had a dermal response of 2 (definite erythema, minimal edema or minimal papular response); 1 subject of 146 (0.7%) had a dermal response of 3 (erythema and papules). A majority of subjects had no evidence of irritation (≥ 95%) at each study visit. With regards to dermal effects, approximately 2-3% of subjects at each visit had a dermal response B (slight glazing). At Day 35, 60, and 90 visits, 1 subject each (0.7%) had dermal response grade C (marked glazing); at Day 60 and 90 visits, 3 and 2 subjects, respectively, had a dermal response grade D (marked glazing with peeling/cracking). A majority of subjects (>95%) had no dermal response across all visits.

Table 7.18 Study FOR01C: Results of Dermato1ogic Exam of Thigh Application Sites by Visit (Safety Population)

	Day 14	Day 35	Day 60	Day 90
Number of patients with an assessment	N=147 n (%)	N=143 n (%)	N=140 n (%)	N=146 n (%)
Dermal Response				
0= No evidence of irritation	146 (99.3)	139 (97.2)	134 (95.7)	138 (94.5)
1 = Minimal erythema, barely perceptible	1 (0.7)	4 (2.8)	3(2.1)	4 (2.7)
2 = Definite erythema. readily visible, minimal edema or minimal popular response	0	0	3(2.1)	3 (2.1)
3 = Erythema and papules	0	0	0	1 (0.7)
4 = Definite edema	0	0	0	0
5 = Erythema, edema and papules	0	0	0	0
6 = Vesicular eruption	0	0	0	0
7 = Strong reaction spreading beyond the test site	0	0	0	0
Other Dermal Effects				
A = No other dermal effects	144 (98.0)	138 (96.5)	132 (94.3)	140 (95.9)
B = Slight glazed appearance	3 (2.0)	4 (2.8)	4 (2.9)	3 (2.1)
C = Marked glazing	0	1 (0.7)	1 (0.7)	1 (0.7)
D = Glazing with peeling and cracking	0	0	3 (2.1)	2 (1.4)
E = Glazing with fissures	0	0	0	0
F = Film of dried serous exudates covering all or Part of the application site	0	0	0	0
G = Small petechial erosions and/or scabs	0	0	0	0

Source: Module 5.3.5.1 FOR01C: Main Report.

***Reviewer's comment**: In study FOR01C, no subject reported a serious ASR, 2 subjects of 149 (1.3%) discontinued prematurely because of an ASR, and 24 of 149 subjects (16%) reported at least one ASR adverse event, none of which was considered severe. Given the AE and dermal response/effect data, Fortesta appears to be similar to other transdermal gel products in skin tolerability.*

Supportive Evidence of ASR safety:

ASRs were assessed with each study; however, the scales used to assess ASRs differed between the studies. Treatment-emergent ASRs in the Phase 3 studies are summarized by testosterone dose level at the time of onset in Table 7.19. Of the 526 subjects in the combined Phase 3 study data, 156 experienced a treatment-related ASRs (rate of 8.7%) No subjects reported a serious ASRs, 25 subjects (rate of 1.4%) discontinued because of an ASR, and 3 subjects developed severe ASRs (rate of 0.2%). There was no consistent dose-related trend for the onset of ASRs.

Table 7.19 Summary of Application Site Reactions by Dose Level in Phase III Studies

	Fortesta (as testosterone mg/day)																	
Daily dose level	**10 mg**		**20 mg**		**30 mg**		**40 mg**		**50 mg**		**60 mg**		**70 mg**		**80 mg**		**Total[b]**	
Person weeks at this dose level	3		114		138		3000		568		8616		194		5345		17978	
Number of subjects	n	Rate[a]	n	Rate[a]	n	Rate[a]	n	Rate[a]	n	Rate[a]	n	Rate[a]	n	Rate[a]	n	Rate[a]	n	Rate[a]
Subjects reporting treatment-related ASRs	0	-	1	8.8	2	14.5	21	7.0	4	7.0	105	12.2	1	5.2	31	5.8	156	8.7
Subjects with ASRs by Maximum severity																		
Mild	0	-	1	8.8	2	14.5	14	4.7	5	8.8	57	6.6	1	5.2	20	3.7	91	5.1
Moderate	0	-	0	-	0	-	77	2.3	0	-	46	5.3	0	-	10	1.9	63	3.5
Severe	0	-	0	-	0	-	0	-	0	-	2	0.2	0	-	1	0.2	3	0.2
ASRs resulting in discontinuation	0	-	0	-	0	-	2	0.7	0	-	19	12.2	0	-	4	0.7	25	1.4

[a] Rate is calculated as the number of subjects reporting an event with onset at this dose level, divided by the total number of person weeks of treatment at this dose level multiplied by 1000.
[b] Since subjects may b~ counted under more than one column, the sum of columns counts may exceed the total subjects.
Events from the TSX/01/C study were only included if the original event term referred to 'application site'
Studies included: T 00-03-01, T 00-03E-01, T 02-03-01, T 02-03E-01, FOR01C and TSX/01/C
Source: Module 5.3.5.3:ISS.

In addition, for Study T 00-03-09 (vehicle study), no overall conclusion can be drawn on the effect of surface area as there were no differences in the visual irritation scores between the different application site surface areas.

In study TSX/01/C in hypogonadal men with metabolic syndrome/diabetes, the incidence of ASRs was similar between Fortesta-treated subjects (10% of subjects with erythema, and 8% with pruritis) and placebo subjects (7% with erythema and 9% with pruritus).

7.4.2 Laboratory Findings

Laboratory measures of hematocrit, HDL cholesterol, and PSA is reviewed in Section 7.3.5 (Submission Specific Safety Concerns); the remainder of the laboratory findings will be reviewed in this section.

7.4.2.1 Hematology

AEs of polycythemia were reported in 22 of the 526 subjects (4.2%) in the Phase 3 studies, and the majority of these cases were from the previous supporting Phase 3 study T 00-03-01. In study FOR01C, 5 subjects with normal baseline hematocrit had high levels at Day 90; another subject had elevated baseline hematocrit level that increased further at Day 90.

Table 7.20 Patients with high Hematocrit on Day 90 (Study FOR01C)

Patient I.D.	Baseline Hematocrit		Day 90 Hematocrit	
	Baseline HCT (%)	Normal or High	Day 90 HCT (%)	Normal or High
003-006	42.4	Normal	53.1	High
005-001	44.3	Normal	51.0	High
012-021	47.0	Normal	51.2	High
018-008	50.0	Normal	50.1	High
027-009	47.8	Normal	51.0	High
032-004	53.5	High	55.7	High

Source: Division's Clinical Analysis.

***Reviewer's comment**: The 6 subjects listed above did not have any clinical signs of high hematocrit levels and none required treatment or discontinued prematurely because of elevated hematocrit levels. These laboratory values did not correlate with testosterone Cmax in these 6 subjects.*

***Reviewer's comment**: Overall, no unexpected changes in hematocrit levels were seen with Fortesta compared with what is already labeled for testosterone products.*

7.4.2.2 Clinical Chemistry

Summary statistics for clinical chemistry laboratory variables for baseline (Day 1) and the exit visit for the integrated Phase 3 studies are presented for all subjects with data available in Table 7.21. Differences between means at baseline and means at last study were small for all clinical chemistry variables. The changes of HDL-cholesterol are reviewed in the Section of 7.3.5.1.

Table 7.21 Summary of Clinical Laboratory Results: Phase 3 Studies (ISS Population)

Parameter (units)	Baseline			Last Visit		
	N	Mean±SD	Range	N	Mean±SD	Range
Cholesterol (mmol/L)	523	4.967±1.104	2.36-10.14	407	4.687±1.115	2.20-9.13
LDL-C (mmol/L)	512	2.996±1.006	0.41-10.13	397	2.730±0.895	0.44-5.70
HDL-C (mmol/L)	523	1.087±0.312	0.06-2.90	397	1.058±0.307	0.44-2.20
Triglycerides (mmol/L)	322	2.019±1.464	0.51-13.58	260	2.170±1.604	0.44-11.46
ALT (IU/L)	523	31.4±17.4	8-186	405	28.2±12.7	6-87
AST (IU/L)	523	26.2±17.1	11-341	405	24.8±10.8	10-149
Alkaline phosphatase (IU/L)	523	77.9±24.3	33-175	407	72.3±22.7	20-194
Total protein (g/L)	322	71.7±4.8	55-92	260	70.6±5.0	58-86
Albumin (g/L)	322	43.7±2.9	35-53	261	43.0±3.2	35-52
Lactate Dehydrogenase (IU/L)	213	162.4±36.1	92-324	184	158.3±32.0	94-292
Creatinine (µmol/L)	523	92.9±21.8	35-256	408	96.9±24.8	27-301
Blood Urea Nitrogen (mmol/L)	415	6.15±2.19	1.8-31.8	337	5.94±2.11	2.1-26.4
Uric Acid (µmol/L)	523	381.8±91.6	101-694	407	382.7±90.6	172-708
Calcium (mmol/L)	322	2.383±0.109	2.10-2.73	260	2.348±0.140	1.40-2.65
Phosphorus (mmol/L)	322	1.117±0.165	0.71-1.81	260	1.105±0.229	0.70-2.84
Glucose (serum) (mmol/L)	523	6.70±2.60	3.2-23.6	402	6.83±2.78	2.5-22.2

[a] Baseline is defined as the last value obtained prior to dosing on Day 1.
[b] Values for subjects continuing in extension studies are taken at the exit from the extension study.
KEY: n/a= data not available, ALT = alanine aminotransferase; AST = aspartate aminotransferase N is the number of subjects with results for parameter at the visit
Studies included: FOR01C, T 00-03-01, T 00-03E-01, T 02-03-01, T 02-03E-01, TSX/01/C, (male subjects only)
Source: Module 5.3.5.3 ISS, modified by this reviewer.

Table 7.22 summarizes the data from subjects with shifts from normal baseline chemistry laboratory values to values above or below the normal range at the final evaluation in the integrated phase 3 database. A notable proportion of subject with normal baseline values had elevations of glucose (25%), triglycerides (19%) and alkaline phosphatase (12%) at the final evaluation.

Table 7.22 Number (%) of Subjects with Chemistry Laboratory Values within the Normal Range at Baseline[a] and Outside the Normal Range at Last Visit[b] for All Phase 3 Studies (ISS Population)

	Low		High	
	n/N	%	n/N	%
Creatinine	1/379	0.3	19/379	5.0
Uric acid	1/329	0.3	29/329	8.8
Alkaline phosphatase	4/381	1.0	6/38	11.6
Blood Urea Nitrogen	0/276	0.0	21/276	7.6
Calcium	8/250	3.2	1/250	0.4
Glucose	4/190	2.1	47/190	24.7
AST	2/374	0.5	14/374	3.7
ALT	1/356	0.3	17/356	4.8
Albumin	0/253	0.0	3/253	1.2
LDH	1/171	0.6	4/171	2.3
Phosphorus	11/244	4.5	7/244	2.9
Total protein	0/249	0.0	3/249	1.2
Triglycerides	1/168	0.6	31/168	18.5

[a] Baseline is defined as the last value obtained prior to dosing on Day 1
[b] Values for subjects continuing in extension studies are taken at the exit from the extension study.
n is the number of subjects with normal hematology values at baseline and low (or high) values at last visit
N is the number of subjects with normal hematology values at baseline who have a baseline and last visit value available
Studies included: FOR01C, T 00-03-01, T 00-03E-01, T 02-03-01, T 02-03E-01, TSX/01/C, (male subjects only)
Source: Module 5.3.5.3 ISS, modified by this reviewer.

***Reviewer's comment**: Most of the blood draws were non-fasting and also included subjects with history of Type 2 diabetes that contributed to slightly higher blood glucose and triglyceride levels.* No shifts from normal qualified as an outlier value.

In the integrated phase 3 database, 29/252 (11.5%) and 26/228 (11.4%) subjects had values for cholesterol and LDL-C, respectively, within the normal range at baseline but outside the upper range of normal at their final evaluation.

***Reviewer's comment**:*
At the final visit, HDL-C values were below the lower limit of normal in 61/268 (22.8%) subjects who had values within the normal range at baseline, and these patients were mainly from the previous study T 00-03-01 For the pivotal study FOR01C, greater 5% of patients had their values within the normal range at baseline but outside the upper range of normal at their final evaluation for uric acid (8/144, 5.6%), glucose (13/1456, 9%), and triglycerides (19/145, 13.1%).

***Reviewer's comment**:*
Elevations in cholesterol and reductions in HDL-C are labeled for testosterone products.

7.4.3 Vital Signs

Vital signs including temperature, respirations, pulse rate, and mean sitting diastolic and systolic blood pressure) were evaluated at baseline and study exit, and at other protocol-defined times during the study period in the Phase 3 studies. Compared with baseline, mean changes on-therapy in vital signs were of small magnitude and did not appear to be clinically meaningful.

In the pivotal study FOR01C, hypertension was reported as an adverse event in 4 (2.7%) subjects, and was assessed as possibly related in 1 (0.7%) of these subjects (Subject # 005-001) by the study investigator. Subject 005-001 was a 46 year-old Caucasian male with a baseline BP of 120/100 mmHg had a BP of 138/03 at Visit 6.

Reviewer's comment: The data from the 4 subjects with an AE of hypertension were reviewed. There were no clinical sequelae from the BP increases and the increases did not appear to be clinically concerning.

Review on hypertension in previously submitted Phase 3 study T 00-03-01 can be seen in Appendix B.

7.4.4 Physical Examination findings

No important changes in baseline physical examination findings were noted in the integrated safety database, other for skin changes associated with ASRs.

7.4.5 Electrocardiograms (ECGs)

No significant ECG changes from baseline to study exit were noted in the integrated safety database.

7.4.6 Long Term Safety

The long term safety information for Fortesta were collected with two supporting Phase 3 studies T 00-03E-01 (12 to 24 months) and T 02-03E-01 (12 months), and the European study TSX/01/C (24 months).

7.4.6.1 Extension Studies T 00-03E-01 and T 02-03E-01

In the extension studies, each subject continued on the same daily dose of Fortesta applied at the end of the initial study. Safety assessments included measurement of vital signs and adverse events at each visit (Months 2, 4, 6, 8, 10 and 12), a serum testosterone level and PSA test at 6 and 12 months, and clinical laboratory tests (hematology, clinical chemistry and urinalysis) and a physical examination at 12 months. During the second 12 months of Study T 00-03E-01, samples were taken every 2 months for serum testosterone, PSA, hematology, clinical chemistry and urinalysis.

One subject (# 012-100) discontinued the extension study T 00-03E-01 due to the adverse event of elevated testosterone, which started during the main phase of the 6-month study T 00-03-01.

***Reviewer's comment**: This subject was not included in the dataset for the main phase study, but has been included in the extension phase dataset for the ISS. Therefore, the total number of subjects reported in other sections of the safety review for the extension study T 00-03E-01 was 83, whereas 82 subjects were reported and discussed in this section. Similarly, Subject # 012-110 was excluded from the 24-month data for extension study T 00-03E-01, but has been included in tables of this ISS. Therefore, there are 11 subjects reported for the 24-month extension study T 00-03E-01 in other sections of this ISS, but 10 subjects are reported and described in this section.*

Study T 00-03E-01: 82 subjects who completed the 6-month study T 00-03-01 elected to continue another 6 months of treatment ("phase 1 extension," a total of 12 months of treatment) and 10 subjects continued for an additional 12 months ("phase 2 extension," total 24-month treatment). The long-term extension study T 00-03E-01 included "phase 1" and "phase 2" extensions. Of the 82 subjects who enrolled in the "phase 1 extension," 57 subjects (69.5%) completed the 12 months and 25 subjects discontinued prematurely. The reasons for premature discontinuation during the l2-month extension were subject choice (10 subjects), lost to follow-up (6 subjects), adverse events (5 subjects), subject non-compliance (3 subjects) and other (1 subject moved out of the area of the study site). Of the 10 subjects who enrolled in the ("phase 2 extension,", 3 subjects completed the total of 24 months of treatment and 7 subjects discontinued. The reasons for discontinuation were adverse event (5 subjects) and non-compliance (2 subjects).

Study T 02-03E-01: A total of 55 subjects from the initial 8-week study (Study T 02-03-01) elected to continue application of Fortesta in the extension study (study T02-03E-01, total of 12 months of treatment). Of these 55 subjects, 25 completed the 12-month extension study and 30 discontinued prematurely. The reasons for premature discontinuation were by subject choice (9 subjects), adverse events (5 subjects), lost to follow-up (4 subjects), subject non-compliance (2 subjects), and in 10 subjects for reasons categorized as other (increased hematocrit [4 subjects], increased hematocrit, bilirubin and ALT [1 subject], sponsor request [3 subjects], CTM unavailable when subject ran out [1 subject], and elevated PSA [1 subject]).

SAEs: No deaths occurred in either safety extension studies. In study T-00-03E-01, 5 subjects (6%) had an SAEs in the phase 1 extension, one of which was considered to be treatment-related (DVT). No SAEs occurred in the phase 2 extension. In study T-02-03E-01, 6 subjects reported at least 1 SAE as follows: 1 subject had combined events of manic depressive disorder and medication error with antipsychotic drugs; 1 subject had combined events of atrial fibrillation, urinary tract infection, acute renal failure and pneumonia, which resulted in withdrawal of the subject from the study; the remaining serious adverse events, in 1 subject each, were chest pain, accidental injury, myocardial infarction and coronary artery disorder. None of the serious adverse events were assessed by the investigator as related to study drug.

AEs leading to drug discontinuation: In study T-00-03E-01, 5 of 82 subjects discontinued drug prematurely because of an adverse event in the phase 1 extension (erythrocytosis [2 subjects], pruritis [2 subjects], and DVT [1 subject]). In the phase 2 extension, 5 of 10 subjects discontinued because of an AE (erythrocytosis [2 cases], abnormal red blood cell count [2 cases], and peripheral edema [1 subject]). For 3 of these 10 subjects, the event also met the criteria for serious (DVT and 2 cases of eryhrocytosis).

Common AEs: In both safety extension studies, the most common AEs were application site reactions (7-9%) and infection (7-9%). The common AEs safety profile of the limited number of subjects in the safety extension studies did not appear to be dissimilar to that observed with the integrated phase 3 studies.

***Reviewer's comment**: The incidence of ASRs did not appear to increase with longer duration of use, although there may be a selection bias in that subjects with ASRs discontinued drug therapy sooner in the course of treatment. Regardless, the long term safety data on ASRs is not concerning.*

Laboratory Findings: In study T 00-03E-01, the mean increases in hemoglobin and hematocrit and, in general, the changes in lipoprotein profie (increases in total cholesterol, LDL-C and very low-density lipoprotein-cholesterol and an increase in HDL-C) observed in this study were consistent with known effects of testosterone replacement.

In study T 02-03E-01, 22 of 55 subjects with markedly abnormal hematocrit values, which were considered clinically significant in 7 subjects. About 40% of the subjects with high serum testosterone concentrations (>1140 ng/dL) shifted from normal to high hematocrit values at the exit visit. Of the 22 subjects with high serum testosterone concentrations, 15 subjects had at least one markedly abnormal hematocrit value. The dose of Fortesta was decreased in 8 subjects because of a hematocrit above 52%. There were no clinically significant changes in the mean clinical chemistry values or vital signs, but hypertension was reported as an adverse event in 2 subjects.

***Reviewer's comment**: In the opinion of this reviewer, the dose used in study T 02-03E-01, was higher than the dose used in study FOR01C and there has been no correlation between a slight increase in Hct (that was not clinically significant) and testosterone Cmax.*

7.4.6.2 European Study TSX/01/C

Study TSX/01/C was a placebo-controlled study that enrolled hypogonadal males, aged at least 40 years, with late onset hypogonadism (total testosterone serum level ≤ 11 nmol/L (316 ng/dL) or calculated free testosterone ≤ 255 pmol/L), and who presented with metabolic syndrome or type 2 diabetes mellitus. Safety and tolerability endpoints in this 2-year study included AEs, skin tolerability, vital signs and laboratory measurements. The incidence of AEs was similar in Fortesta-treated subjects (66.7%) and placebo (62.5%). The most frequently reported AEs (≥ 5%) are summarized by severity for Fortesta and placebo in Table 7.23. The most common AEs by

PTs were erythema (Fortesta, 10.2%; placebo, 7.1%), pruritus (Fortesta, 8.3%; placebo, 8.9%) and nasopharyngitis (Fortesta, 7.4%; placebo, 7.1 %). TEAEs. There were no notable differences between Fortesta and placebo in the incidence or severity of the most frequently reported TEAEs for this 2-year study.

Table 7.23 Incidence of Frequently Reported (≥ 5%)[a] TEAEs Summarized by Maximum Severity[b] for Study TSX/01/C (Safety Population)

MedDRA SOC / PT	Fortesta (N=108)					Placebo(N=1l2)				
	Mild	Moderate	Severe	Total	%	Mild	Moderate	Severe	Total	%
Subjects With TEAEs	22	42	8	72	66.7	24	37	9	70	62.5
Skin and subcutaneous tissue disorders	16	11	2	29	26.9	14	5	1	20	17.9
Erythema	8	3	0	11	10.2	7	1	0	8	7.1
Pruritus	7	2	0	9	8.3	7	2	1	10	8.9
Infections and infestations	12	6	1	19	17.6	12	6	0	18	16.1
Nasopharygitis	7	1	0	8	7.4	7	1	0	8	7.1
Nervous system disorders	13	3	0	16	14.8	12	3	0	15	13.4
Dizziness	6	0	0	6	5.6	3	1	0	4	3.6
Musculoskeletal & connective tissue disorders	7	8	0	15	13.9	8	8	0	16	14.3
Arthralgia	4	3	0	7	6.5	1	4	0	5	4.5
Back pain	2	0	0	2	1.9	4	3	0	7	6.3
General disorders & administration site conditions	11	4	0	15	13.9	11	4	0	15	13.4
Gastrointestinal disorders	8	5	0	13	12.0	8	7	1	16	14.3
Respiratory, thoracic and mediastinal disorders	8	4	1	13	12.0	10	3	0	13	11.6
Metabolism & nutrition disorders	5	5	1	11	10.2	6	3	1	10	8.9
Injury, poisoning & procedural complications	6	4	1	11	10.2	3	3	0	6	5.4
Psychiatric disorders	4	5	1	10	9.3	1	1	0	2	1.8
Investigations	6	3	0	9	8.3	7	2	0	9	8.0
PSA increased	5	1	0	6	5.6	2	1	0	3	2.7
Vascular disorders	8	1	0	9	8.3	3	4	1	8	7.1
Renal and urinary disorders	4	4	1	9	8.3	0	2	0	2	1.8
Ear and labyrinth disorders	5	1	0	6	5.6	1	1	0	2	1.8
Cardiac disorders	2	2	1	5	4.6	2	6	2	10	8.9

a PT reported by:≥ 2 5% of Fortesta or placebo subjects. Percentages are of N
b Subjects who reported multiple events at any level (event, SOC, PT) are categorized according to the highest severity for the events at that level
NOTE: There were no missing severities
Source: Module 5.3.5.4 Clinical Study Report TSX/01/C.

7.4.7 Special Safety Studies/Clinical Trials

No special safety studies were conducted for Fortesta.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

The relationship of adverse events and the applied dose Fortesta was investigated. TEAEs in the Phase 3 are summarized by testosterone dose level at the time of onset in Table 7.48 and Table 7.49, with the most frequent TEAEs summarized by testosterone dose level at the time of onset in Table 7.50 and Table 7.51, for the Phase 3 studies. Phase 3 studies evaluated doses ranging from 10 mg to 80 mg testosterone administered as Fortesta. No evidence of a dose relationship was observed for TEAEs in Phase 3 studies. In the Phase 3 studies, the rate of events per 1000 person-weeks was highest at the 30 mg dose level (50.7), followed by the 50 mg dose level (45.8). Importantly, neither the overall rate of events nor the rate of treatment-related events increased with the higher doses (60 mg to 80 mg). Similarly, there was no evidence of a higher rate of severe events, serious events or events that led to discontinuation at higher doses.

Table 7.48 Summary of TEAEs by Dose Level Received at Onset of Adverse Event in the Phase 3 Studies (Safety Population)

	Fortesta (as testosterone mg/day)																	
Daily dose level	**10 mg**		**20 mg**		**30 mg**		**40 mg**		**50 mg**		**60 mg**		**70 mg**		**80 mg**		**Total**	
Person weeks at this dose level	3		114		138		3000		568		8616		194		5345		17978	
	n	Rate[a]	n	Rate[a]	n	Rate[a]	n	Rate[a]	n	Rate[a]	n	Rate[a]	n	Rate[a]	n	Rate[a]	n	Rate[a]
Number of subjects with at least one AE	0	-	3	26.3	7	50.7	68	22.7	26	45.8	239	27.7	6	30.9	93	17.4	361	20.1
Subjects with at least one drug-related AE	0	-	1	8.8	4	29.0	41	13.7	10	17.6	161	18.7	1	5.2	65	12.2	246	13.7
Maximum AE severity reported per subject																		
Mild	0	-	1	8.8	4	29.0	28	9.3	14	24.6	103	12.0	5	25.8	36	6.7	129	7.2
Moderate	0	-	2	17.5	2	14.5	33	11.0	11	19.4	115	13.3	1	5.2	47	8.8	190	10.6
Severe	0	-	0	-	1	7.2	7	2.3	1	1.8	21	2.4	0	-	10	1.9	42	2.3
Number of subjects dis-continued due to AE	0	-	0	-	0	-	6	2.0	2	3.5	47	5.5	0	-	18	3.4	73	4.1
Number of subjects with at least one serious AE	0	-	0	-	1	7.2	6	2.0	2	3.5	12	1.4	0	-	10	1.9	32	1.8

[a] Rate is calculated as the number of subjects reporting an event with onset at this dose level, divided by the total number of person weeks of treatment at this dose multiplied by 1000.
[b] Since subjects may be counted under more than one column, the sum of columns counts may exceed the total subjects. Total includes TEAEs where dose level could not be determined.
Subjects who reported the same TEAE at more than one dose are counted more than once.
NOTE: No deaths were reported in Fortesta-treated subjects during any of the Phase I/II or Phase II clinical studies. However, one death due to myocardial infarction was reported in Study TSX/01/C. This event occurred in a placebo-treated subject and was not considered to be related to study drug. Studies included: T 00-03-01,
T 00-03E-01, T 02-03-01, T 02-03E-01, FOR01C, and TSX/01//C
Source: Module 5.3.5.3 ISS.

There was no consistent dose-related trend for the most common AEs of various application site reactions (e.g., erythema, pruritis, and dryness), nasopharyngitis, sinusitis, or hypertension. The rate of application site erythema, dryness and pruritus was highest for the 60 mg dose, whereas the rate of all application site reactions (ASRs) was highest for the 30 mg dose. No clear dose effect on the severity of these common AEs was observed.

7.5.2 Drug-Drug Interactions

Drug-drug interaction studies were not conducted with Fortesta.

7.6 Additional Safety Evaluations

Testosterone Transfer from Patients to Partners

An open-label, vehicle-controlled, pharmacokinetic study in healthy couples evaluated whether transference of FORTESTA 2% Gel from a male to a female would significantly raise serum testosterone level in the females, and if transference occurred, whether covering the application site with clothing would prevent it. Two hours after FORTESTA 2% Gel application to males, the female partner engaged in vigorous skin-to-skin contact with the application site for 15 consecutive minutes. Mean C_{avg} and C_{max} values for total testosterone were significantly higher (approximately two-fold) in female subjects who rubbed an uncovered application site of males compared to an application site covered with clothing. Despite this increase, the mean value remained within the physiologic range for females of reproductive age. Concentrations of total testosterone provide evidence that transference and absorption is prevented by covering the application site with clothing. This demonstrates that covering the application site effectively prevented transference and absorption of testosterone by the female partner.

Effect of Showering on Testosterone Pharmacokinetics

In an open-label, non-vehicle-controlled, randomized, two-treatment, two-period crossover study, the effects of showering on the pharmacokinetics of total testosterone following topical application of FORTESTA 2% Gel in hypogonadal males was assessed. Based on the analysis of C_{avg}, C_{min} and C_{max}, it was concluded that showering 2 hours after application of FORTESTA had no meaningful effect on the pharmacokinetics of topically applied testosterone.

"Wash Off" Study

No washing study to demonstrate if there is any residual amount of Fortesta left at the application site after washing the site with soap and water was conducted until the submission of this Complete Response (CR). However, the sponsor has been asked to conduct such a study as a postmarketing requirement and the sponsor has agreed to comply.

7.6.1 Human Carcinogenicity

Testosterone is an endogenous androgenic hormone, no human carcinogenicity effect has been found.

7.6.2 Human Reproduction and Pregnancy Data

Fortesta is intended for use in hypogonadal men.

Testosterone is contraindicated in pregnancy. Testosterone is a pregnancy X and can cause masculinization of the female fetus.

7.6.3 Pediatrics and Assessment of Effects on Growth

The efficacy and safety of Fortesta therapy has not been established in pediatric patients. The Applicant requested and was granted a full pediatric waiver because only a very limited number of pediatric patients would be affected by hypogonadism.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

7.6.4.1 Overdose

There is no experience with overdose experience with of Fortesta. There is one report in the literature of acute overdosage with testosterone enanthate injection: testosterone levels of up to 11,400 ng/dL were implicated in a cerebrovascular accident.

Treatment of transdermal overdosage is by washing the site of application with soap and water as soon as possible, discontinuing application of Fortesta and treatment of any symptoms with supportive care.

7.6.4.2 Drug Abuse

All forms of testosterone including Fortesta are Schedule III controlled substances under the Anabolic Steroids Control Act.

Controlled Substance Staff under Office of CDER Center Director has recommended that the Fortesta labeling under Section 9 "Drug Abuse and Dependence" be changed to reflect the warning for abuse and addiction:

> *Abuse (b) (4): Anabolic steroids, such as testosterone, are reported to be abused. Abuse is often associated with adverse physical and psychological effects.*
>
> *Dependence: Although drug dependence is documented in individuals using therapeutic doses of anabolic steroids for approved indications, dependence is observed in some*

individuals abusing high doses of anabolic steroids. In general, anabolic steroid dependence is characterized by any three of the following:

1) *taking more drug than intended*
2) *continued drug use despite medical and social problems*
3) *significant time spent in obtaining adequate amounts of drug*
4) *desire for anabolic steroids when supplies of the drugs are interrupted*
5) *difficulty in discontinuing use of the drug despite desires and attempts to do so*
6) *experience of a withdrawal syndrome upon discontinuation of anabolic steroid use.*

(b) (4)

***Reviewer's comment**:*
The CSS recommendations will be consolidated into the modified labeling.

7.6.4.3 Withdrawal and Rebound

Withdrawal or rebound effects following abrupt discontinuation of topical testosterone replacement therapy have not been reported in the literature.

7.6.4.4 Effects on Ability to Drive or Operate Machinery

Testosterone is not known to negatively affect mental ability. Therefore, no precautions with regard to driving or operating machinery are needed for Fortesta testosterone replacement.

7.7 Additional Submissions / Safety Issues

Since the submission on April 17, 2009, the sponsor submitted additional information in several occasions:

Date	Submission
May 08, 2009	Draft labeling and list of Module 5, and list of 54 literature references
May 15, 2009	Response to FDA information request about PK data
July 02, 2009	Response to FDA inspection request
July 22, 2009	Response to FDA clinical information request
August 03, 2009	Pediatric waiver request
August 19, 2009	Proposed REMS
September 03, 2009	GCP investigation on clinical site #32 and corrective action

7.8 Safety Conclusions

- The safety and tolerability of Fortesta (testosterone gel 2%) at a daily dose of 40 mg with a dose adjustment ranging between 10 mg to 70 mg depending upon serum testosterone level, was overall acceptable.
- No deaths occurred with Fortesta treatment and a majority of non-fatal SAEs were not drug-related.
- The most common reason for drug discontinuation was application site reactions.
- The most common adverse events considered to be related to Fortesta were application site reactions (ASRs) including contact dermatitis, application site erythema, dryness, and skin reaction. The majority of ASRs were mild to moderate in severity and required no further medical intervention.
- The next common treatment-related AEs were increase in hematocrit (that was not clinically significant) and prostate specific antigen (PSA), and a decrease in HDL-cholesterol (also not clinically significant).
- The safety findings in the Fortesta safety database are consistent with the known safety profile of other testosterone products (transdermal and non-transdermal).
- No cases of testosterone secondary transfer to children have been reported in the post-marketing experience with Fortesta.

8 Postmarket Experience

Fortesta is approved in 23 countries and is currently marketed in 19 of these countries. The drug was first launched in Sweden in September 2005; the remaining approvals followed from late 2007. The total estimated patient exposure from first launch to December 21, 2008, is 6,767 patient years.

Since the first launch, the sponsor has received a total of 20 spontaneous reports from health care professionals and consumers of adverse events which occurred during the use of Fortesta up to and including the data lock point of December 21, 2008. The 20 cases comprised 31 individual adverse events. None of these reported cases were considered serious by the reporters.

All adverse events are summarized in Table 8.1.

Table 8.1 Postmarketing Adverse Events Reported for Fortesta

System Organ Class	MedDRA Preferred Term
Blood and lymphatic system disorders	Polycythaemia
Eye disorders	Vitreous detachment
Gastrointestinal disorders	Abdominal symptoms
General disorders and administrative site conditions	Application site erythema, irritation, pruritus, and swelling; fatigue, influenza like illness, and malaise.
Investigations	Decreased blood testosterone, increased hematocrit and hemoglobin
Musculoskeletal and connective tissue	Pain in extremity
Nervous system disorders	Dizziness, headache, and migraine
Reproductive system and breast disorders	Erectile dysfunction, and priapism
Skin and subcutaneous tissue disorders	Allergic dermatitis, erythema, rash, and popular rash.

Source: Module 5.3.5.3 ISS, modified by this reviewer.

Reviewer's comment:
No new safety data of Fortesta was noted in the post-marketing information.

9 Appendices

9.1 Literature Review/References

The sponsor submitted 177 literature references to the NDA. No additional literature review is planned.

9.2 Labeling Recommendations

The following major labeling changes are recommended and have been made to the proposed label:

1) Potential for secondary exposure to Testosterone.
2) Patients shoud be evaluated for presence of prostate cancer prior to initiating and during treatment with Fortesta.
3) Hematocrit concentrations should be determined periodically in patients on long term Fortesta.
4) Fortesta, is a schedule III controlled substance as defined under the Controlled Substances Act.

9.3 Appendix A

Appendix A

Study FOR01C: An open-label, Phase 3 Study of Fortigel (testosterone) 2% Gel in Hypogonadal Males

Study starting date: August 15, 2007
Study complete date: March 25, 2008

The study was conducted in 26 centers in the US.

A.1 Study Objectives and Design

A.1.1 Primary Objective: Primary Objective: To supplement testosterone in hypogonadal males so that the time averaged serum total testosterone (total testosterone C_{avg}) on Day 90 ± 3 days was ≥ 300 and ≤ 1140 ng/dL in ≥ 75% of patients (lower bound of 95% confidence interval [CI] ≥ 65%).

A.1.2. Secondary Objectives:

1) To supplement testosterone in hypogonadal males so that the maximum serum total testosterone (C_{max}) on Day 90 ± 3 days was

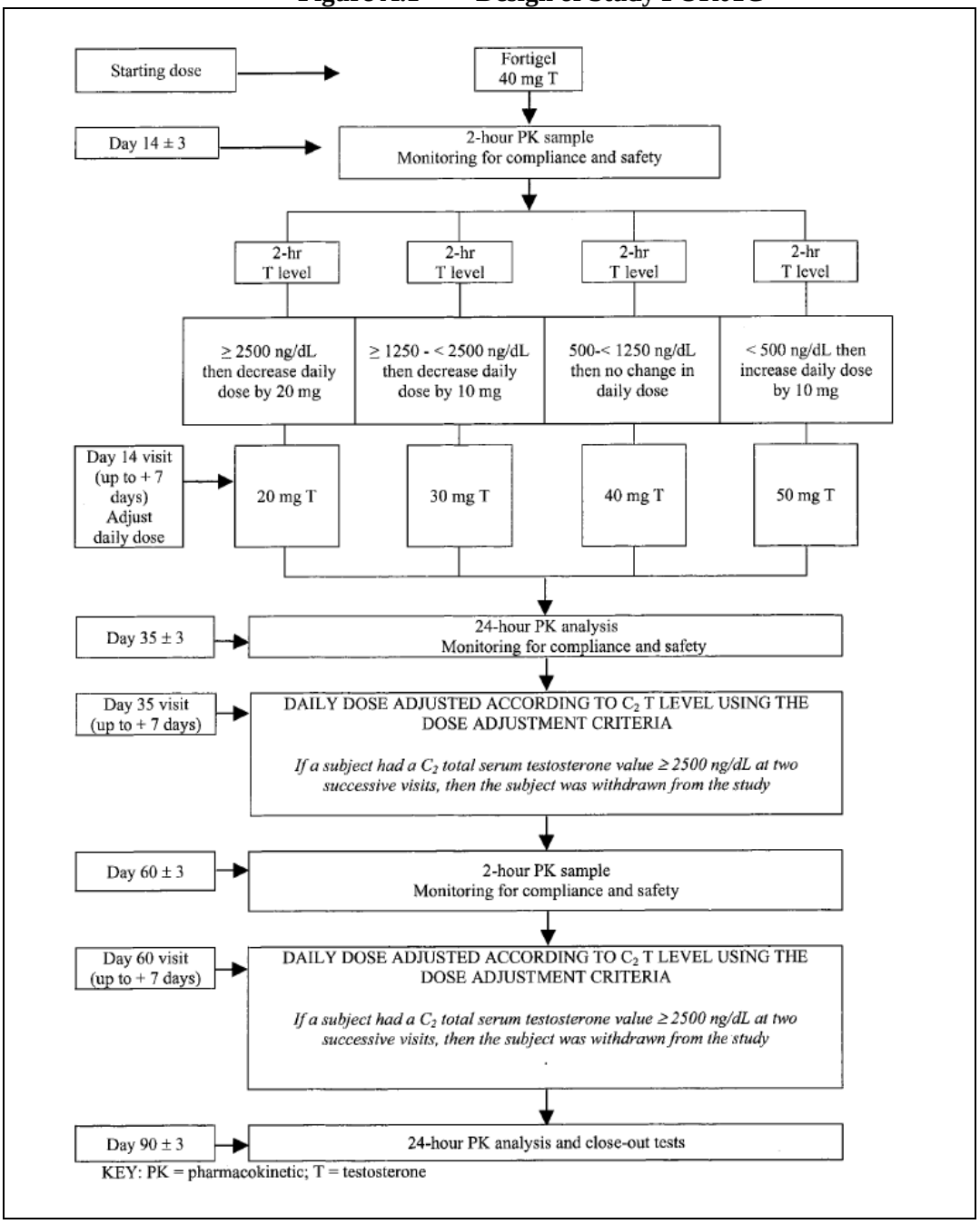
- ≤ 1500 ng/dL in ≥ 85% of patients
- ≥ 1800 to ≤ 2500 ng/dL in ≤ 5% of patients
- 2500 ng/dL in 0 patients

2) To determine the safety of Fortesta (testosterone) 2% Gel [Fortesta] in hypo-gonadal males.

A.1.3 Study Design: This study was a multicenter, open label, non-comparative trial in 149 hypogonadal males. Patients who had received prior testosterone replacement therapy completed a washout period, the length of which depended on the type of testosterone replacement therapy. All patients enrolled in the study applied Fortesta once each morning to the thighs, at a starting dose of 40 mg per day. The dose of study drug was adjusted to between a minimum of 10 mg per day and a maximum of 70 mg per day on the basis of total serum testosterone concentrations obtained at two hours after study drug application on Days 14, 35, and 60 (± 3 days). Serum testosterone concentrations (including total testosterone, free testosterone, and dihydrotestosterone [DHT] were obtained at two hours after study drug application on Days 14, 35, 60, and 90 (± 3 days). In addition, 24-hour pharmacokinetic (PK) profiles for these parameters were obtained on Days 35 and 90 (± 3 days). Sex hormone-binding globulin (SHBG), luteinizing hormone (LH), follicle stimulating hormone (FSH), and estradiol (E2) concentrations were obtained at two hours after study drug application on Days 35 and 90 (± 3 days). Safety was monitored throughout the study.

A.1.4 Diagnosis and Main Criteria for Inclusion: Patients eligible for this study were hypogonadal men, aged 18-75 years, defined as males having a single morning serum testosterone concentration < 250 ng/dL or < 300 ng/dL on two consecutive occasions at least one week apart. In addition, patients eligible for this study were required to have a body mass index (BMI) ≥ 22 kg/m^2 and < 35 kg/m^2.

Figure A.1 Design of Study FOR01C



Reviewer's comment: The study objectives and design were acceptable.

A.1.5 Dose Adjustment criteria

Table A.1 Dose Adjustment Criteria for Study FOR01C

Total serum Testosterone Concentration (C2)	Dose Titration
C2 ≥ 2500 ng/dL	Decrease daily dose by 20 mg T (1 g gel)
1250 ≤ C2 < 2500 ng/dL	Decrease daily dose by 10 mg T (0.5 g gel)
500 ≤ C2 < 1250 ng/dL	No change continue on current dose
C2 < 500 ng/dL	Increase daily dose by 10 mg T (0.5 g gel)
If a patient had a C2 total serum T value > 2500 ng/dL at 2 successive visits, then the patient was withdrawn from the study.	

KEY: T = testosterone

A.2 Study Results

A.2.1 Subject Disposition

The disposition of patients in the Study FOR01C is presented in TableA.2. A total of 406 patients were screened for possible study participation, 149 of whom subsequently entered the study and received at least one application of Fortesta. 257 patients failed screening because they did not meet the inclusion/exclusion criteria. Overall, 138 (92.6%) patients completed the study. Eleven (11) patients discontinued prematurely from the study. The most common reason for discontinuation was because of AEs (5 patients).

Table A.2 Patient Disposition for Study FOR01C

	Number (%) of Patients[1]
Patients screened	406
Screen failures	257 (63.3)
Patients entering the study	149
Patients completing the study	138 (92.6)
Patients discontinuing the study	11 (7.4)
Primary reason for discontinuation:	
Adverse event	5 (3.4)
Protocol violation	2 (1.)
Patient non-compliance	1 (0.7)
Patient choice	2 (1.)
Lost to follow-up	0
Other	1 (0.7)

1. Percentage for number of screen failure is based on the number of patients screened. All over percentages are based on the number of patients entering the study

The numbers of patients with specific inclusion/exclusion criteria violations are shown in Table A.3. Of the 257 patients who failed screening, 194 (75.5%) failed inclusion because their serum testosterone was not low enough.

Table A.3 Reasons for Screen Failure (All Screen Failure Patients)

	Number (%) of Patients
Number of patients who failed screening	257
Inclusion Criteria	
Does patient have primary or secondary hypogonadism with a single serum total testosterone concentration < 250 ng/dL or two consecutive serum total testosterone concentrations < 300 ng/dL	194 (75.5)
Does patient have a BMI ≥ 22 kg/m^2	7 (2.7)
Does patient have hematocrit level ≤ 50%	8 (3.1)
If patient has sexual partner of childbearing potential, does patient use reliable contraception	1 (0.4)
Does patient voluntarily agree to participate following full explanation of the study and obligations by signing the IRB/lEC approved informed consent document prior to screening	13 (5.1)
Exclusion Criteria	
Does patient have severe concomitant ilness which may put the patient at risk when participating in the trial, influence the results or affect the patient's ability to take part in the trial	1 (0.4)
Does the patient have ALT or AST levels > 2.5 x ULN	26 (10.1)
Does patient have clinically significant, abnormal, baseline laboratory result(s) which affect(s) the patients suitability for the trial	1 (0.4)
Is there a detection of the patient having a prostatic abnormality on digital rectal examination without further urological evaluation	2 (0.8)

Abbreviations: ALT = alanine aminotransferase, AST = aspartate aminotransferase, Ex = exclusion criteria, lEC = independent ethics committee, In = inclusion criteria, IRB = institutional review board, ULN = upper limit of normal.

Adverse events leading to discontinuation and Protocol violation were reviewed in the main Clinical Review.

A.2.2 Demographics

The Study analysis populations are shown in Table A.4. All enrolled patients were included in the safety analysis and ITT population. Overall, 92.6% (138/149 patients) of patients contributed to the efficacy mITT analysis set, and 56.4% (84/149 patients) contributed to the mPP analysis set.

Table A.4 Populations Analyzed for Study FOR01C

	Number (%) of Patients
Safety population	149 (100)
Intent-to- Treat (ITT) population	149 (100)
Modified Intent-to- Treat (mITT) population (Efficacy)	138 (92.6)
Per-Protocol (PP) population	35 (23.5)
Modified Per-Protocol (mPP) population	84 (56.4)

A summary of demographic and baseline characteristics including age, ethnicity, race, weight, height, and BMI is presented for the safety population in Table A.5. The mean age of patients in this study was 54.5 years (range 29 to 77 years) and the majority of patients were white (87.9%).

Table A.5 Demographic Characteristics (All enrolled patients)

Demographic Variable	Patients (N=149)
Age (years)	
Mean (SD)	54.5 (10.1)
Median	55.0
Range	29-77
Ethnicity (n[%])	
Hispanic or Latino	11 (7.4)
Not Hispanic or Latino	138 (92.6)
Race, (n[%])	
White	131 (87.9)
Black or African American	15 (10.1)
American Indian	0
Asian	0
Native Hawaiian or Other Pacific Islander	0
Other[a]	3 (2.0)
Weight (kg)	
Mean (SD)	97.65 (14.73)
Median	97.10
Range	65.3 – 147.6
Height (cm)	
Mean (SD)	178.08 (6.53)
Median	177.80
Range	162.6 - 198.1
Body Mass Index (kg/m2)	
Mean (SD)	30.61 (3.50)
Median	30.80
Range	22.1 -41.

A.2.3 Efficacy Results

A.2.3.1 Primary efficacy results: In the mITT population, the mean $C_{avg0\text{-}24hr}$ was 442.41 ± 177.73 ng/dL and 76.1 % of patients had testosterone levels within the physiologic range (≥ 300 and ≤ 1140 ng/dL) on Day 90. The lower bound of the 95% CI, 69.0% in the mITT population was above the predefined limit of ≥ 65%.

Table A.6 Primary efficacy endpoint

Efficacy	Target	Results
Primary endpoint C_{avg}		
on Day 90 (ng/dL)		442.41±177.73 (Mean±SD)
% patients $300 \leq C_{avg} \leq 1140$	≥ 75	76.1
95% CI limit	lower bound at 65%	(69.0, 83.2)
95% CI limit	lower bound at 65%	(69.0, 83.2)

Reviewer's comment: The primary endpoint is satisfied.

A.2.3.2 Secondary endpoint

Table A.7 Secondary Efficacy Endpoint for Pivotal Study FOR01C

Secondary endpoint C_{max}		
	Target	**Results**
on Day 90 (ng/dL)		863.92±408.01 (Mean±SD)
% patients $C_{max} \leq 1500$	≥ 85	93.1
% patients $1800 \leq C_{max} \leq 2500$	< 5	4.3
$C_{max} > 2500$	none	0

All with mITT population (N=138) for efficacy analyses

Reviewer's comment: During the second dose adjustments (Day 35), there were 92.0% of the patients whose measurements of C_{max} were within 1500 ng/dL, but there were still 1.4 % (n=2) of patients whose C_{max} reached above 2500 ng/dL. After three dose adjustments, the mean C_{max} on Day 90 was 863.92 ± 408.01 ng/dL. Overall, 91.3% of patients had C_{max} values ≤1500 ng/dL, 4.3% had C_{max} values within 1800 to 2500 ng/dL range, and there were no patients who had C_{max} values above 2500 ng/dL. These values finally met the pre-determined secondary efficacy endpoint objectives on Day 90; ≤1500 ng/dL in ≥85% of patients, ≥1800 – ≤2500 ng/dL in ≤ 5% of patients and > 2500 ng/dL in 0 patients.

A.2.4 Safety Results

A.2.4.1 Extent of Exposure

Table A.8 Duration of Exposure to Study Drug (FOR01C)

Duration of Exposure[a]	**Patients (N=149)**
Duration of Exposure (days)	
n	149
Mean (SD)	93.0 (18.7)
Median	93.0
Range	15 – 177[b]
Numbers of patients by days exposed to drug, N (%)	
1-14 days	0
15-35 days	5 (3.4)
36-60 days	2 (1.)
61-90 days	21 (14.1)
> 90 days	121 (81.2)

Reviewer's comment: The extent of the exposure is adequate.

A.2.4.2 Adverse Events

A.2.4.2.1 Summary of AEs: The percentage of patients with at least one AE was 46.3% (69 patients). Five patients (3.4%) experienced an SAE and five patients (3.4%) experienced an AE that caused them to discontinue the study (only one of these was classified as Serious).

A.2.4.2.2 AEs leading to discontinuation:

AEs leading to discontinuation: In 5 patients whose AEs led to discontinuation, 3 were considered to be probably or possibly related to study medication.

Table A.9 Patients with Adverse Events Leading to Discontinuation of Study Medication

Patient Number	Preferred Term	Severity	Relationship
006-004	Dermatitis contact	Moderate	Probably related
014-058	Dyspnea	Severe	Unrelated
027-004	Skin reaction	Moderate	Probably related
032-024	Contusion	Moderate	Unrelated
032-052	Gastric Hypomotility	Moderate	Possibly related

A.2.4.2.3 Common AEs

Table A.10 TEAEs Sorted by SOC and Preferred Term (Safety Population)

System Organ Class Number (%) of Patients Preferred Term	#of Patients (N=149)
Skin and Subcutaneous Tissue Disorders	29 (19.5)
Skin reaction	25 (16.8)
Rash	2 (1.3)
Infections and Infestations	21 (14.1)
Upper respiratory tract infection	10 (6.7)
Sinusitis	6 (4.0)
Cellulitis	2 (1.3)
Gastrointestinal Disorders	13 (8.7)
Diarrhea	3 (2.0)
Vomiting	3 (2.0)
Abdominal pain	2 (1.3)
Intestinal obstruction	2 (1.3)
Musculoskeletal and Connective Tissue Disorders	11 (7.4)
Arthralgia	2 (1.3)
Back pain	2 (1.3)
Muscle spasms	2 (1.3)
Metabolism and Nutrition Disorders	6 (4.0)
Hypocalcaemia	2 (1.3)
Respiratory, Thoracic and Mediastinal Disorders	6 (4.0)
Cough	3 (2.0)
Pharyngolaryngeal pain	2 (1.3)
Renal and Urinary Disorders	5 (3.4)
Hematuria	2 (1.3)
General Disorders and Administration Site Conditions	4 (2.7%)
Investigations	4 (2.7)
PSA increased	2 (1.3)
Vascular Disorders	4 (2.7)
Hypertension	4 (2.7)
Injury, Poisoning and Procedural Complications	3 (2.0)
Psychiatric Disorders	3 (2.0)
Abnormal dreams	2 (1.3)
Reproductive System and Breast Disorders	3 (2.0)
Ear and Labyrinth Disorders	2 (1.3)
Eye Disorders	2 (1.3)
Nervous System Disorders	2 (1.3)

Most common TEAEs (> 2%) in pivotal study FOR01C were skin reaction (application site reactions, ASRs, 25 patients, 16.8%, i.e., skin reaction, dermatitis contact), upper respiratory infection (6.7%), sinusitis (4%), and hypertension (2.7%). All ASRs were considered mild (13.4%) to moderate (3.4%) in severity.

A.2.4.2.4 Serious Adverse Events (SAE's): Five patients experienced serious adverse events (SAEs) and none were assessed as related to study drug.

Table A.11 Patients with Serious Adverse Events during the Study

Patient Number	SAE Preferred Term	Severity	Relationship
014-034	Rectal hemorrhage Colon cancer	Severe Severe	Unrelated Unrelated
014-058	Dyspnea	Severe	Unrelated
026-007	Intestinal obstruction	Moderate	Unrelated
027-004	Cellulitis	Moderate	Unrelated
028-007	Intestinal obstruction	Severe	Unrelated

A 2.4.2.5 Relationship between AEs and study medication: (Table A.12) Most common study medication related TEAEs were ASRs (24 patients, 16.1%) and PSA increased (2 patients, 1.3%).

A 2.4.3 Vital signs, physical examinations, weight, BMI: There were no clinically relevant differences from baseline to Visit 6 in vital signs, physical examinations, weight, or BMI.

Table A.12 TEAEs by Relationship to Study Medication, SOC, and PT

System Organ Class* Preferred Term	Unrelated	Possibly Related	Probably Related**	Possibly or Probably Related
Patients with any AE	**35 (23.5%)**	**14 (9.4%)**	**20 (13.4%)**	**34 (22.8%)**
Skin and Subcutaneous Tissue Disorders	4 (2.7%)	6 (4.0%)	19 (12.8%)	25 (16.8%)
Skin reaction	1 (0.7%)	5 (3.4%)	19 (12.8%)	24 (16.1%)
Rash	2 (1.3%)	0	0	0
Infections and Infestations	19 (12.8)	2 (1.3)	0	2 (1.3)
Upper respiratory tract infection	10 (6.7%)	0	0	0
Sinusitis	5 (3.4%)	1 (0.7%)	0	1 (0.7%)
Cellulitis	2 (1.3%)	0	0	0
Gastrointestinal Disorders	10 (6.7%)	3 (2.0%)	0	3 (2.0%)
Diarrhea	3 (2.0%)	0	0	0
Vomiting	2 (1.3%)	1 (0.7%)	0	1 (0.7%)
Abdominal pain	2 (1.3%)	0	0	0
Intestinal obstruction	2 (1.3%)	0	0	0
Musculoskeletal & Connective Tissue Disorders	8 (5.4%)	3 (2.0%)	0	3 (2.0%)
Arthralgia	2 (1.3%)	0	0	0
Back pain	2 (1.3%)	0	0	0
Muscle spasms	1 (0.7%)	1 (0.7%)	0	1 (0.7%)
Metabolism and Nutrition Disorders	4 (2.7%)	2 (1.3%)	0	2 (1.3%)
Hypocalcaemia	2 (1.3%)	0	0	0
Respiratory, Thoracic & Mediastinal Disorders	5 (3.4%)	1 (0.7%)	0	1 (0.7%)
Cough	3 (2.0%)	0	0	0
Pharyngolaryngeal pain	2 (1.3%)	0	0	0
Renal and Urinary Disorders	3 (2.0%)	2 (1.3%)	0	2 (1.3%)
Hematuria	1 (0.7%)	1 (0.7%)	0	1 (0.7%)
General Disorders and Administration Site Conditions	3 (2.0%)	1 (0.7%)	0	1 (0.7%)
Investigations	1 (0.7%)	3 (2.0%)	0	3 (2.0%)
PSA increased	0	2 (1.3%)	0	2 (1.3%)
Vascular Disorders	3 (2.0%)	1 (0.7%)	1 (0.7%)	1 (0.7%)
Hypertension	3 (2.0%)	1 (0.7%)	0	1 (0.7%)
Injury, Poisoning and Procedural Complications	3 (2.0%)	0	0	0
Psychiatric Disorders	1 (0.7%)	0	2 (1.3%)	2 (1.3%)
Abnormal dreams	0	0	2 (1.3%)	2 (1.3%)
Reproductive System and Breast Disorders	0	3 (2.0%)	0 3	3 (2.0%)
Ear and Labyrinth Disorders	2 (1.3%)	0	0	0
Eye Disorders	2 (1.3%)	0	0	0
Nervous System Disorders	1 (0.7%)	1 (0.7%)	0	1 (0.7%)

A.2.4.4 Safety of Special Interest: Changes of hematocrit (HCT), HDL-C, and PSA: The changes of HCT (ΔHCT) and HDL-cholesterol (ΔHDL-C), and PSA (ΔPSA) are the safety with special interest when comparing with the results from previous Phase 3 studies.

In 5 patients, the hematocrit went from normal at the baseline to high at Day 90; HCT went from high at the baseline to higher at Day 90 in another one patient. None of these patients discontinued from the study.

Patient I.D.	Baseline HCT (%)	Normal or High	Day 90 HCT (%)	Normal or High
003-006	42.4	Normal	53.1	High
005-001	44.3	Normal	51.0	High
012-021	47.0	Normal	51.2	High
018-008	50.0	Normal	50.1	High
027-009	47.8	Normal	51.0	High
032-004	53.5	High	55.7	High

Also, in13 patients (9.0%) their HDL-C went from normal at the baseline to low at Day 90, and two patients (1.3%) had their Day 90 PSA increased from the baseline.

This clinical review and the statistical reviewer for the current submission performed their own analysis for the changes of hematocrit (HCT), HDL, and PSA for the pivotal study FOR01C:

Table A.13 Statistics of Changes of Day 90 from Baseline for HCT, HDL, and PSA

	N	Mean	SD	Minimum	Maximum	Median	Lower 95%	Upper 95%
Δ HCT (%)	131	0.01	3.15	−8.2	10.70	−0.10	−0.53	0.56
Δ HDL (mg/dL)	137	−0.55	7.48	−20.00	38.00	−1.00	−1.82	0.71
Δ PSA (ng/mL)	135	0.24	0.62	−1.00	3.60	0.10	0.14	0.35

In addition, our review team analyzed the correlation of Day 90 serum testosterone C_{max}, C_{avg} with Day 90 changes from baseline for hematocrits, HDL, and PSA and the results are shown in Table 7.26.

Table A.14 Correlation of D90 serum T C_{max}, C_{avg} with D90 Δ HCT, Δ HDL, and Δ PSA

Correlation with serum T C_{max} or C_{avg} on Day 90		Δ Hematocrit (%)	Δ HDL (mg/dL)	Δ PSA (ng/mL)
with C_{max}	Pearson coefficients	0.00802	−0.10390	−0.14863
	p for correlation	0.9276	0.2269	0.08
with C_{avg}	Pearson coefficients	0.07025	−0.10390	−0.11334
	p for correlation	0.4258	0.2043	0.1904

Reviewer's comment: In contrast to previous results for the correlation between the supraphysiological C_{max} and the changes of hematocrits, and HDL, the results of the pivotal study FOR01C showed that the Day 90 serum testosterone C_{max} or C_{avg} were not correlated with the changes on Day 90 from the baseline for the hematocrit, HDL, and PSA.

A.2.4.5 Safety conclusion: In conclusion, this reviewer believes that results from this pivotal study did not suggest any new or unexpected safety concerns related to the use of Fortesta.

Appears This Way On Original

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21463	ORIG-1	ENDO PHARMACEUTICALS INC	FORTIGEL (TESTOSTERONE GEL) 2%

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

GUODONG FANG
10/16/2009

SURESH KAUL
10/16/2009

Cross-Discipline Team Leader Review

Date	**October 12, 2009**
From	**Suresh Kaul, MD, MPH**
Subject	**Cross-Discipline Team Leader Review**
NDA #	**21-463**
Applicant	**Endo Pharmaceuticals, Inc.,**
Date of Submission	**April 17th, 2009**
PDUFA Goal Date	**October 17th, 2009**
Proprietary Name / Established (USAN) names	**Fortesta** **Testosterone**
Dosage forms / Strength	**Fortesta (testosterone) Gel, 2% supplied in 60 mg metered dose canisters.**
Proposed Indication(s)	**Replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone.**
Recommended:	***Complete Response***

Cross Discipline Team Leader Review

1. Introduction

The objective of this complete response (CR) to non approvable action for NDA 21-463 dated July 3, 2003, is to seek marketing approval for an indication for testosterone replacement therapy in men for conditions associated with a deficiency or absence of endogenous testosterone.

Fortesta 2% Gel is a topical once daily formulation supplied in a metered-dose canister and is applied to the front and inner thighs. The proposed starting dose is 40 mg testosterone 2.0 g gel per day, with subsequent dose adjustment to between 10 mg and 70 mg testosterone per day (0.5 g and 3.5 g gel, respectively) based on total serum testosterone levels.

Fortesta 2% testosterone Gel, is an anabolic steroid and is the principal male sex hormone. Testosterone is produced primarily in the Leydig cells of the testes in males. It is also produced in smaller quantities in the thecal cells of the ovaries in women, and in the adrenal cortex in both males and females. Similar to other steroid hormones testosterone is derived from cholesterol.

The applicant has submitted (1) data from a single adequate and well controlled clinical trial (FOR01C) conducted in the US as the primary support for the safety and efficacy of Fortesta for the proposed indication and (2) supporting Phase 3 study (TSX/01/C) conducted in Europe. The sponsor also integrated data for safety from the previously submitted Phase III trials.

The Primary Medical Reviewer, Dr. Guodong Fang did not identify any issues during this review that would preclude approval of Fortesta 2% gel for the replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone.

2. Background

2.1 DESCRIPTION OF PRODUCT

Fortesta is clear and colorless gel containing 2% Testosterone USP in a hydroalcoholic/propylene glycol gel base for topical application. It is supplied in a 60-g canister with a metered-dose pump that delivers 0.5 g/actuation which translates to 10 mg of testosterone. The initial daily dose is 40 mg testosterone which translates into 4 actuations of the pump mechanism. Depending on the testosterone levels, the dose can be titrated up or down.

Currently available testosterone formulations have limitations. Injectable depot solutions are associated with pain at the injection site, trans dermal patches may result in inflammation at the site of application and pellet implants can result in rejection and infection, as well as being associated with higher medical costs and greater risks due to the placement procedure.

Fortesta provides a low-volume treatment option that is easily applied and may be adjusted to each individual's dosing requirements.

2.2 REGULATORY HISTORY

The original NDA 21-463 included three studies (Pivotal phase III trial T 00-02-01, Showering study T 00-02-03 and a Transfer study T 01-02-02). This NDA was submitted on May 31, 2002, and received a not approvable action under section 505(d) of the ACT and 21 CFR 314.125(B) on July 3, 2003, based on the following deficiencies:

1. There is insufficient information to establish that the high supra-physiologic daily Cmax serum testosterone levels achieved in a significant proportion of participants in the major clinical study supporting this application are safe under conditions of chronic administration. This deficiency is evidenced by the observation that 9% of patients had testosterone Cmax values between 1500 and 1800, 14% had values between 1800 and 2500, and 6% had values greater than 2500 ng/dL.

2. There is insufficient information provided to demonstrate that the dose of this product can be adjusted to consistently preclude achieving these high supra-physiological testosterone levels.

In order to address these deficiencies, the sponsor was asked to conduct clinical trial(s) using lower doses of Fortesta or another testosterone gel formulation and demonstrate that physiologic levels of testosterone can be attained while avoiding high supra-physiologic Cmax levels of serum testosterone.

In response to the above deficiencies, sponsor was asked to include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b) with data from all non-clinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

Additionally, the sponsor was asked to:

1. Describe in detail any significant changes or findings in the safety profile.
2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

    - Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.
    - Present tabulations of the new safety data combined with the original NDA data.
    - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
    - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature study discontinuation by incorporating the dropouts from the newly completed studies. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

6. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

7. Provide English translations of current approved foreign labeling not previously submitted.

As a C**omplete Response** to the 2003 action, the sponsor submitted the current NDA. The main basis of the current re-submission is a pivotal, controlled, open-label; Phase 3 study (FOR01C) in hypogonadal males that was conducted in the US.

149 patients in this study applied Fortesta once each morning to the thighs at a starting dose of 40 mg per day, and the dose was adjusted to between 10 mg and 70 mg per day on the basis of total serum testosterone concentration obtained at two hours after study drug application on Days 14, 35, and 60 (±3 days). The primary endpoint for the pivotal study was serum testosterone daily average level C_{avg}, that was found to be within physiological range (≥ 300 and ≤ 1140 ng/dL) on Day 90 in ≥ 75% of patients with lower bound of the 95% confidence interval at 65% and the secondary endpoint was Day 90 serum testosterone daily maximum level C_{max} < 1500 ng/dL in ≥ 85% of patients, C_{max} between ≥ 1800 and < 2500 in < 5% of patients and C_{max} > 2500 ng/dL in none. Both these end points were achieved at Day 90 in comparison to study T00-02-01 from the previous submission.

In comparison to study FOR01C, the previously submitted study T 00-02-01 had a starting dose of 60 mg that was titrated up or down from 40 to 80mg and the dosage adjustment was based on 24 hour total testosterone concentration profile obtained after 14 days of continuous treatment.

3. CMC/Device

The majority of the CMC information was reviewed during the initial NDA submission in 2002. Updated CMC information submitted in the Complete Response on April 17th, 2009, included addition of a new manufacturing site and the data to support the transfer, and updated methods and stability information.

Site Inspections

The final recommendation from the Office of Compliance involving all facilities pertaining to the cGMP inspections of drug substance and drug product manufacturing and testing operations is ACCEPTABLE.

The following recommendations were made by the Review Chemist, Dr. Donna F. Christner in her final CMC review dated October 5th, 2009:

> This NDA has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product. Labels have required information. The final recommendation from the Office of Compliance involving all facilities pertaining to the cGMP inspections of drug substance and drug product manufacturing and testing operations is ACCEPTABLE.
>
> Therefore, from the CMC standpoint, this NDA is recommended for APPROVAL.

Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps:

As proposed and committed to by the sponsor in the Complete Response submission dated April 17th, 2009, it is acceptable to establish a specification for in vitro release within 12 months following product approval.

Dr. Christner's Summary of CMC Assessment:

Drug Substance
The drug substance, testosterone USP is supplied by (b) (4) or (b) (4) and LOAs are supplied to reference the DMFs for CMC information. Both DMFs are adequate.

Drug Product
Fortesta is a clear, colorless hydroalcoholic gel containing 2% w/w testosterone USP in a hydroalcoholic/propylene glycol gel base for topical application. It is supplied in a 60-g canister with a metered-dose pump that delivers 0.5 g/actuation which translates to 10 mg of testosterone. The initial daily dose is 40 mg testosterone which translates into 4 actuations of the pump mechanism. Depending on the clinical response, the dose can be titrated up or down. Fortesta is indicated for hormone replacement for hypogonadal men.

Description of How the Drug Product is Intended to be Used
Fortesta is packaged in (b) (4) canister with a metered-dose pump. The initial dose is once daily application of 40 mg testosterone (4 pump actuations), with the option to change the dose to 10 mg or 70 mg/day depending on blood levels.

The sponsor has requested an expiration dating period of 24 months. Based on the stability data submitted to date, **24 months of expiration dating period is granted**. The recommended storage conditions are at controlled room temperature.

Basis for Approvability or Not-Approval Recommendation

This NDA provided adequate information on the raw material controls, manufacturing process, adequate specifications, and container/closure for assuring consistent product quality of the drug substance and drug product. It also provided sufficient stability data to assure identity, strength, purity and quality of the drug product during the expiration dating period. Labels have required information. The final recommendation from the Office of Compliance involving all facilities pertaining to the cGMP inspections of drug substance and drug product manufacturing and testing operations is ACCEPTABLE.

CTDL Comment:
I fully agree with Dr. Christner's assessment and final recommendation.

4. Nonclinical Pharmacology/Toxicology

The Pharmacology/Toxicology review team, Krishan Raheja and Lynnda Reid, made the following recommendations in their final reviews dated 7-10-2009.

Conclusion*: Based on Pharmacology/toxicology information submitted and reviewed under original NDA submission dated 5-31-02, there are no safety concerns from the P/T perspective.*

Unresolved Toxicology Issues*: None*

Suggested Labeling*: Labeling is in accordance with PLR and provided in SPL format.*

Recommendations*: Nonclinical data support approval of the resubmitted NDA 21-463 and no new nonclinical studies are required.*

Dr. Raheja in his review reiterates that there were no P/T issues identified during the original review cycle in the year 2002/2003, and an approval was recommended on the basis of extensive preclinical published literature available on the safety of testosterone and the clinical experience with testosterone in various formulations for the same indication as for the proposed testosterone gel. Dr. Raheja again recommends an approval for the resubmission as complete response (CR).

CTDL Comment*: I fully concur with Dr. Raheja's recommendation.*

5. Clinical Pharmacology/Biopharmaceutics

The Clinical Pharmacology Review team, Hyunjin Kim and Myong-Jin Kim, made the following recommendation in their review dated October 14, 2009:

"The Division of Clinical Pharmacology 3/Office of Clinical Pharmacology finds the clinical Pharmacology information submitted in NDA 21-463 not acceptable based on the major deficiencies identified in the DSI Report".

Clinical Pharmacology reviewer in his final review further writes that T transfer potential after the washing of primary user's application site has not been assessed in the current resubmission. Therefore, this needs to be addressed in the subsequent submission.

Dr. Kim, further reiterates that Sections 1.3 through 2.5 of his review were written before the DSI findings were available. Because the data from FOR01C were found to be unreliable based on the DSI report, the findings of his review in sections 1.3 through 2.5 should not be used to support the efficacy and safety of Fortesta at this time.

***CTDL Comment**:*

1). Based on the major deficiencies identified by the DSI in their report of October 8th, 2009, it was determined that the data generated from the trial FOR01C were not reliable to determine efficacy and safety of Fortesta for approval. Therefore, NDA 21-463 cannot be approved at this time. The recommended action at this time is a Complete Response.
2). Conducting a pharmacokinetic "wash off" study to evaluate the amount of testosterone remaining on the skin from application of Fortesta after washing will be a deficiency listed in the Complete Response letter.

The Clinical Pharmacology review team reviewed the efficacy results and dose adjustment scheme for Phase III trial (FOR01C) submitted with complete response. The Clinical Pharmacology team also reviewed the Transfer and Showering studies that were submitted in 2002 with the original submission.

The principle Clinical Pharmacology concern during the review involved comparison of dose and dose adjustment between study T 00-0201 (submitted under the original NDA 21- 463 in 2002) and study FOR01C of current resubmission. This was to achieve both primary and secondary end points as specified by the Division. As per the Clinical Pharmacology Reviewer, a starting dose of 40 mg applied topically once daily to the thighs and adjusted between 10-70 mg/day at Days 14, 35 and 60 (+/_3days) achieved both primary and secondary endpoints (i.e. Cavg and Cmax) as agreed upon previously by the Division. There were no patients with Cmax above 2500 ng/dL as was seen during the original submission. In addition, 24-hour pharmacokinetic (PK) profiles for these parameters were obtained on Days 35 and 90 (± 3 days). Sex hormone-binding globulin (SHBG), luteinizing hormone (LH), follicle stimulating hormone (FSH), and estradiol (E2) concentrations were obtained at two hours after study drug application on Days 35 and 90 (± 3 days). Safety was monitored throughout the study.

Efficacy Results:

Figure 1: **Mean (SD) Concentration-Time Profile of Total Testosterone**

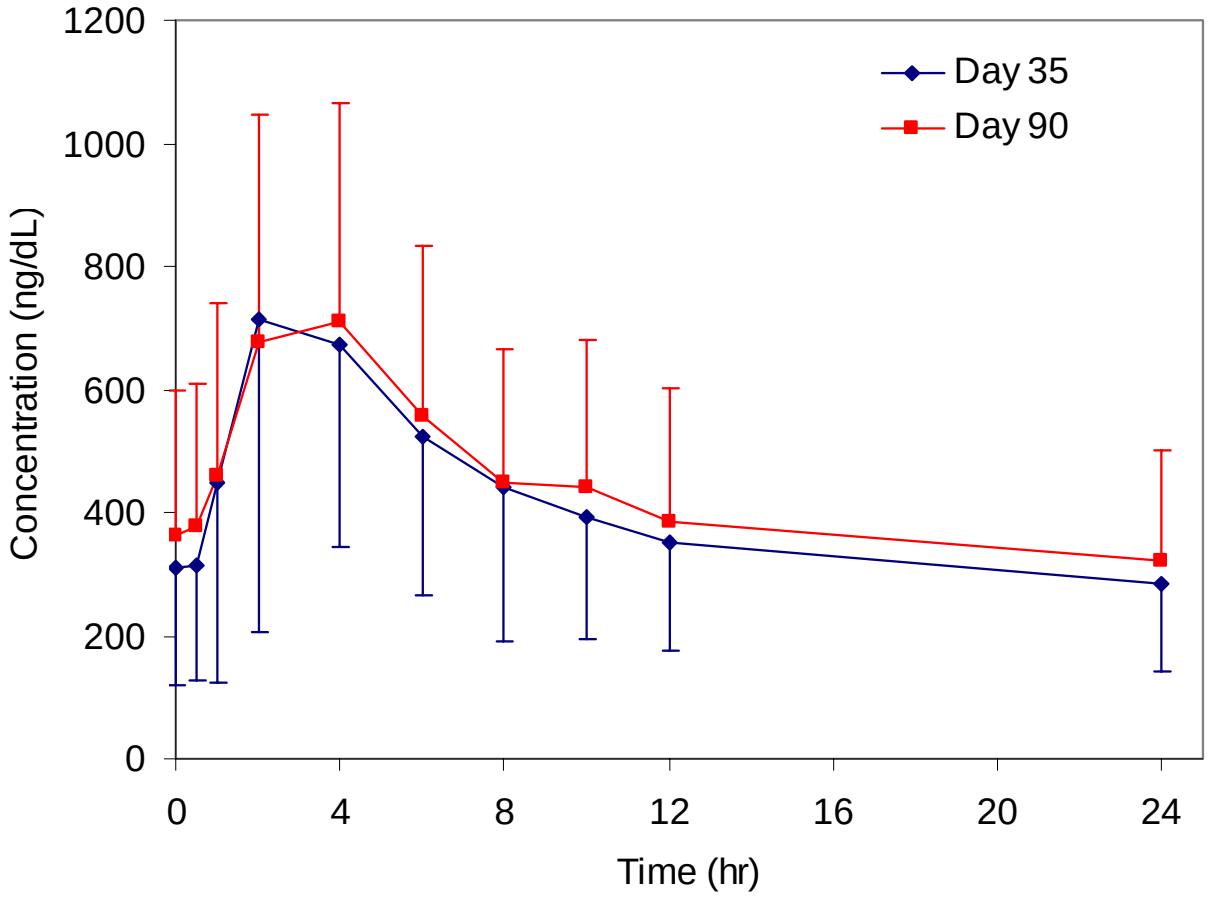


Table 1: **Results (MITT Population)**

Primary Endpoint (Cavg of total T at Day 90)		***Endpoints for approval***
Mean (SD)	442.4 (177.7) ng/dL	-
% Patients with Values ≥300 and ≤1140 ng/dL, n/n	76.1%, 105/138	***≥75%***
95% CI for % Patients with Values ≥300 and ≤1140 ng/dL	69.0 - 83.2%	***Lower bound 65%***
% Patients with Values <300 ng/dL, n/n	23.9%, 33/138	-

% Patients with Values >1140 ng/dL, n/n	0%, 0/138	-
Secondary Endpoints (Cmax of total T at Day 90)		-
Mean (SD)	863.9 (408.0) ng/dL	-
% Patients with Values ≤1500 ng/dL, n/n	91.3%, 126/138	***≥85%***
% Patients with Values ≥1800 and <2500 ng/dL, n/n	4.3%, 6/138	***≤5%***
% Patients with Values ≥2500 ng/dL, n/n	0%, 0/138	***0%***

Dr. Kim concluded that in the mITT population, the mean (SD) Cavg-24hr was 442.41 (177.73) ng/dL and 76.1% of patients had T levels within the predetermined range (300-1140 ng/dL) at Day 90. The lower bound of the 95% CI was 69.0% in the mITT population was above the predefined limit of 65%. For secondary endpoint, 91.3% of patients had Cmax values <1500 ng/dL, 4.3% had Cmax values within 1800 to 2500 ng/dL range and there were no patients who had Cmax values above 2500 ng/dL. All these values met the predetermined secondary endpoints.

CTDL Comment*:*

I fully concur with Dr. Kim's assessment of efficacy endpoints.

Dose adjustment:

According to the Clinical Pharmacology Reviewer, Dr. Hyunjin Kim, the dose adjustment for study FOR01C was properly instituted to achieve both primary and secondary endpoints.

% Patients with Cavg ≥300 and ≤1140 ng/dL

- Day 35: 73.2% vs. Day 90: 76.1%

From Day 35 to Day 90

- More patients of Cavg were out of range to within range vs. Cavg within range to out of range: 23 vs. 19

Cmax > 2500 ng/dL

- Day 35: 1.4% (2 pts) vs. Day 90: 0%

During the review cycle for this complete response, the Clinical Pharmacology Reviewer was concerned about slightly higher number of protocol violations/discontinuation (11) in study FOR01C. However, after further discussion with the clinical review team the Clinical Pharmacology reviewer was convinced that the actual protocol violations were only two and

the patients who discontinued secondary to an adverse events (5) were determined not related to the study drug.

Patients entering the trial: 149 (23 patients were ≥65 years old)
Patients completing the trial: 138
Patients discontinuing the trial: 11
Primary reason for discontinuation
Adverse event: 5 (3.4%)
Protocol violation: 2 (1.3%)
Patient non-compliance: 1 (0.7%)
Patient choice: 2 (1.3%)
Lost to follow-up: 0
Other: 1 (0.7%)

***CTDL Comment**:*

Protocol violation/discontinuation no longer remains a concern in study FOR01C.

In his recommendation for a washing study, the Clinical Pharmacology reviewer reiterates that, although there is no transfer of Fortesta from male to female subjects when clothed, a wash off study should be conducted to demonstrate any residual Fortesta after washing the application site with soap and water that otherwise would have a potential to transfer to another person.

***CDTL Comment**:*

This recommendation was conveyed to the sponsor and an agreement to conduct a wash off study was obtained. In view of the deficiencies identified by the Division of Scientific investigations (DSI),that resulted in a change in the regulatory action, this recommendation now will be reflected as a deficiency in the Complete Response action letter.

6. Clinical Microbiology

The microbiology review was done during the original submission and with the current response. The microbiology reviewer recommends approval of the application from a microbiology perspective.

No phase 4 microbiology commitments are requested.

7. Clinical/Statistical- Efficacy

7.1 Clinical Program for Efficacy

The primary source of efficacy data for Fortesta to support the applicant's proposed indication for replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone was a single adequate and well controlled clinical trial (study FOR01C). The applicant has proposed a starting dose of 40 mg once daily applied topically to the thighs with a dose adjustment scheme ranging from 10 mg to a maximum of 70 mg/day depending upon the serum testosterone level.

7.2 Design and Primary Objective of Study FOR01C

Study FOR01C was a multicenter, open label, non-comparative trial in 149 hypogonadal males conducted in the United States. All patients enrolled in the study applied Fortesta once each morning to the thighs, at a starting dose of 40 mg per day. The dose of study drug was adjusted to between a minimum of 10 mg per day to a maximum of 70 mg per day on the basis of total serum testosterone concentrations obtained at two hours after study drug application on Days 14, 35, and 60 (± 3 days). A shower or bath could only be taken either before the daily application or after two hours following the application of Fortesta. The application site was covered with clothing once the gel had dried. Serum testosterone concentrations [including total testosterone, free testosterone, and dihydrotestosterone (DHT)] were obtained at two hours after study drug application on Days 14, 35, 60, and 90 (± 3 days). In addition, 24-hour pharmacokinetic (PK) profiles for these parameters were obtained on Days 35 and 90 (± 3 days). Sex hormone-binding globulin (SHBG), luteinizing hormone (LH), follicle stimulating hormone (FSH), and estradiol (E2) concentrations were obtained at two hours after study drug application on Days 35 and 90 (± 3 days). Safety was monitored throughout the study.

Entry Criteria
Patients eligible for this study were hypogonadal men, aged 18-75 years, defined as males having a single morning serum testosterone concentration < 250 ng/dL or < 300 ng/dL on two consecutive occasions at least one week apart. In addition, patients eligible for this study were required to have a body mass index (BMI) ≥ 22 kg/m^2 and < 35 kg/m^2.

Dose adjustment was done on Days 14, 35 and 60 C2h (ie, to capture Cmax at 2 hours). Although, C2h and C4h would represent Cmax of 77% of patients, the Division had agreed to use a single time point of C2h for dose titration for the benefit of being feasible in the clinical settings such as to minimize patient's waiting time in the clinic.

Table 2: Dose Adjustment Criteria for Study FOR01C

Total serum Testosterone Concentration (C2)	Dose Titration
C2 ≥ 2500 ng/dL	Decrease daily dose by 20 mg T (1 g gel)
1250 ≤ C2 < 2500 ng/dL	Decrease daily dose by 10 mg T (0.5 g gel)
500 ≤ C2 < 1250 ng/dL	No change continue on current dose
C2 < 500 ng/dL	Increase daily dose by 10 mg T (0.5 g gel)
If a patient had a C2 total serum T value > 2500 ng/dL at 2 successive visits, then the patient was withdrawn from the study.	

KEY: T = testosterone

CTDL Comment:

With a lower starting dose of 40 mg once daily (compared to 60 mg once daily in the study from the original submission), and the dose adjustment between 10 mg and 70mg /day depending upon serum testosterone level, sponsor has achieved both primary and secondary endpoints at Day 90 as previously agreed upon.

7.3 Efficacy Assessments and Endpoints (study FOR01C)

- **Primary Endpoint**
  - Cavg of total T at Day 90 ± 3 days are ≥300 and ≤1140 ng/dL in ≥ 75% of patients (lower bound of 95% CI ≥ 65%)

- **Secondary Endpoints**
  - Cmax of total T at Day 90 ± 3 days are:
    - ≤1500 ng/dL in ≥85% of patients
    - ≥1800 and <2500 ng/dL in ≤5% of patients
    - ≥2500 ng/dL in no patients

The population analyzed:

- ITT population (n=149): patients who had an assessment of at least one total T measurement subsequent to the first application of Fortesta.

- mITT population (n=138): patients in the ITT population who had more than one PK sample obtained during the 24-hour PK profile at Day 90.

CTDL Comment:
The data from the mITT population was used as the primary data to address primary and secondary endpoints since mITT population included all patients enrolled in the trial except 11 patients who discontinued from the trial.
There were 5 patients with BMI >35 who were excluded from mITT analysis. The subject with highest BMI excluded was 41.5 kg/m^2

Dr. Fang in his review wrote, that study FOR01C was not designed to specifically detect disparities among these subgroups as this was not factored during subject enrollment. Also, there were only 5 subjects in the BMI > 35 kg/m^2 subgroup, all of whom were protocol violators because the BMI inclusion criterion was < 35 kg/m^2.

***CTDL Comment*:**
I concur with the Primary clinical Reviewer, Dr. Fang's assessment.

Table 3: Primary efficacy endpoint

Efficacy	Target	Results
Primary endpoint C_{avg}		
on Day 90 (ng/dL)		442.41±177.73 (Mean±SD)
% patients $300 \leq C_{avg} \leq 1140$	≥ 75	76.1
95% CI limit	lower bound at 65%	(69.0, 83.2)
95% CI limit	lower bound at 65%	(69.0, 83.2)

CTDL Comment:

In the mITT population, the mean $C_{avg0-24hr}$ was 442.41 ± 177.73 ng/dL and 76.1 % of patients had testosterone levels within the physiologic range (≥ 300 and ≤ 1140 ng/dL) on Day 90. The lower bound of the 95% CI, 69.0% in the mITT population was above the pre-defined limit of ≥ 65%.

Table 4:

Secondary Efficacy Endpoint for Pivotal Study FOR01C

Secondary endpoint C_{max}		
	Target	**Results**
on Day 90 (ng/dL)		863.92±408.01 (Mean±SD)
% patients C_{max} ≤ 1500	≥ 85	93.1
% patients 1800 ≤ C_{max} ≤ 2500	< 5	4.3
C_{max} > 2500	none	0

All with mITT population (N=138) for efficacy analyses

***CTDL Comment*:**
After three dose adjustments, the mean C_{max} on Day 90 was 863.92 ± 408.01 ng/dL. Overall, 93.1% of patients had C_{max} values ≤1500 ng/dL, 4.3% had C_{max} values within 1800 to 2500 ng/dL range, and there were no patients who had C_{max} values above 2500 ng/dL. These values met the pre-determined secondary efficacy endpoint objectives on Day 90; (ie. ≤1500 ng/dL in ≥85% of patients, ≥1800 – ≤2500 ng/dL in ≤5% of patients and > 2500 ng/dL in 0 patients).

The Primary Medical Officer, Dr. Guodong Fang, states in his review that there were 9% of patients whose Cmax was within 1500-1800, 14% of patients had their Cmax between 1800 - 2500 and 6% of patients had a Cmax of > 2500 in the original submission phase III trial T 00-02-01.

Therefore, it is the impression of this CTDL, that with a lower starting dose of 40 mg/day (compared to 60 mg/day in the original submission) and the current dose adjustment/titration both primary and secondary endpoints in study FOR01C have been successfully achieved.

Additional Endpoints

Results for other laboratory parameters that were considered to be of interest in the mITT population, including SHBG, LH, FSH, E2, free testosterone, total testosterone and ratio of DHT to total testosterone, are summarized in Table 5.

Table 5: Other Endpoints of Interest – Change from Baseline in Study FOR01C (mITT Population)

	Baseline Mean (SD)	Mean change from baseline (SD) Visit 3 (Day 14)	Visit 4 (Day 35)	Visit 5 (Day 60)	Visit 6 (Day 90)
SHBG (nmol/L)	37.1 (20.3)	–	0.6 (12.4)	–	–1.0 (11.0)
LH (mIU/mL)	5.50 (7.33)	–	–3.55 (6.31)	–	–4.41 (7.38)
FSH (mIU/mL)	10.51 (15.94)	–	–5.34 (8.68)	–	–6.52 (12.45)
E2 (ng/dL)	1.69 (0.79)	–	1.09 (1.3) -	–	1.2 (1.5)
Mean (SD)					
Free testosterone (pg/dL)	33.1 (16.0)	87.2 (113.8)	136.1 (178.6)	146.8 (163.0)	127.9 (116.1)
Total testosterone (ng/dL)	190.2 (64.4)	375.9 (429.6)	527.0 (519.0)	554.8 (536.2)	485.2 (377.6)
Ratio DHT/Total testosterone	0.13 (0.07)	0.02 (0.10)	0.04 (0.08)	0.01 (0.12)	0.04 (0.09)

Source: Module 5.3.5.1 FOR01C: Main Report.

The SHBG level remained about the same, with a slight reduction at Day 90. This decline is suggestive of an androgen effect, since testosterone will decrease SHBG production from the liver. Both serum gonadotropins were lower at Day 35 and 90, but again were consistent with increased circulating testosterone which suppresses LH and FSH secretion from the pituitary gland. This is observed in both primary and centrally-mediated causes of male hypogonadism. Estradiol concentrations increased over time, consistent with aromatization of the exogenous testosterone to its metabolite estradiol.

Total and free testosterone levels increased over time as expected. Finally, the ratio of DHT/Total testosterone declined from baseline indicating that the testosterone levels were rising without an excessive amount of metabolism to DHT via skin 5α-reductase.

Analyses of SHBG, LH, FSH, E2, free testosterone, total testosterone and ratio of DHT to total testosterone were also performed for the ITT population, and the results showed similar trends as in the mITT population on Day 90.

Dr. Fang, the Primary Clinical Reviewer for this application detected 6 patients with Cmax >1800 ng/dL on Day 90. These six patients were labeled as outliers and further analyzed as a subgroup by Dr. Fang.

Table 6: Dose adjustments for 6 patients with outlier C_{max} at Day 90

Patient ID	Baseline		Day 14		Day 35				Day 60		Day 90			
	Dose	C_{avg}	Dose	C_2	Dose	C_{avg}	C_{max}	T_{max}	Dose	C_2	Dose	C_{avg}	C_{max}	T_{max}
005-001	40	272	40	246	50	415	757	360	60	245	70	774	1800	240
032-042	40	370	40	241	50	592	1410	240	50	384	60	1132	1930	360
016-006	40	479	40	873	40	512	1360	240	40	994	40	759	1944	240
016-003	40	176	40	1170	40	491	1160	240	50	1790	40	607	2010	60
018-002	40	313	40	334	50	476	1260	240	50	980	50	702	2100	240
018-001	40	174	40	364	50	426	1740	120	40	1360	30	477	2460	120

Source: Division's Clinical Analysis.

The Primary Medical Reviewer, Dr. Fang writes that the above six patients in study FOR01C had C_{max} above 1800. (ie. 1800-2460 ng/dL*). The data for these six patients was further analyzed by this clinical reviewer for higher C_{max} but within the accepted cut off point of 2500* ng/dL *and also matched for any association with an increase in hematocrit (HCT) and PSA and a decrease in HDL cholesterol. There were two patients with a decrease in HDL from baseline (−7 and −11). Another two patients showed an increase in HCT from baseline (+6.7% and +1.5%). None of the patients showed any significant increase in PSA.*

CTDL Comment:
I concur with Dr. Fang's subgroup analysis and assessment and a review of these subjects in more detail and comparison with the study population as a whole leads to the conclusion that these patients form a part of the natural distribution of C_{max} values following testosterone replacement in hypogonadal males. There are no study data suggesting that these 6 patients have different demographic or treatment related parameters. Additionally, none of these six patients showed any statistically significant change that would have otherwise lead to a safety concern and these slight changes in HDL, HCT and PSA did not correlate with the Patient Cavg or Cmax.

7.4 Disposition of Subjects (FOR01C)

Patients entering the trial: 149 (23 patients were ≥65 years old)
Patients completing the trial: 138
Patients discontinuing the trial: 11
Primary reason for discontinuation
Adverse event: 5 (3.4%)
Protocol violation: 2 (1.3%)
Patient non-compliance: 1 (0.7%)
Patient choice: 2 (1.3%)
Lost to follow-up: 0
Other: 1 (0.7%)

CTDL Comment:
The percentage of patients who withdrew from the study is relatively low.

7.5 Statistical Review:

The Statistical Reviewer, Kate Dwyer and Mahboob Sobhan reviewed the study FOR01C and provided the following conclusion:

"Results from Phase 3 study FOR01C support the efficacy of Fortesta for testosterone replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone. The study confirmed that with the right starting dose of Fortesta, sampling time points and the titration schedule, testosterone levels were achieved within the physiologic range. Fortesta also minimized supra-physiologic concentrations of testosterone levels".

Statistical Results:
Of the total 149 treated patients, 138 patients were evaluable for PK assessment. As shown in Table 7, 76.1 % of the patients had their testosterone levels within the normal range and the lower bound of the 95% CI was 69.0% on Day 90, which achieved the threshold. Using Cmax assessment on Day 90, the results also met the pre-defined criteria. As shown in Table 8, more than 91.3% patients had Cmax less than 1500 ng/dL, fewer than 5% of patients exceed 1800 ng/DL and none exceeded to 2500 ng/DL. Therefore, these data are acceptable.

Table 7: Summary Statistics of C_{avg} on Day 90 ± 3

	N (%)	95% CI
Cavg (300, 1000) ng/dL	105 (76.1)	(69.0, 83.2)
C_{avg} Outside (300, 1000) ng/dL	33 (23.9)	---

Table 8: Summary Statistics of C_{max} on Day 90 ± 3

Cmax	N (%)
% Patients with Values ≤ 1500 ng/dL	126 (91.3)
% Patients with Values 1800 – 2500 ng/dL	6 (4.3)
% Patients with Values > 2500 ng/dL	0 (0)

CTDL Comment:
I concur with the results derived from the analyses conducted by the reviewer's from the Division of Biometrics III.

7.5 Overall Assessment of Efficacy

It is the overall impression of the Primary Medical Officer, Dr. Guodong Fang, that Fortesta, at a lower starting dose of 40 mg applied topically to the thighs once daily, is effective in achieving pharmacokinetic profile of mean serum testosterone (T) level (C_{avg}) within the physiologic range in men with hypogonadism. Supra-physiologic concentrations of T are avoided by using the 40 mg (2.0 g gel) starting dose and adjusting the subsequent dose in 10 mg increments, to a final dose ranging from 10 mg to 70 mg daily (0.5 g to 3.5 g gel), with three appropriate dose adjustments based on total serum testosterone levels.

8. Safety

The primary Medical Reviewer for this application, Dr. Guodong Fang, has thoroughly reviewed the safety data for study FOR01C, the pivotal study for CR and the integrated safety data from Phase I/II and supporting Phase III studies from the original submission.
In his review of this application, Dr. Fang has paid particular attention not only to common adverse events associated with the use of Fortesta but, he spent a considerable amount of time to review three important safety signals as pointed out during the review of the original application in the year 2002/2003. These include an increase in Hct, an increase in PSA, and a decrease in HDL level.

8.1 Safety Populations and Overall Exposure

The primary sources of clinical trial safety data included in this application were study FOR01C and all the integrated safety data from previously submitted Phase I/II and III studies as shown in the Table 9.

Table 9: Fortesta Safety Population

Study Description	Phase	Protocol #
Dose ranging study	I/II	T 98-02-01
Transfer of testosterone	I/II	T 01-02-02
Effect of showering	II	T 00-02-03
Application site area	II	T 00-02-07
Application site selection	II	T 00-02-08
Pivotal study	III	FOR01C
6-month study	III	T 00-02-01
Extension to 6-month study	III	T 00-02E-01
Rotation study	III	T 02-02-01
Extension to rotation study	III	T 02-02E-01

For an overview of study FOR01C, see section 7.2.
Dr. Fang's safety review primarily focused on Phase III pivotal study FOR01C and a supporting European study TSX/01/C along with a general overview of safety from other phase III studies.

Table 10: Duration of Exposure to Study Drug (IFOR01C)

Duration of Exposure[a]	Patients (N=149)
Duration of Exposure (days)	
n	149
Mean (SD)	93.0 (18.7)
Median	93.0
Range	15 – 177[b]
Numbers of patients by days exposed to drug, N (%)	
1-14 days	0
15-35 days	5 (3.4)
36-60 days	2 (1.)
61-90 days	21 (14.1)
> 90 days	121 (81.2)

Source: Module 5.3.5.1 FOR01C: Main Report.

CTDL Comment:
The overall exposure of Fortesta in study FOR01C in conjunction with the much larger safety exposure to Fortesta from Phase I/II and III studies, is adequate to assess the likely safety of Fortesta used for the treatment in hypogonadal men.

8.2 Demographics

Table 11: Study FOR01C – Demographic Characteristics

Demographic Variable	Patient (N=149)	Demographic Variable	Patient (N=149)
Age (years)		Weight (kg)	
Mean (SD)	54.5 (10.1)	Mean (SD)	97.65 (14.73)
Median	55.0	Median	97.10
Range	29-77	Range	65.3 – 147.6
Ethnicity (n[%])		Height (cm)	
Hispanic or Latino	11 (7.4)	Mean (SD)	178.08 (6.53)
Not Hispanic or Latino	138 (92.6)	Median	177.80
		Range	162.6 – 198.1
Race, (n[%])		Body Mass Index (kg/m^2)	
White	131 (87.9)	Mean (SD)	30.61 (3.50)
Black or African American	15 (10.1)	Median	30.80
American Indian	0	Range	22.1 – 41.5
Asian	0		
Native Hawaiian or Other Pacific Islander	0		
Other	3 (2.0)		

Source: Module 5.3.5.1 FOR01C; Main Report

Dr. Fang in his review of the application writes that there is a fair representation of age, ethnicity and race in study FOR01C.

CDTL Comment*:*
I concur with the primary reviewer's assessment.

8.3 Discontinuation due to Adverse Events

There were five subjects in study FORO1C, who resulted in discontinuation from an adverse event. One of the five patients presented with moderate contact dermatitis and the second patient presented with moderate skin reaction. The two patients with contact dermatitis and skin reaction were considered to be probably related to study medication by the study investigator. The third patient who had gastrointestinal hypo motility was considered as possibly related to study medication, and the remaining two patients (one with dyspnea and the other with contusion) that discontinued from the study were considered unrelated to the study medication.

***CTDL Comment**:*
I agree with the Primary Medical Reviewer's assessment, in which he states that most of the adverse events that lead to study discontinuation were as a result of application site reaction, since Fortesta is topically applied to the skin of thighs.

Table 12: Patients with Adverse Events Leading to Discontinuation of Study Medication

Patient Number	Preferred Term	Severity	Relationship
006-004	Dermatitis contact	Moderate	Probably related
014-058	Dyspnea	Severe	Unrelated
027-004	Skin reaction	Moderate	Probably related
032-024	Contusion	Moderate	Unrelated
032-052	Gastric Hypomotility	Moderate	Possibly related

Source: Module 5.3.5.1 FOR01C: Main Report.

8.4 Deaths

No deaths were reported in Fortesta-treated subjects during any of the Phase I/II or Phase III clinical studies including study FOR01C. However, one death due to myocardial infarction was reported in Study TSX/01/C (a supporting study from Europe). This event occurred in a placebo-treated subject, who had other pre-existing co-morbid medical conditions.

CTDL Comment:
Dr. Fang, during his review of this application, carefully reviewed the case narrative for the patient who was treated with placebo and died, agrees with the investigator's conclusion that there were pre-existing co-morbid medical conditions that could have contributed to the subjects death.
I concur with Dr. Fang.

8.5 Common Adverse Events

Table 13: Overview of Adverse Events: Safety Population (study FOR01C)

Category	Number (%) of Patients Experiencing Event N=149	
Any Adverse Events	69	(46.3)
Serious Adverse Events	5	(3.4)
Severe Adverse Events	3	(2.0)
Adverse Events Causing Discontinuation	5	(3.4)
Deaths	0	(0.0)

Source: Module 5.3.513: FOR01C: Main Report.

Table 14: Treatment Emergent AEs Sorted by System Organ Class and Preferred Term (Safety Population) (Study FOR01C)

System Organ Class Number (%) of Patients Preferred Term	Number of Patients N=149
Skin and Subcutaneous Tissue Disorders	29 (19.5)
Skin reaction	25 (16.8)
Rash	2 (1.3)
Infections and Infestations	21 (14.1)
Upper respiratory tract infection	10 (6.7)
Sinusitis	6 (4.0)
Cellulitis	2 (1.3)
Gastrointestinal Disorders	13 (8.7)
Diarrhea	3 (2.0)
Vomiting	3 (2.0)
Abdominal pain	2 (1.3)
Intestinal obstruction	2 (1.3)
Musculoskeletal and Connective Tissue Disorders	11 (7.4)
Arthralgia	2 (1.3)
Back pain	2 (1.3)
Muscle spasms	2 (1.3)
Metabolism and Nutrition Disorders	6 (4.0)
Hypocalcaemia	2 (1.3)
Respiratory, Thoracic and Mediastinal Disorders	6 (4.0)
Cough	3 (2.0)
Pharyngolaryngeal pain	2 (1.3)
Renal and Urinary Disorders	5 (3.4)
Hematuria	2 (1.3)
General Disorders and Administration Site Conditions	4 (2.7%)
Investigations	4 (2.7)
PSA increased	2 (1.3)
Vascular Disorders	4 (2.7)
Hypertension	4 (2.7)
Injury, Poisoning and Procedural Complications	3 (2.0)
Psychiatric Disorders	3 (2.0)
Abnormal dreams	2 (1.3)
Reproductive System and Breast Disorders	3 (2.0)
Ear and Labyrinth Disorders	2 (1.3)
Eye Disorders	2 (1.3)
Nervous System Disorders	2 (1.3)

Source: Module 5.3.5.1: FOR01C: Main Report.

Most common TEAEs (> 2%) in pivotal study FOR01C were application site reaction (16.8%), upper respiratory infection (6.7%), sinusitis (4%), and hypertension (2.7%).

Dr. Fang, Primary Clinical Reviewer writes:
All the TEAE's seen in study FOR01C were mild and did not require any further medical intervention.

CTDL Comment:
The relationship of testosterone treatment and TEAE's in Study FOR01C was reviewed alone as shown in Table14. Application site reactions (24/149, 16.8%) are still the most common treatment-related TEAE's. A change in hematocrit was seen in five patients (an increase from

baseline to Day 90), and increase in PSA was seen in 2 (2/149, 1.3%). In Study FOR01C, the incidence of ASRs that were considered to be related to Fortesta were lower than in Study T 00-03-01 (24 subjects, 16.1% vs. 112 subjects, 55.7%). Study T00-03-01 was the pivotal study submitted with the original submission in year 2002.

8.6 Safety Issues of Particular Interest

The specific safety concerns during the original review cycle (2002/2003) that lead to not approval action included a decrease in HDL and an increase in the hematocrit and PSA that was statistically significantly correlated with elevated serum C_{max} T levels. The increasing hematocrit was thought to be associated with an increase in blood viscosity that in turn would exacerbate vascular disease, sleep apnea and chronic obstructive pulmonary disease. The decrease in HDL is clearly associated with an increasing risk of cardiovascular disease. Increasing PSA is associated with an increasing risk of prostate cancer.

A comprehensive review was conducted to examine the relationship between the changes in hematocrit, HDL as well as PSA with serum pharmacokinetics of Fortesta.

Table 15: Correlation of D90 serum testosterone C_{max}, C_{avg} with Day 90 changes from baseline for hematocrits (HCT), HDL, and PSA

Correlation with serum T C_{max} or C_{avg} on Day 90		Δ Hematocrit (%)	Δ HDL (mg/dL)	Δ PSA (ng/mL)
with C_{max}	**Pearson coefficients**	0.00802	–0.10390	–0.14863
	p for correlation	0.9276	0.2269	0.08
with C_{avg}	**Pearson coefficients**	0.07025	–0.10390	–0.11334
	p for correlation	0.4258	0.2043	0.1904

Source: Division's Clinical Analysis.

Changes in hematology on Day 90 from the baseline in pivotal study FOR01C are listed in Table 16

Table 16: Study FOR01C: Shifts from Baseline to Visit 6 (Day 90)

Parameter	n[a]	Visit 6 Value	Baseline Value		
			Number (%) of Patients		
			Low	Normal	High
Hemoglobin (g/L)	138	**Low**	2 (1.4)	5 (3.6)	0
		Normal	1 (0.7)	122 (88.4)	2 (1.4)
		High	0	5 (3.6)	1 (0.7)
Hematocrit (L/L)	138	**Low**	1 (0.7)	3 (2.2)	0
		Normal	1 (0.7)	125 (90.6)	2 (1.4)
		High	0	5 (3.6)	1 (0.7)

Source: Module 5.3.5.1: FOR01C: Main Report

CTDL Comment:
Although five subjects (3.6%) had hematocrit changes from normal baseline to high at Day 90, none of these five patients had any clinically significant symptoms that rose to the level of being diagnosed as Polycythemia. Additionally, these cases did not correlate with the Cmax as was seen during the first review cycle in 2002/2003. Therefore, there is no safety concern at this time.

Changes of HDL

Table 17: Study FOR01C: Cholesterol Value Shifts from Baseline to Visit 6 (Day 90)

HDL Cholesterol (mmol/L)	145	Low Normal High	52 (35.9) 9 (6.2) 1 (0.7)	13 (9.0) 48(33.1) 4 (2.8)	0 3 (2.1) 15 (10.3)

CTDL Comment:
Although, there are 13 subjects who were found to have slightly lower HDL cholesterol after the drug therapy, the decrease in the HDL level was not clinically significant and did not correlate with the C_{max} as was seen during the original submission in the year 2002. Therefore, in my opinion there is no safety concern at this time for a slight decrease in HDL cholesterol that is seen to be associated with the use of Fortesta.

Changes in PSA

Table 18: Changes of Day 90 from Baseline for HCT, HDL, and PSA

	N	Mean	Lower 95%	Upper 95%
Δ HCT (%)	131	0.01	–0.53	0.56
Δ HDL (mg/dL)	137	–0.55	–1.82	0.71
Δ PSA (ng/mL)	135	0.24	0.14	0.35

CTDL Comment:
There were 2 patients (2/149, 1.3%) in study FOR01C that showed a non-significant increase in PSA. Therefore, there is no safety concern as regards the PSA increase.

Dr. Fang in his review writes: in the opinion of this clinical reviewer, the change in HCT, HDL and PSA did not correlate with Day 90 C_{avg} or Cmax in patients treated with Fortesta during their 90-day therapy in pivotal study FOR01C, since for correlation the p-value should be less than 0.05.

CTDL Comment:
I concur with the Primary Clinical Reviewer's assessment.

Changes in HCT, HDL and PSA in a group of patients with special interest

During the review of pivotal study FOR01C, there were six patients with Day 90 serum testosterone $C_{max} \geq 1800$ ng/dL. The changes in HCT, HDL, and PSA on Day 90 from baseline are reviewed and the results are shown in the Table.

Table 19: Safety PD of Patients with Day 90 Cmax ≥ 1800 ng/dL (Study FOR01C)

Patient I.D.	Dose	C_{avg}	C_{max}	Δ HDL (mg/dL)	Δ Hematocrit (%)	Δ PSA (ng/mL)
005-001	70	774	1800	0	6.7	0.1
032-042	60	1132	1930	–2	1.5	–0.2
016-006	40	759	1944	–7	–3.8	–0.1
016-003	40	607	2010	–11	-3	–0.2
018-002	50	702	2100	2	–2.2	0
018-001	30	477	2460	–3	0.1	–0.1

Source: Division's Clinical Analysis.

The results showed that a significant increase of hematocrits (> 5 %) in 1 patient (#005-001), a decrease of > –5 mg/dL for HDL that was seen in 2 patients (#016-006 and #016-003), and no significant increase in PSA was seen.

The Primary Clinical reviewer wrote the following:

- *There were 5 patients that had HCT values shifted from low to high or normal to high over the course of the study, but no patients were withdrawn because of raised HCT.*
- *Overall 35% of patients started with a low HDL value and had no change, and 9% of patients started with a normal HDL and had a low HDL at Day 90. Additionally, the results of the 6 patients of interest did not appear any different from the overall population.*
- *In these 6 patients of interest, no patient had a significant rise in PSA and no value was above the ULN (4 ng/mL).*

***CTDL Comment**:*
It is safe to conclude that the safety profile, including changes in Hct, HDL, and PSA for these 6 patients with serum testosterone $C_{max} \geq 1800$ ng/dL is comparable to the study population without special safety concern.

Additional safety Evaluations

Testosterone Transfer from Patients to Partners

An open-label, vehicle-controlled, pharmacokinetic study in healthy couples evaluated whether transference of FORTESTA 2% Gel from a male to a female would significantly raise serum testosterone level in the females, and if transference occurred, whether covering the application site with clothing would prevent it. Two hours after FORTESTA 2% Gel application to males, the female partner engaged in vigorous skin-to-skin contact with the application site for 15 consecutive minutes. Mean C_{avg} and C_{max} values for total testosterone were significantly higher (approximately two-fold) in female subjects who rubbed an

uncovered application site of males compared to an application site covered with clothing. Despite this increase, the mean value remained within the physiologic range for females of reproductive age. Concentrations of total testosterone provide evidence that transference and absorption is prevented by covering the application site with clothing. This demonstrates that covering the application site effectively prevented transference and absorption of testosterone by the female partner.

Effect of Showering on Testosterone Pharmacokinetics

In an open-label, non-vehicle-controlled, randomized, two-treatment, two-period crossover study, the effects of showering on the pharmacokinetics of total testosterone following topical application of FORTESTA 2% Gel in hypogonadal males was assessed. Based on the analysis of C_{avg}, C_{min} and C_{max}, it was concluded that showering 2 hours after application of FORTESTA had no meaningful effect on the pharmacokinetics of topically applied testosterone.

***CTDL Comment*:**
The transfer study has clearly demonstrated that covering the application site with clothing effectively prevents transference and absorption of testosterone in a partner. The showering study concluded that showering 2 hours after application of Fortesta had no meaningful effect on the pharmacokinetics of topically applied testosterone.

However, the sponsor has not conducted a "Wash off" study to demonstrate the transference of residual Fortesta (if any) from the application site after washing the site with soap and water.

The sponsor was previously asked to conduct such a study in human subjects as a post-marketing requirement to demonstrate that there is no remaining amount of Fortesta left at the application site after washing with soap and water which they agreed to. Since the recommended regulatory action for this application will be a complete response (in view of the analytical site deficiencies identified by the DSI), this post marketing requirement will reflect as a deficiency in the CR action letter and need to be conducted prior to approval.

8.7 Overall Safety

CTDL Assessment of Safety:

Fortesta (testosterone gel 2%) was well-tolerated in the Phase 3 trial (FOR01C) with the dose ranging from 10 mg to 70 mg. The dose adjustment was done with a consistent increment or decrement of 10 mg at Days 14, 35 and 60.

The incidence of treatment emergent adverse events (TEAE's) considered related to study drug in study FOR01C was 46.8% that is lower from previously submitted data. The previously submitted data showed an incidence of 63.7% in the 6-month Phase 3 study (T 00-03-01).

- *The most common treatment emergent adverse events considered to be related to Fortesta were application site reactions (ASRs) including contact dermatitis, application site erythema, dryness, and skin reaction. The majority of ASRs were mild in severity and required no further medical intervention.*
- *The next common treatment-related AEs were insignificant increase in hematocrit and prostate specific antigen (PSA), and a decrease in HDL-cholesterol.*
- *The most common treatment emergent adverse events (TEAEs) that led to premature study discontinuation were application site reactions (ASR's) including erythema, dryness and pruritus.*

CTDL Comment on PMR:
The sponsor was asked to conduct a washing study as a post-marketing requirement to demonstrate that Fortesta is completely washed off the skin after it is washed with soap and water. This was communicated to the sponsor on October 1, 2009, via a teleconference. The sponsor agreed to comply. However, due to the deficiencies identified by the Division of Scientific Investigations (DSI) during their analytical site inspection, the "wash-off" study will be requested to be performed prior to approval and the results are to be submitted with a Complete Response.

9. Advisory Committee Meeting

An Advisory Committee was not held for this application. Testosterone is currently approved in various dosage forms. All safety concerns that were identified during this NDA review were resolved in collaboration with the Office of Surveillance and Epidemiology, through labeling and a REMS, including institution of a new Medication Guide.

10. Pediatrics

The Applicant requested a full waiver of the requirement to conduct assessments of Fortesta in pediatric patients. The Sponsor stated that studies would be impossible or highly impracticable and because the disease/condition does not exist in children and because the product does not represent a meaningful therapeutic benefit over the existing therapies for pediatric patients and is not likely to be used in a substantial number of pediatric patients. In June, 2009, the Division recommended to the Pediatric Review Committee (PeRC) that the Sponsor's request be granted. The PeRC agreed with the request. On August 26, 2009, George Greely of the Pediatric and Maternal Health Staff provided an eMAIL to DRUP stating:

> "*The Fortesta (testosterone 2% gel) full waiver was reviewed by the PeRC PREA Subcommittee on August 19, 2009. The Division recommended a full waiver because too few children with the disease/condition to study. The PeRC PREA Subcommittee stated that this application does not need PREA.*

11. Other Relevant Regulatory Issues

Division of Scientific Investigation (DSI)

Site inspections by the Division of Scientific Investigation (DSI) were requested. Two clinical site inspections on the basis of the site's sample size and no previous history of inspection, were requested. Additionally, Office of Clinical Pharmacology requested an analytical inspection of one of the sites for a review of assay methodology used for the measurement of testosterone.

DSI forwarded (on October 1, 2009) copies of 483 forms issued to a) Mark R Akerson, MD (Arizona site) and b) (b) (4)

Dr. Akerson's form 483 contained a) four instances in which adverse conditions were identified within the subjects' medical charts and not reported in the CRF's per the protocol b) four instances in which the subjects full medical history was not captured during screening and not reported on the CRF's per the protocol c) three instances in which subject inclusion/exclusion criteria were not met to enroll subjects per the protocol d) failure to report promptly to the IRB all unanticipated problems involving risk to human subjects or others (a patient who was hospitalized was not reported), and e) failure to report to the sponsor adverse effects that may reasonably be regarded as caused by, or probably caused by, an investigational drug (this adverse event involved a subject being hospitalized).

(b) (4) form 483 contained multiple deficiencies including "the incurred sample reproducibility (ISR) of the LC/MS/MS method for TT (total testosterone) was not evaluated. TT concentrations determined by this method were used to calculate the primary and secondary efficacy endpoints of the study."

A meeting involving DSI, clinical-pharmacology, and the clinical review team was held on October 7, 2009, and a draft report from DSI reviewed. The DSI review was finalized on October 8, 2009, and stated:

"Data from the subjects listed in Attachment 6 should be omitted from data evaluation. The review division should consider if subjects with high number of failed samples be entirely removed." (More than 20 patients with multiple numbers of failed samples are included in Attachment 6).

"The DHT assessments are not acceptable at this time. The firm should provide data to demonstrate that solvent calibrators used in the DHT RIA are equivalent to serum-based calibrators, and did not affect accuracy of data generated by this assay."

"PSA measurements <0.5 ng/ml should be considered BLOQ. The remaining measurements can be accepted for review."

"LH measurements <0.59 mIU/ml can not be assured and should be considered BLOQ."

"The accuracy of the F/T and long term frozen storage stability data are questionable, as freshly prepared standard curves were not used in these stability experiments. The response provided by the firm is not adequate. The firm should repeat the F/T and long term frozen storage stability studies of all the analytes using freshly prepared standard curves."

"To confirm that the "Analyst" software audit trails are available, the firm should provide the audit trail records of the analytical runs in Attachment 5 to DSI for review."

"Panhandle Family Care Associates enrolled subjects that did not meet the study inclusion/exclusion criteria. DSI recommends that data from subjects 032-014, 032-051, and 032-050 be excluded from study evaluation.

Panhandle Family Care Associates failed to report all adverse conditions within four subject's medical chart in the CRF's; failed to capture full medical history of four subjects during screening and did not report them on the CRF's: did not report the SAE (032-042) to the sponsor and promptly to the IRB. The medical reviewer should evaluate any impact of these findings on the safety evaluation of Fortesta."

Additional material was forwarded from DSI on October 9, 2009, which stated:
The application is not acceptable based on the results of audits conducted and arranged by the Division of Scientific Investigations (DSI) for phase III study (FOR01C). The major deficiencies identified in this study can be summarized as follows:

- Although (b) (4) response to the FDA 483 explains a silent audit trail was active during the study, it did not provide evidence that the audit trail was active for the total testosterone measurements. To confirm that the 'Analyst' software audit trails are available, the firm should provide the audit trail records for the following analytical runs for the total testosterone assay to DSI for review:
    - 07082326, 07091884, 07092604, 07100219, 07100531, 07100939, 07101142, 07101967, 07102375, 07102479, 07102786, 07110103, 07111226, 07111634, 07111635, 07111740, 07112146, 07112655, 07113065, 07113068, 07120578, 07120783, 07120786, 07121194, 07121397, 07121813, 07122019, 07122124, 07122433, 08010244, 08010653, 08011168, 08011375, 08011580, 08011992, 08012298, 08013029, 08020134, 08020240, 08021584, 08021481, 08022208, 08022310, 08022717, 08030228, 08030637, 08030638, 08031255, 08032804, 08041447
- The accuracy of the F/T and long term frozen storage stability data for all the analytes is questionable, as freshly prepared standard curves were not used in the stability experiments. (b) (4) should repeat the F/T and long term frozen storage stability studies of all the analytes using freshly prepared standard curves and provide the data to DSI for review.
- Due to inaccurate QCs, testosterone data from the subjects listed below are not acceptable. The original samples, if still available, must be reanalyzed to determine accurate testosterone concentrations and provided to DSI for review. The stability evaluations noted above must cover the storage time for the study samples until reanalysis.

  - 001-001, 003-005, 003-006, 004-004, 005-001, 005-002, 005-007, 005-010, 006-010, 007-001, 007-004, 007-009, 008-003, 009-003, 009-004, 009-010, 010-004, 011-001, 012-001, 012-019, 012-023, 013-003, 014-001, 014-014, 014-016, 014-048, 014-057, 014-064, 014-065, 014-068, 015-003, 015-006, 015-008, 015-009, 016-003, 018-009, 018-017, 022-001, 024-003, 024-004, 024-005, 025-001, 025-009, 026-001, 026-006, 026-008, 026-013, 026-019, 026-021, 027-009, 027-013, 027-014, 028-009, 028-012, 031-002, 031-003, 032-026, 032-036, 032-038, 032-040, 032-041, 032-042, 032-051, 032-052.
- The dihydroxytestosterone (DHT) radioimmunoassay (RIA) measurements are not acceptable. (b) (4) should demonstrate the accuracy of the DHT RIA by comparing the results of QC samples back calculated from: (1) calibrators prepared in solvent and (2) calibrators prepared in serum (including extraction and oxidation) and provide these data to DSI for review.
- Due to improper application of enrollment criteria as noted in the 483 for Panhandle Family Care Associates, the data from subjects 032-014, 032-051, and 032-050 should be excluded from study evaluation.

CTDL Comment:
An internal meeting which included participants from DSI and the clinical, clinical-pharmacology, pharmacology/toxicology, chemistry, and statistical teams was held on October 8, 2009, and teleconferences were held with the sponsor on October 8 and 9, 2009. Representatives from (b) (4) *were present on the October 9, 2009, teleconference after obtaining a letter of authorization from them to discuss the DSI findings with Endo. Following all of these discussions concerning the deficiencies noted in the DSI* (b) (4) *inspection, the clinical and clinical-pharmacology reviewers concluded that the inability to rely on the laboratory values currently precludes the approval of Fortesta. The testosterone PK values are used to calculate the primary endpoint (C_{avg}) and the C_{max} of testosterone is an important secondary safety endpoint. The extent of the problems at* (b) (4) *is not entirely clear. However, after discounting only those patients whose testosterone levels enabled them to be classified as "responders" in the MITT population, the primary endpoint would not be met. In addition, the uncertainty concerning the audit trail complicates matters further. In addition, the results of the clinical site inspection require that three patients be removed from the analysis. The status of the other hormonal evaluations is also in question. In summary, the data submitted to support the efficacy and safety of this product can not be currently relied upon.*

CTDL Comment:

I agree with the recommendation provided by the Division of Scientific Investigations (DSI). A complete response (CR) action is recommended to correct these deficiencies.

Financial Disclosure

All of the clinical investigators in the United States pivotal Phase 3 Study FORO1C clinical sites responded to request for financial disclosure and none had any relevant financial disclosure information to declare. There were no investigators with a proprietary interest in the product and none with significant equity in the Sponsor as defined in 21 CFR 54.2 (b).

Controlled Substances Staff (CSS)

DRUP requested a consult from CSS to verify the scheduling status of Fortesta and to assess the labeling as it applies to Abuse and Dependence.

CSS Review and recommendations (August 19, 2009)
Testosterone, and therefore the product Fortesta (testosterone) Gel 2%, is in Schedule III of the Controlled Substances Act. Testosterone is specifically designated a Schedule III anabolic steroid under 21 U.S.C. 802(41)(A)(xlvii).

The CSS staff also provided recommendations for revisions to Section 9 (Drug Abuse and Dependence) of the label. The CSS labeling recommendations were incorporated into the Fortesta labeling

Division of Medication errors and Prevention (DMEPA)
DMEPA was asked to consult on 1) the trade name, and 2) the container/carton and the Full Prescribing Information (FPI) and Medication Guide labeling, with regard to potential medication errors.

The Proprietary Name Risk Assessment findings indicate that the proposed name Fortesta is not vulnerable to name confusion that could lead to medication errors. Thus, the Division of Medication Error Prevention and Analysis (DMEPA) has no objection to the proprietary name, Fortesta, for this product at this time.

DMEPA also reviewed the Medication Guide and provided their comments/recommendations. All the comments were incorporated into the Medication Guide Labeling. The Medication Guide was finalized and sent out to the sponsor on October, 6th, 2009 for their agreement.

Division of Drug Advertising, Marketing and Communication (DDMAC)
A consultation regarding labeling for Fortesta was requested and completed by DDMAC. In their final consult report dated October 1, 2009, Janice Maniwang provided comments on various sections of the label.

Each of the DDMAC comments were considered individually and discussed within the clinical review team and most of the DDMAC recommendations were incorporated into the labeling and negotiated with the sponsor toward an agreeable label.

Division of Risk Management (DRISK)

DRISK reviewed the Prescribing Information and the Medication Guide.

CTDLComment: The label and the Medication Guide will be re-assessed at the time of submission of a Complete Response.

Division of Pharmacovigilance (DPV)

The DPV agreed with the Division that REMS (including a Medication Guide) and labeling (that includes a black box warning for Secondary Exposure to Testosterone) should be required for approval of Fortesta. Transfer of testosterone from patients using testosterone gel products to others (including children) was the subject of a June 23, 2009, Advisory Committee Meeting.

Risk Evaluation and Mitigation Strategy (REMS): The sponsor submitted REMS consisting of a Medication Guide and Timetable for Assessments. These were reviewed by the Division and by DRISK. The REMS (including the Medication Guide) will be re-assessed following submission of a Complete Response.

Labeling

Labeling discussions with the review team and with the Sponsor were very productive and an agreement was reached towards a final label.

- A box warning for secondary exposure to testosterone was incorporated into the Highlights section of the label.
- A section for Secondary Exposure to Testosterone in children was incorporated in the post-marketing section.
- The recommendations of the Controlled Substance Staff were incorporated into the **Drug Abuse & Dependence** section of the label.
- Medication Guide that informs patients of known androgen related side effects was finalized on October 7th, 2009, and included in the label with all the recommendations made by DRISK.

12. Recommendations/Risk Benefit Assessment

12.1 Recommended Regulatory Action

In my opinion, the sponsor has provided an acceptable complete response, in response to a non-approvable action of 2003 and there is sufficient evidence to consider all the deficiencies as resolved except for the clinical and analytical site inspections.

There are two outstanding issues: 1). Sponsor is asked to conduct a wash-off study to demonstrate that Fortesta is completely washed off from the application site. Completion of such a study should be prior to approval. The sponsor has agreed to comply with the requirement. 2). Review team from the Division of Scientific Investigations (DSI) has identified deficiencies from one of the clinical sites and recommended not to include data for analysis for three identified subjects. Additionally, the team has identified major deficiencies that are otherwise essential in meeting the quality control practice and procedures at the analytical site and recommend an evaluation of the audit trail, evaluation of the stability data, and re-evaluation of analytical runs for TT assay.

With the unresolved issue that pertains to the analytical site inspection as identified by the Division of Scientific Investigation (DSI), I recommend a complete response (CR) action at this time.

12.2 Risk Benefit Assessment

In regard to efficacy, the 40 mg once daily, starting dose with 10-70 mg/day dose adjustment, Fortesta was found to provide adequate replacement of testosterone in hypogonadal men (as measured by testosterone Cavg), while not providing excessive testosterone (as measured by testosterone Cmax). The product is effective for the proposed indication.

In regard to safety, the results from study FOR01C and other Phase III trials revealed the expected adverse reactions associated with the pharmacological action of testosterone (e.g., slight increase in serum PSA, worsening BPH, edema, change in lipid profile, and application site reactions etc).

Therefore, based upon the demonstrated efficacy of Fortesta from study FOR01C and overall safety as shown from the integrated safety data, along with Medication Guide Labeling, and a Post-marketing requirement of conducting a wash-off study, Fortesta will be a beneficial in the replacement of testosterone in hypogonadal men.

12.3 Recommendation for Post marketing Requirement

The sponsor has been asked to conduct a Wash-off study in humans to demonstrate that there is no residual amount of Fortesta left at the application site, after the site has been washed with soap and water. This recommendation of a PMR was made by both Clinical Review Team and the Clinical-Pharmacology Reviewer and was communicated to the sponsor via a Teleconference on October 1, 2009. A written agreement to conduct this proposed study was subsequently received by the Division of Reproductive and urological Products (DRUP).

However, due to the deficiencies identified by the Division of Scientific Investigations (DSI) at the analytical site, completion of a "Wash Off" study will be a part of the deficiencies identified in the Complete Response action letter.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21463	ORIG-1	ENDO PHARMACEUTICALS INC	FORTIGEL (TESTOSTERONE GEL) 2%

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SURESH KAUL
10/15/2009

GEORGE S BENSON
10/15/2009

NDA 21-463

Deputy Director's Memorandum

From: Donna J. Griebel, MD
Division of Reproductive and Urologic Drug Products

Date NDA submitted: May 31, 2002
Date NDA received: June 3, 2002 (Goal date extended by three months for a major amendment received on January 30, 2003.)
Date memo completed: July 3, 2003

Sponsor: Cellegy Pharmaceuticals, Inc.
349 Oyster Point Blvd., Suite 200
South San Francisco, CA 94080

Drug name: Fortigel (testosterone 2% gel)
Strength: 40, (b) (4)
Route of administration: transdermal

Proposed indication: "testosterone replacement therapy in men with primary or secondary hypogonadism"

Related IND's:

(b) (4)

1.0 Regulatory Background

The efficacy endpoints that have been the basis of approval for previous applications for the indication "testosterone replacement therapy in men with primary or secondary hypogonadism" were pharmacokinetic endpoints. Sponsors are advised in their clinical development plans that they must show that their product achieves both C_{min} and C_{avg} testosterone levels within the physiological range. Throughout the development of the testosterone gel Fortigel, DRUDP has advised the sponsor Cellegy that the high supraphysiological C_{max} testosterone levels found in the product's pharmacokinetic profiles are a safety concern. This communication included a teleconference on May 25, 2000, held at Cellegy's request to "clarify DRUDP's safety concerns regarding high testosterone levels," and discussion at the pre-NDA meeting October 29, 2001. The DRUDP clinical reviewers expressed concern at the pre-NDA meeting regarding the C_{max} values

over 5,000 ng/dl observed in the major clinical trial supporting the application. The clinical pharmacology reviewers commented that the data submitted suggested that the testosterone exposure may not be proportional to the dose administered. The DRUDP clarified that outliers with elevated testosterone levels are of concern due to possible adverse clinical events. The sponsor indicated that the high levels observed in the 60 mg group of their study before titration could be managed with dose adjustment. (Sixty mg applied daily is the proposed starting dose for this product.) They cited studies of injectable testosterone, in which the serum testosterone levels remain high for several days, to support the lack of adverse events associated with high testosterone levels.

2.0 NDA Data and Analyses

In addition to five small pharmacokinetic trials that were performed to evaluate impact of site of product application, size of area of application, vehicle formulation effects, effects of showering and the potential of product transfer to partners, there was a single pharmacokinetic study conducted to evaluate the efficacy and safety of Fortigel. This study was an open label, non-comparative trial that was designed to show that Fortigel achieved both average (C_{avg}) and minimum (C_{min}) serum testosterone concentrations within physiological range (defined as C_{min} >300 ng/dL and C_{avg} 300-1140 ng/dL) in a proportion of patients that exceeded 20%, based on a lower bound of the confidence interval. The latter goal was selected after initiating the protocol, modifying the sponsor's original target of 80% of patients achieving the primary endpoint, based on a historical review of the pharmacokinetic data from other transdermal products. These historical data suggested that the point estimate for efficacy (as defined using both C_{min} and C_{avg}) achievable with such products was more realistically in the range of 35%.

The study enrolled 201 patients, but only 89 of those patients met the sponsor's definition of efficacy evaluable, the primary analysis population for the primary efficacy endpoint. The sponsor increased the population available for efficacy analysis to 163 by defining a "modified intent to treat population". Efficacy analyses were presented in the NDA for the ITT, efficacy evaluable and the modified intent to treat populations, and the efficacy goal was achieved in all three. The proportion of patients whose C_{avg} and C_{min} met the pharmacokinetic target on Day 42/56 was 42.7% (95% CI= 32.4, 53.0) in the efficacy evaluable population, 41.7% (95% CI= 34.1, 49.3) in the modified ITT population, and 33.8% (95% CI = 27.3, 40.4) in the ITT population. The FDA review team concurred with these findings and agreed that the product had met the defined efficacy goals.

The safety review, however, focused on the high supraphysiological C_{max} observed in a number of participants in the study. The FDA examined the proportion of patients with high C_{max} values, the extent of C_{max} elevation, the predictability of achieving high C_{max} values, whether dose adjustment could adequately and predictably address a high C_{max}, and whether the safety data set demonstrated adverse events were associated with high supraphysiological levels. Participants in the study all started treatment with the same dose, testosterone 60 mg, delivered in 3g of Fortigel 2% gel applied daily. The product is dispensed to users in 0.5 g gel

increments from a pump, which the applicant states facilitates dose adjustment. Twenty-four hour PK data were collected on Day 14 of the dosing, and dose adjustment was performed on Day 28 based on the Day 14 C_{min} and C_{max} data as follows:

> If the minimum serum concentration (C_{min}) of testosterone measured in the Day 14 samples was <300 ng/dL and the maximum serum concentration (C_{max}) was <1000 ng/dL, the patient's dose was increased to 4 g gel (80 mg testosterone) daily.
>
> If the C_{min} was >400 ng/dL and C_{max} was >1000 ng/dL, the dose was decreased to 2 g gel (40 mg testosterone) daily.
>
> If C_{min} was >300 ng/dL and C_{max} was <1140 ng/dL, the dose was to be maintained at 3 g gel daily.
>
> If the testosterone concentrations did not meet any of the above criteria, a Cellegy Medical Monitor made a decision about the dose adjustment.

If the dose remained at 60 mg (3g gel) repeat 24 hour PK evaluations were performed at Day 42 (7 weeks) and Day 182 (27 weeks). If the dose was changed at day 28, the next PK evaluation was delayed to Day 56 to allow steady state to be reached. Repeat 24 hour PK data were collected on Day 182 in these patients as well.

Ninety-five (43%) of the ITT population had their dose adjusted at Day 28. (Similar proportions were dose adjusted in the applicant's efficacy evaluable and modified intent to treat populations – 40% and 44%, respectively.) From a safety standpoint, focusing on high C_{max}, the FDA review team evaluated the success of the study's dose adjustment by using a testosterone C_{max} >1500ng/dL as the level that would be desirable to avoid. The 1500 ng/dL cut point was selected based on available evidence that the high end of the diurnal testosterone fluctuation in eugonadal men is approximately 1100 ng/dL. In addition the division considered the testosterone levels reported in the literature that the sponsor had cited as evidence that commonly used intramuscular testosterone injections result in high testosterone levels. (*Sokol RZ, et. Al., Comparison of the Kinetics of Injectable Testosterone in Eugonadal and Hypogonadal Men, Fertil Steril 37:425, 1982* and *Synder PJ and Lawrence, DA, Treatment of Male Hypogonadism with TestosteroneEnanthate, J Clin Endocrinol Metab 51:1335, 1980.*) The latter reports suggest that in hypogonadal men, the mean C_{max} achieved with intramuscular injections of testosterone enanthate and cypionate are in the 1200-1400 ng/dL range. In the paper by Sokol, et. al., the mean C_{max} following a 200 mg injection in 7 hypogonadal men was 1233 +/- 484 ng/dL. The mean testosterone level fell below 1100 ng/dL at approximately Day 4 post-injection. The highest levels of C_{max} produced by the 200 mg injection are not reported. In the paper by Snyder and Lawrence, 23 hypogonadal men were injected with 100, 200, 300, and 400 mg testosterone enanthate. Following the 200 mg dose, testosterone levels were measured every 2 days for 2 weeks and following the 300 mg dose, testosterone levels were determined every 3 days for 3 weeks. According to the figures in the manuscript, the mean C_{max} levels were approximately 1400 ng/dL for both

the 200 and 300 mg doses. The highest serum testosterone levels with the 200 and 300 mg doses are not reported.

Using the 1500 ng/dl cut point, the review team found that dose reduction to **40 mg** failed to avoid levels >1500 ng/dl C_{max} levels in subsequent 24 hour PK evaluations in 59% of the patients that were dose reduced. In addition 56% of patients who were maintained at the **60 mg** testosterone dose level after the Day 14 evaluation, were found to have a C_{max}that exceeded 1500 ng/dl at subsequent evaluations. Forty-six per cent of patients whose doses were increased to **80 mg** at Day 14 in an effort to increase C_{min} to above the 300 ng/dl efficacy goal subsequently had a C_{max} that exceeded 1500 ng/dl on a subsequent evaluation. These findings are summarized in the table below.

Table 1. Number and Percentage of Patients in the 40 and 80 mg Dose Adjusted Groups with C_{max}>1500 ng/dL at Days 42/56 and 182; and in Patients Maintained at 60 mg.

Dose (mg gel)	C_{max}> 1500 ng/dL			Total
	D42/56 & D182	D 42/56 only	D 182 only	
40 (N=32)	**8 (25%)**	**10 (31.3%)**	**1 (3.1%)**	**19 (59.4%)**
80 (N=63)	**11 (17.5%)**	**14 (22.2%)**	**4 (6.3%)**	**29 (46%)**
Total (N=95)	**19 (20%)**	**24 (25.3%)**	**5 (5.3%)**	**48 (50.5%)**
60 (N=71)	**11 (15.5%)**	**22 (31%)**	**7 (9.8%)**	**40 (56.3%)**

The review team's concerns regarding the proportion of patients with supraphysiological levels of testosterone in this trial were discussed with the applicant during the course of the review. Among the applicant's arguments to support that these values are in fact not a basis for concern was the applicant's belief that levels achieved by Fortigel are not unlike those associated with other transdermal products that have been approved by the FDA. The review team performed a comparative summary of the C_{max} values observed in the NDA reviews of those other products. The designs of the trials used to evaluate the various products were not identical, including differing timing of dose changes and PK evaluation. These comparative C_{max} (and C_{avg}) levels are summarized in the two tables below.

Table 2 Comparison of PK Outliers inT-Gels at Steady State (6 months post treatment for Fortigel and Androgel, 3 months for Testim)

Products	Cmax (ng/dL)				Cavg (ng/dL)	N
	1200-1500	1501-1800	1801-2500	>2500	>1100	
Fortigel	**20 (14%)**	**13 (9%)**	**20 (14%)**	**9 (6%)**	**0**	**147**
Androgel	14 (9%)	11 (7%)	7 (5%)	0	5 (3%)	151
Testim	4 (2%)	4 (2%)	4 (2%)	0	2 (1%)	162

Table 3. Comparison of Testosterone C_{max} (ng/dL) and C_{avg} Values of Fortigel with Androgel and Testim at Steady State after Dose Adjustment

	Fortigel (Day 42/56)	**Fortigel (Day 182)**	**Androgel (Day 180)**	**Testim (Day 90)**

	Fortigel (Day 42/56)	**Fortigel (Day 182)**	**Androgel (Day 180)**	**Testim (Day 90)**
Cavg	631	**562**	**713** (10g dose)	**612** (100mg dose)
Cavg > 1100		0 (0%)	5 (3%)	2 (1%)
Cmax (average)	1651	1244	1083 +/- 434	897 +/- 565
Cmax > 1500	77/164 (47%)	**42/146 (29%)**	**18/129 (14%)**	**8/199 (4%)**
Cmax between 1500 and 1800	23 (14%)	13 (9%)	11 (7%)	4 (2%)
Cmax between 1800 and 2500	28 (17%)	**20 (14%)**	**7 (5%)**	**4 (2%)**
Cmax >2500	26 (16%)	**9 (6%)**	**0 (0%)**	**0 (0%)**

Despite the fact that the C_{avg} value for Fortigel is lower than either Androgel or Testim, the number of "outlier patient" C_{max} levels (particularly those between 1800 and 2500 and those >2500 ng/dL) are higher in the Fortigel group.

In discussions with the review team regarding the high Cmax levels during the course of the review, the applicant has made frequent references to the ability of the product pump delivery system to dispense 0.5g increments, which will allow dose adjustment to avoid high C_{max} values. As noted in the discussion above, the dose adjustment plan used in the trial submitted to support the efficacy and safety of the product failed to produce C_{max} levels below 1500 ng/dL in a substantial proportion of patients on study. The label submitted for review in the application outlined a dose adjustment plan that was not prospectively studied , and there are no prospectively collected data presented in the NDA to support the dose plan's ability to avoid these high supraphysiologic testosterone levels. The label's DOSAGE AND ADMINISTRATION section outlines the dose adjustment as follows:

(b) (4)

Examination of the PK data from the major study supporting the approval of this NDA reveals that the two hour testosterone levels were frequently lower than the actual C_{max} levels. The sponsor evaluated how many patients in the dataset would have their doses "accurately" predicted by a 2-hour blood draw at 14 days. The "accuracy" was defined by whether the dose determined at 2 hours, as defined in the label instructions above, would be the same that patients were ultimately adjusted to under the conditions of the study. The applicant found that approximately a third of the modified ITT population would have received a dose that differed from the protocol specified dose using the proposed label dose adjustment. When the review team examined the C_{max} and C_{2hour}

data, there were instances where the C_{max} was >1500 and C_{2hour} was not, such that dose reduction in actual practice (using the label instructions) would not have been performed to address the actual high C_{max}.

Additional concerns regarding the potential to adequately dose adjust with this testosterone gel formulation were raised by the data from the dose finding trial T 98-02-01. In that trial various dose levels, schedules, and application sites were evaluated. A 10 mg dose of testosterone gel (one-fourth the lowest dose recommended by the sponsor) applied to the upper arm (albeit a site that demonstrates higher absorption than the thighs) resulted in a patient with a C_{max} level as high as 3696 ng/dL. In summary, no convincing data were presented in the application to show that lowering the dose of Fortigel to 30, 20, or even 10 mg would consistently lower C_{max} levels, and no efficacy data for doses lower than 40 mg were submitted

The clinical relevance of the high supraphysiological testosterone levels was examined by the FDA review team. Testosterone therapy is reported to be associated with toxicities that include polycythemia (textbooks state that men receiving testosterone therapy should have a periodic hemoglobin and hematocrit checked, and treatment should be interrupted for elevated hematocrit), exacerbation of sleep apnea, gynecomastia, elevated PSA, and lowering of HDL. There is additional concern regarding the potential for stimulating the growth of subclinical prostate cancer. A literature search revealed no data examining whether higher testosterone levels are associated with a higher level of adverse events associated with testosterone replacement. The FDA review team performed PK/PD analyses to evaluate whether the limited dataset submitted in this NDA revealed any correlation between testosterone concentrations and various clinical safety endpoints. A statistically significant correlation between rising testosterone concentrations and rising hematocrit was found. In addition there was a statistically significant correlation between rising testosterone levels and lowering of the serum HDL. Although 33/201 (16.4%) from the major PK study supporting this application withdrew from the study for treatment emergent adverse events, most withdrawals (20; 61%) were for application site reactions - erythema (11 patients), pruritis (11 patients), xerosis (6 patients), rash (5 patients), and paresthesia (4 patients). None of the ASRs were assessed as serious. The non-application site reactions most commonly leading to discontinuation were cardiac-related (4 patients) and erythrocytosis (3 patients). While the safety review did not reveal conclusive evidence of a negative safety impact of the high supraphysiologic levels in this study, the data were too limited to conclude that these levels, and chronic exposure to these high levels, is safe.

Given the paucity of evidence in the literature regarding the safety of the testosterone exposure in the range of the high C_{max} values observed in this application, and given the limited patient numbers exposed for evaluation, two Special Government Employees, (b) (4) who are specialists in urology, were provided summary PK data and safety data from the NDA for purposes of consultation regarding this question. They did not participate together in the same teleconference, giving them the opportunity to give their independent opinions to the review team. Both consultants concurred that although there is little data to show that such high levels are unsafe, exposure to high supraphysiologic levels of testosterone are not the clinician's goal for testosterone replacement, and they would want to avoid such high levels in the interest of

assuring patient safety. One of the consultants deemed the levels achieved with this product "unacceptable" and the other did not believe the potential benefit of this product outweighed its unknown risk, given the availability of other testosterone replacement therapy for patients.

3. Clinically Relevant Issues from the Clinical Pharmacology and Biopharmaceutics Review:

The clinical pharmacology reviewer concluded that "this NDA is not acceptable to OCPB based on the fact that the high maximal (C_{max}) serum testosterone levels (observed in a significant number of patients) make this product supra-physiologic in term of testosterone replacement, and may not mimic the true endogenous profile of serum testosterone. Moreover, within the scope of the limited phase 3 clinical trial, elevated serum testosterone levels could be correlated to a decrease in HDL and increasing hematocrits." Furthermore, "based on the results from in vitro formulation screening studies, the sponsor may not have optimized the formulation prior to conducting clinical studies, since the final formulation used showed considerably high serum testosterone levels even at steady state. The phase 2 dose finding study was complicated in design with a very small number of patients on each dose/regimen. It appears that the sponsor did not optimize the dose based on all essential PK information resulting in selection of a sub-optimal dose/regimen or formulation, or both."

4. **Clinically Relevant Issues from the Pharmacology/toxicology Review**:

"Based on extensive pre-clinical published literature available on the safety of testosterone and clinical experience with testosterone in various formulations for the same indication as for the proposed testosterone gel, Pharmacology recommends approval of NDA 21-463" for Fortigel.

5. **Clinically Relevant Issues from the Biometrics Review**:

The statistical reviewer concluded that a written statistical review is not needed. "A single principal study (T-00-02-01) supports efficacy. This is an open label, uncontrolled study. Efficacy is based on percentage of patients who achieve and maintain pre-defined average and minimum testosterone concentration levels. Study results are descriptive only."

6. **Clinically Relevant Issues from the Chemistry Review**:

The chemistry reviewer concluded that "this application is recommended for approval from a Chemistry, Manufacturing, and Controls point of view." Post-marketing commitments were agreed to by the sponsor: 1) The criteria for Density and viscosity will be re-evaluated after 20 batches are manufactured. 2) The specifications for *in vitro* release testing will be set within 6 months of approval. The criteria will also be re-evaluated after 20 batches.

7. Comments from the Office of Drug Safety and the Division of Drug Marketing, Advertising, and Communications:

The sponsor initially submitted the tradename Tostrex. DMETS did not recommend use of the proprietary name Tostrex (b) (4) The name Tostran was not recommended for the same reasons. The sponsor then proposed the tradename Fortigel, which DMETS had no objection and DDMAC found acceptable from a promotional perspective. (b) (4)

8. Clinical Inspection Review (DSI):

Overall, "the data submitted in support of the NDA by Drs. McDavid, Meikle, and Pino appear acceptable."

Three clinical sites were inspected. At site #1, the inspection found issues related to inadequate informed consent, protocol deviation, and inadequate and inaccurate record keeping. The inspector did not think that these observations had a significant impact upon the acceptability of the data. At site #2, no significant problems were found. At site #3, 7 patients were enrolled into the extension study before each patient completed the efficacy study and 4 patients were enrolled into the extension study before an IRB approved consent form was available at the site.

9. Conclusion and Regulatory Recommendation

I concur with the review conclusions of Medical Team Leader Dr. George Benson, M.D., the primary medical reviewer, Dr. Guodong Fang, M.D., and the Clinical Pharmacology Reviewer, Dr. Dhruba Chatterjee, Ph.D., and I concur with their recommendation that this NDA for Fortigel (2% testosterone gel) should not be approved. There is insufficient information available from the data submitted in this NDA and in the literature to determine whether this product is safe for use under the conditions recommended in the proposed labeling. The specific safety concern is the insufficient information to establish that the high supraphysiologic daily Cmax serum testosterone levels achieved in a significant proportion of participants in the major clinical study supporting this application are safe under conditions of chronic administration. (Twenty-nine percent of patients achieved C_{max} levels >1500 ng/dL, and 20% of those had C_{max} levels >2500 ng/dL.) The proportion of patients with high supraphysiological testosterone levels and the degree of elevation was higher than observed in the reviews of previous transdermal products approved by this division (more than doubling the proportion of patients with C_{max} >1500 ng/dL.) There was also insufficient information provided within the application to show that the dose of this product can be adjusted to consistently preclude achieving these high supraphysiological testosterone levels

The nonapproval letter that will be sent to the applicant will state that in order to address the deficiencies they will need to examine either lower doses of Fortigel and show that lower and physiological levels can be achieved with the product, or they will need to develop a new formulation that does not produce these high levels. The review team has

concerns that the latter may be necessary given the apparent unpredictability of testosterone levels associated with the dose of the product in many patients in the data set.

Donna J. Griebel, MD
Deputy Division Director
Division of Reproductive and Urologic Drug Products

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Donna Griebel
7/3/03 04:39:12 PM
MEDICAL OFFICER

NDA 21-463

Supervisory Medical Officer's Memorandum

From: George S. Benson, MD, Medical Team Leader
Division of Reproductive and Urologic Drug Products

To: Donna Griebel, MD, Deputy Division Director
Division of Reproductive and Urologic Drug Products

Regarding: Recommendation for regulatory action

Date NDA submitted: May 31, 2002
Date NDA received: June 3, 2002 (Goal date extended by three months because of major amendment received on January 30, 2003.)
Date memo completed: July 1, 2003

Sponsor: Cellegy Pharmaceuticals, Inc.
349 Oyster Point Blvd., Suite 200
South San Francisco, CA 94080

Drug name: Fortigel (testosterone 2% gel)
Strength: 40, (b) (4)
Route of administration: transdermal

Proposed indication: "testosterone replacement therapy in men with primary or secondary hypogonadism"

Related IND's:

(b) (4)

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2. Executive Summary and Recommendation:

In my opinion, Fortigel (2% testosterone gel) applied once daily should not be approved for the indication "testosterone replacement therapy in men with primary or secondary hypogonadism." There is insufficient information available from the phase 3 data and in the literature relating to possible adverse effects of daily high C_{max} serum testosterone levels achieved in the one phase 3 clinical study and insufficient information relating to the ability to prescribe a dose of this product to preclude achieving these high serum testosterone levels.

The reasons for this decision based primarily on high C_{max} testosterone levels and dosing issues are as follows:

A. Regulatory history pertaining to high C_{max} levels: The Division has expressed concerns to the sponsor concerning high levels of serum testosterone (C_{max}) throughout the drug development program. A teleconference was held with the

sponsor on May 25, 2000 (at the request of Cellegy), to "clarify DRUDP's safety concerns regarding high testosterone levels." DRUDP told the sponsor that the "effects on the prostate, lipids, and hemoglobin are known side effects of high serum testosterone levels, particularly chronic exposure to elevated levels of testosterone; the length of time that levels must be above the upper limit of normal to cause adverse effects is not known, however, effects have been seen by DRUDP with intermittent elevations of testosterone levels; Cellegy's testosterone gel is proposed for chronic use. High testosterone levels remain a safety concern for DRUDP."

At the pre-NDA meeting held on October 29, 2001, the following comments were made by DRUDP:

Clinical: "DRUDP expressed concern with C_{max} values over 5,000 ng/dl; sponsor indicated that the levels are high in the 60 mg group before titration and that the C_{max} decreases after dose adjustment; sponsor cited studies using injectable testosterone in which the serum testosterone levels remain high for several days; Division clarified that outliers with testosterone levels that are elevated and remain elevated are of concern due to possible adverse clinical events."

Clinical pharmacology: "C_{max} values were high in many patients.
The exposure to T may not be proportional to the doses administered."

In my opinion, concerns about the supraphysiologic serum testosterone levels have not been resolved.

B. C_{max} levels in phase 3 Fortigel study and comparison to two previously approved testosterone gel products: In the single phase 3 clinical trial (**Protocol T-00-02-01),** at steady state at day 182 there were 42 of 146 (29%) patients who had a testosterone C_{max} of > 1500 ng/dL. Of these 42 patients, 13 had a C_{max} between 1500 and 1800 ng/dL, 20 had a C_{max} between 1800 and 2500 ng/dL, and 9 had a C_{max} between 2500 and 4071 ng/dL. At steady state at day 42/56 (after dose adjustment based on Day 14 testosterone PK levels), 77 of 164 (47%) patients had a C_{max} of > 1500 ng/dL. Of these 77 patients, 23 had a C_{max} between 1500 and 1800 ng/dL, 28 had a C_{max} between 1800 and 2500 ng/dL, and 26 had a C_{max} between 2500 and 5311 ng/dL. Although the mean C_{max} values are 1651 +/- 939 ng/dL at Day 42/56 and 1240 +/- 749 ng/dL at Day 182, the number of patients with C_{max} values greater than 2 and 3 times the upper limit of normal (1140 ng/dL) is significant.

These C_{max} (and C_{avg}) levels are compared to the two approved testosterone gel products in Table 1.

Table 1. Comparison of Testosterone C_{max} (ng/dL) and C_{avg} Values of Fortigel with Androgel and Testim at Steady State after Dose Adjustment

	Fortigel (Day 42/56)	Fortigel (Day 182)	Androgel (Day 180)	Testim (Day 90)
Cavg	631	**562**	**713** (10g dose)	**612** (100mg dose)
Cavg > 1100		0 (0%)	5 (3%)	2 (1%)
Cmax (average)	1651	1244	1083 +/- 434	897 +/- 565
Cmax > 1500	77/164 (47%)	**42/146 (29%)**	**18/129 (14%)**	**8/199 (4%)**
Cmax between 1500 and 1800	23	13 (9%)	11 (7%)	4 (2%)
Cmax between 1800 and 2500	28	**20 (14%)**	**7 (5%)**	**4 (2%)**
Cmax >2500	26	**9 (6%)**	**0 (0%)**	**0 (0%)**

Despite the fact that the C_{avg} value for Fortigel is lower than either Androgel or Testim, the number of "outlier patient" C_{max} levels (particularly those between 1800 and 2500 and those >2500 ng/dL) are higher in the Fortigel group. The risk of daily exposures to high Cmax testosterone levels is not known, but in my opinion, is not currently acceptable.

C. Adverse events associated with testosterone therapy: Testosterone therapy is associated with the risks of increased hematocrit, thromboembolic events, liver toxicity, and symptoms of benign prostatic hyperplasia. Although testosterone has not been directly implicated as an etiologic factor in producing prostate cancer, testosterone may stimulate otherwise "latent" prostate cancer to proliferate and metastasize. The effects of exogenous testosterone administration on serum lipids and the cardiovascular system are controversial. There is insufficient data (in this NDA and from a literature search) to determine whether the prolonged daily use of a product which causes high serum testosterone levels results in a higher incidence of significant adverse events than does a product which replaces testosterone nearer to the physiologic range. Because the effects of high C_{max} levels achieved daily (even for 2-4 hours) are not known, I believe that it is not appropriate to approve a product for "testosterone replacement" which results in significant supraphysiologic testosterone levels (2 to 3+ times the upper limit of normal) in a significant number of patients.

D. Dosing issues: The sponsor has argued that "the levels are high in the 60 mg group before titration and that the C_{max} decreases after dose adjustment." In the single phase 3 clinical trial, a complicated schema was used to dose titrate at Day 14. The 24 hour pharmacokinetic profile obtained on Day 14 was used to determine the final dose of testosterone which was decided upon on Day 28. The testosterone dose could be modified at Day 28 as follows:

If the minimum serum concentration (C_{min}) of testosterone measured in the 14 Day samples were <300 ng/dL and the maximum serum concentration (C_{max}) were <1000 ng/dL, the patient's dose was increased to 4g gel (80 mg testosterone) daily.

If the C_{min} were >400 ng/dL and C_{max} were >1000 ng/dL, the dose was decreased to 2g gel (40 mg testosterone) daily.

If C_{min} were >300 ng/dL and C_{max} were <1140 ng/dL, the dose was to be maintained at 3g gel daily.

If the testosterone concentrations did not meet any of the above criteria, a Cellegy Medical Monitor was to make a decision about the dose adjustment.

In the single phase 3 trial, dose adjustments were made based on a full 24-hour testosterone PK profile on Day 14. The sponsor recognizes that this is not a practical method to determine optimal dose. Furthermore, the sponsor believes that "a single testosterone concentration point (instead of a complete 24-hour PK profile) and other measures (e.g., BMI) can have clinical utility in making dose adjustment decisions." In the dosage section of the proposed label, the sponsor has proposed the following:

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The sponsor notes that 15 patients (9%) would have been assigned "too high" a dose and 35 patients (21%) would have been assigned "too low" a dose based on a 2 hour post-drug application testosterone serum level versus dose adjusting by the per-protocol 24 hour PK data.

In the phase 3 trial, 18 of the 77 patients with a C_{max} > 1500 ng/dl at Day 42/56 had been titrated to the lowest dose of Fortigel (40 mg), 25 had been titrated up to 80 mg, and 34 had remained on the initial 60 mg dose. At Day 182, 10 of the 42 patients with a C_{max} >1500 had been titrated to the lowest dose, 15 had been titrated up to 80 mg, and 17 remained on the initial 60 mg dose. At Day 182, 4 of the 16 patients with C_{max} > 2200 ng/dL were on the 40 mg dose of Fortigel (C_{max} levels of 2247, 2276, 2411, and 3198 ng/dL). I have no explanation as to why the percentage of patients with high testosterone C_{max} levels is greater at Day 42/56 than at Day 182 since both PK evaluations were done at steady state.

Despite dose adjustment based on PK data obtained on Day 14, a significant percentage of patients had high C_{max} levels at both Days 42/56 and 182. Of the patients who were maintained on the 60 mg dose and, therefore, had C_{max} values < 1140 ng/nL at Day 14, 33 had C_{max} values greater than 1500 ng/mL at Day 42/56 and 17 had C_{max} values >1500 on Day 182. The number and percentage of patients who had C_{max} values >1500 ng/dL at Days 42/56 and 182 after being down or up titrated to 40 or 80 mg is shown in Table 2.

Table 2. Number and % of patients in 40 and 80 mg dose groups with C_{max} >1500 ng/dL at Days 42/56 and 182.

Dose (mg gel)	C_{max}> 1500 ng/dL			Total
	D42/56 & D182	D 42/56 only	D 182 only	
40 (N=32)	8 (25%)	10 (31.3%)	1 (3.1%)	19 (59.4%)
80 (N=63)	11 (17.5%)	14 (22.2%)	4 (6.3%)	29 (46%)
Total (N=95)	19 (20%)	24 (25.3%)	5 (5.3%)	48 (50.5%)

These data, coupled with the observation that many patients in the highest C_{max} groups had been down titrated to the lowest dose of Fortigel (40 mg), raises the question as to whether this product can be properly dosed regardless of the method proposed in labeling. Additionally, in dose finding trial T 98-02-01, when a 10 mg dose of testosterone gel (one-fourth the lowest dose recommended by the sponsor) was applied to the upper arm (albeit a site which demonstrates higher absorption than the thighs), C_{max} levels as high as 3696 ng/dL were reported. In summary, no data are presented which are convincing that lowering the dose of Fortigel to 30, 20, or even 10 mg would consistently lower C_{max} levels and no efficacy data for lower doses are submitted.

E. Sponsor's responses to Divisions's concerns about supraphysiologic testosterone C_{max} levels: The sponsor argues that the high levels of testosterone observed with Fortigel are not clinically important because 1) high serum levels of testosterone (as seen with intramuscular injections of testosterone esters) do not cause significant clinical problems and 2) in analyzing the adverse event data from the phase 3 clinical trial, there is no evidence that patients with high serum levels of tesosterone (C_{max} levels > 1800 ng/dL) experience more adverse events (elevated hematocrit levels, prostate cancer, elevated PSA, thromboembolic events, etc.) than do patients with C_{max} levels <1800 ng/dL. In addition, the sponsor believes that the adverse events experienced with Fortigel compare favorably with the reported adverse event experience with the approved testosterone gel preparations Androgel and Testim.

1) The sponsor believes that "all the available testosterone products in the US produce supraphysiologic levels in some subjects. Estimates of the duration of supraphysiologic serum levels following testosterone ester injections can be estimated from the pharmacokinetic studies by Sokol (*Sokol R.Z., et al, Comparison of the Kinetics of Injectable Testosterone in Eugonadal and Hypogonadal Men, Fertil Steril 37: 425, 1982*) and Snyder (*Snyder, P. J. and Lawrence, D.A., Treatment of male Hypogonadism with Testosterone*

Enanthate, J Clin Endocrinol Metab 51: 1335, 1980), These studies provide evidence that intramuscular injection of 200-400 mg of testosterone enanthate or testosterone cypionate produces continuous supraphysiologic serum T concentrations during the first 6-9 days of each administration followed by a gradual decline to sub-physiologic testosterone concentrations before the next injection. Peak testosterone concentrations are typically above 1200 ng/dL following 200 mg or 300 mg TE or TC injections. In an analysis of pharmacokinetic data for subjects on their prescribed doses of testosterone enanthate, the mean C_{max} is 1204 +/- 973 ng/dL with the range 311-5112 ng/dL. Clearly a significant number of subjects have circulating testosterone levels markedly above the upper limit of the physiological range in men. Meikle (*Meikle, A.W. et al: Enhanced Transdermal Delivery of Testosterone across Nonscrotal Skin Produces Physiological Concentrations of Testosterone and Its Metabolites in Hypogonadal Men, J Clin Endocrinol Metab 74: 623, 1992*) reported that the 5 mg Androderm patch applied to hypogonadal men is associated with C_{max} T concentrations of 1273 +/- 138 ng/dL, evidence that a significant proportion of men treated with this non-genital patch had circulating testosterone concentrations above the upper limit of physiological range for some period of the dosing interval. In another study with this patch, 2/25 (8%) of subjects had T concentrations above the physiologic range." In addition, the sponsor believes that the "use of high dose testosterone as a contraceptive that produces continuous supraphysiologic testosterone concentrations for up to 16 months, provides additional evidence for the safety of testosterone replacement treatment."

In the paper by Sokol, serum testosterone levels were measured serially after eugonadal and hypogonadal men had received either 100 mg or 200 mg of intramuscular testosterone enanthate. In the 7 eugonadal men who received the 200 mg dose, the mean C_{max} was approximately 2000 ng/dL. Serum testosterone levels remained above 1100 ng/dL for approximately 4 days. In the 7 hypogonadal men, however, the mean C_{max} following the 200 mg injection was 1233 +/- 484 ng/dL. The mean testosterone level fell below 1100 ng/dL at approximately day 4 post-injection. The highest levels of C_{max} produced by the 200 mg injection are not reported.

In the paper by Snyder, 23 hypogonadal men were injected with 100, 200, 300, and 400 mg testosterone enanthate. Following the 200 mg dose, testosterone levels were measured every 2 days for 2 weeks and following the 300 mg dose, testosterone levels were determined every 3 days for 3 weeks. According to the figures in the manuscript, the mean C_{max} levels were approximately 1400 ng/dL for both the 200 and 300 mg doses. The highest serum testosterone levels with the 200 and 300 mg doses are not reported.

The sponsor submitted six papers which address the use of high-dose testosterone in male contraceptive studies. In the trials which used testosterone enanthate intramuscularly, the dose generally used was 200 mg

weekly. C_{max} levels and times of PK determinations are not given. In one of the studies (*WHO Task Force on Methods for the Regulation of Male Fertility, Lancet 336: 955, 1990*) using 200 mg IM testosterone enanthate weekly, the serum testosterone is said to increase 142% over baseline, although the time of blood drawing is not specified.

The sponsor is correct that other approved testosterone preparations, including intramuscular use preparations, including testosterone enanthate and testosterone cypionate, produce supraphysiologic serum testosterone levels in some patients. None of these products, however, was shown in the publications submitted to the NDA to produce C_{max} levels high as Fortigel. With intramuscular injections of testosterone enanthate and cypionate in hypogonadal men, the mean C_{max} levels are in the 1200 to 1400 ng/dL range and no information is given in the cited literature for high "outliers." The number of patients with high testosterone C_{max} levels (particularly those over 2000 ng/dL) and the levels of testosterone C_{max} observed with the two approved testosterone gel products are not as high as that observed with Fortigel. The C_{avg} of Fortigel (562 ng/dL) is actually lower than that of Androgel (713 ng/dL with the 10 g dose) and Testim (612 ng/dL with the 100 mg dose). In my opinion, the risk(s) associated with the use of a drug product which produces daily serum testosterone levels of 2 and 3+ times the upper limit of normal levels is not known. Risk is possible, however, and has not been excluded by the data and literature submitted to this NDA. The sponsor argues that concentrations above the normal range for more than 20% of the dosing interval occur in only 4-8% of patients and that the mean duration above the upper limit of normal (1140 ng/dL) is 2.2 to 2.3 hours/24 hour dosing interval and that this is "limited exposure." In my opinion, the clinical significance (or lack thereof) of this "limited exposure" to high testosterone levels is not known. Specifically, no data are available to assess the risk of daily exposure to exogenous testosterone which results in serum levels in the 2000 to 4000 ng/dL range.

2) The sponsor analyzed the hematocrit changes observed in Trial T-00-02-01 and compared them with data from Androgel and Testim studies. The mean hematocrit in patients in study T-00-02-01 increased from 44.0 at baseline to 46.6 at 26 weeks (increase of 5.9%). Three patients were discontinued from the study due to increased hematocrits. One of the three patients had a serum testosterone concentration above the physiologic range. The sponsor submitted the available data from the ongoing extension study. Of the 82 patients who entered the extension phase, 61 had both hematocrit determinations at screening and at the one year visit as well as a testosterone concentration profile at Day 182. Eleven patients, 5 with elevated testosterone C_{max} values above above 1800 ng/dL and 6 with values below 1800 ng/dL, had normal hematocrit results at screening but became elevated (Hct > 52%) at the one year visit during the extension study. The sponsor believes that the overall incidence of elevated hematocrit with Fortigel is lower than that reported for Androgel. The sponsor reports that, in a recent trial of Androgel, the percentage of

hypogonadal men in whom hematocrit inceased above the upper limit of normal during testosterone administration was 11.3% and 17.9% in the 50 and 100 mg dose groups, respectively. The sponsor also cites data which show that the 100 mg Testim dose produces hematocrit levels of 58% in 2.8% of patients and concludes that "these levels are exceedingly high; no subject receiving Fortigel reached levels this high."

The sponsor believes that "newer data do not support the widespread perception that testosterone supplementation adversely affects the plasma lipoprotein profile and increases the risk of atherosclerotic heart disease." "While supraphysiologic doses of non-aromatizable androgens frequently employed by body builders decrease plasma HDL-C levels, physiologic testosterone replacement in older men has been associated with only a modest or no decrease in plasma HDL-C. In Cellegy's study T-00-02-01 the mean HDL-C concentrations were decreased by 5%. HDL-C concentrations below 35 mg/dL were observed in 20.3% of those patients whose C_{max} serum testosterone concentration increased above the upper physiologic limit compared to 13.3% in those patients whose C_{max} testosterone concentrations were less than the ULN. The sponsor also reports that Androgel testosterone replacement therapy is associated with a reduction of HDL-C levels below the LLN in 4%, 9.1%, and 12.5% in the 5g, 7.5g and 10g dose groups, respectively. Finally, the sponsor believes that "dosing flexibility offered by Fortigel "may permit greater control of increases in hematocrit and decreases in HDL-C. As with all medications, labeling is the appropriate method used to inform physicians and patients about the appropriate use of a product."

Dr. Bhasin's (consultant for Cellegy) letter states that "the average decrease in plasma HDL concentration, total cholesterol, and LDL cholesterol observed in this phase 3 study is similar to what has been reported with other approved androgen formulations, and did not appear to be correlated with the transient increase in testosterone concentrations above the physiologic range. Furthermore, "although the effects of testosterone replacement on cardiovascular risk have not been directly examined, previous cohort and cross-sectional studies, and open label studies of testosterone replacement collectively suggest a modest change in plasma HDL cholesterol during testosterone administration, as was observed in this study, and neutral or favorable effect of testosterone on coronary heart disease in men." On the other hand (as demonstrated in the WHI estrogen study in women), randomized, controlled trials may demonstrate findings contrary to cross-sectional studies. With regard to hematocrit levels, Dr. Bhasin believes that the overall frequency of increase in hemoglobin and hematocrit in this phase 3 study was similar to that reported in previous studies of other androgen formulations. In this study, the transient increase in testosterone concentrations above the physiologic range did not appear to be correlated to the occurrence of erythrocytosis."

In literature cited by the sponsor (*Bhasin, S. and Buckwalter, JG: Testosterone Supplementation in Older Men: A Rational Idea Whose Time Has Not Yet Come, J Androl 22: 718, 2001*), Dr. Bhasin also states that "the long-term risks of testosterone replacement are poorly understood." "There is agreement that short-term testosterone administration is relatively safe in androgen-deficient men. The risks include erythrocytosis, induction or exacerbation of sleep apnea, and breast tenderness or enlargement. However, the two major areas of concern and uncertainty are the effects of long-term testosterone administration on prostate cancer and progression of atherosclerotic cardiovascular disease." When addressing testosterone deficiency in older men, Dr. Bhasin states that "the testosterone dose-regimen in these intervention trials should assure maintenance of serum testosterone concentrations in the testosterone treatment arm in the mid-to-high normal range to maximize the chances of demonstrating treatment effects."

Dr. Meikle (consultant for Cellegy) also believes that testosterone replacement therapy in hypogonadal men can safely be accomplished with Fortigel. He believes that the increased risk of elevated hemoglobin and hematocrit can be managed by through dose reduction or drug discontinuation. He also believes that "the reduction in HDL-C appears to be counteracted as a coronary artery risk profile by beneficial effects on LDL-C and other risk factors."

In my opinion, the primary difficulty in assessing risk secondary to the high C_{max} levels attained with Fortigel is the fact that the single phase 3 trial enrolled a relatively small number of patients for a relatively short period of time (147 patients completed 6 months of therapy and 60-80 patients completed the one year extension phase.). This study does not, therefore, answer the question as to the possible risks associated with high C_{max} testosterone levels with long term use. The medical and clinical pharmacology reviewers have plotted the changes in hematocrit and HDL versus C_{max} levels. It does appear that there is a relationship (albeit with relatively few data points) which achieves statistical significance correlating increasing hematocrit and decreasing HDL levels with increasing testosterone C_{max} values.

F. Teleconference consultations with Special Government Employees (b) (4) concerning the high testosterone levels observed with the use of Fortigel.

(b) (4) notes that "the peak levels are significantly higher than for preparations like Androgel and Testim, which are already on the market. As to the question of whether a high C_{max} should impact approval, I think that very little is known about the consequences of periodic high testosterone levels." Furthermore, "given that this is a "me-too" drug, which adds nothing to the medical armamentarium, my feeling is that it should not be approved without

far more long-term safety data. At the very least, a phase four study should be instituted if it is approved to gather such data, but safety considerations would seem to me to opt for the former approach in this situation. It sounds like the drug was mistakenly dosed in the clinical trial, and the question of how these drugs should be dosed, and what endpoint the companies should shoot for, is a major one that formed a part of out discussion. To summarize, I would not approve the drug, and would want to see more safety data before concluding that such high, unphysiologic serum concentrations for up to 5 hours per day are safe in the long term."

(b) (4) expressed similar opinions and found the high C_{max} levels to be "unacceptable" because of the unknown risks associated with them.

G. Overall risk/benefit summary:

Fortigel application in hypogonadal men results in testosterone C_{avg} levels in the normal range in an acceptable percentage of men, but produces C_{max} levels well above the normal range in approximately 30% of men. These C_{max} "outliers" are higher in number and severity than those "outliers" seen with the two approved testosterone gel preparations (Androgel and Testim). It does appear that hematocrit increases and HDL decreases in the phase 3 clinical study are related to the C_{max} of testosterone. I do not believe that it is appropriate to approve a product for "testosterone replacement" which results in supraphysiologic testosterone levels (2 to 3+ times the upper limit of normal in a significant number of patients) when the clinical consequences of daily high C_{max} levels even for relatively short periods of time each day are not known. In addition, the sponsor has not shown that the dose can be adjusted to consistently and predictably reduce C_{max} levels to acceptable levels. In my opinion, the potential risks can not be managed by labeling (because of uncertainty with regard to optimal dosing) or other means.

3. Clinically Relevant Issues from Other Discipline's Reviews:

Clinical pharmacology and biopharmaceutics: The clinical pharmacology reviewer concluded that "this NDA is not acceptable to OCPB based on the fact that the high maximal (C_{max}) serum testosterone levels (observed in a significant number of patients) make this product supra-physiologic in term of testosterone replacement, and may not mimic the true endogenous profile of serum testosterone. Moreover, within the scope of the limited phase 3 clinical trial, elevated serum testosterone levels could be correlated to a decrease in HDL and increasing hematocrits." Furthermore, "based on the results from in vitro formulation screening studies, the sponsor may not have optimized the formulation prior to conducting clinical studies, since the final formulation used showed considerably high serum testosterone levels even at steady state. The phase 2 dose finding study was complicated in design with a very small number of patients on each dose/regimen. It appears that the sponsor did not optimize the dose based on all essential PK information resulting in selection of a sub-optimal dose/regimen or formulation, or both."

Pharmacology/toxicology: "Based on extensive pre-clinical published literature available on the safety of testosterone and clinical experience with testosterone in various formulations for the same indication as for the proposed testosterone gel, Pharmacology recommends approval of NDA 21-463" for Fortigel.

Biometrics: The statistical reviewer concluded that a written statistical review is not needed. "A single principal study (T-00-02-01) supports efficacy. This is an open label, uncontrolled study. Efficacy is based on percentage of patients who achieve and maintain pre-defined average and minimum testosterone concentration levels. Study results are descriptive only."

Chemistry: The chemistry reviewer concluded that "this application is recommended for approval from a Chemistry, Manufacturing, and Controls point of view." Post-marketing commitments were agreed to by the sponsor: 1) The criteria for density and viscosity will be re-evaluated after 20 batches are manufactured. 2) The specifications for *in vitro* release testing will be set within 6 months of approval. The criteria will also be re-evaluated after 20 batches.

4. Efficacy Summary:

A. Design and conduct of Phase 3 trial: One phase 3 study was submitted to support efficacy ("A Phase 3 evaluation of CP601B (testosterone gel) in hypogonadal males" (Protocol **T 00-02-01**; Clinical Study Report T 00-03-01)

This was a multicenter (19 US sites), open-label, non vehicle-controlled trial in which hypogonadal men were treated with CP601B (Fortigel) for 182 days. All patients began treatment using 3g gel (60 mg testosterone applied to the skin) each day. A 24-hour pharmacokinetic profile was obtained after application of the first dose and on Day 14. Depending upon the testosterone concentrations measured on Day 14, the patient's dose was either changed to 2g gel (40 mg testosterone) or 4g gel (80 mg testosterone) on Day 28 or the dose remained unchanged (dose change criteria are defined below). The patient continued once daily application of the dose assigned on Day 28 for the remainder of the study. Follow-up visits occurred on Days 42, 56, 70, 98, 140, and 182. The 24-hour pharmacokinetic profile was repeated on Day 42 for patients who continued using 3g gel after the Day 28 visit, and on Day 56 for patients who were changed to 2 or 4g gel on Day 28. A final 24-hour pharmacokinetic profile was performed on Day 182. Patients who completed the study through Day 182 could participate in a 12-month extension study to assess long-term safety.

The 24-hour pharmacokinetic profile obtained on Day 14 was used to determine the final dose of testosterone which was decided upon on Day 28. The testosterone dose could be modified at Day 28 as follows:

If the minimum serum concentration (C_{min}) of testosterone measured in the 14 Day samples were <300 ng/dL and the maximum serum concentration (C_{max}) were <1000 ng/dL, the patient's dose was increased to 4g gel (80 mg testosterone) daily.

If the C_{min} were >400 ng/dL and C_{max} were >1000 ng/dL, the dose was decreased to 2g gel (40 mg testosterone) daily.

If C_{min} were >300 ng/dL and C_{max} were <1140 ng/dL, the dose was to be maintained at 3g gel daily.

If the testosterone concentrations did not meet any of the above criteria, a Cellegy Medical Monitor was to make a decision about the dose adjustment.

Originally 80 patients were planned for the 3g group, with a "undisclosed" number for the 2 and 4g groups. Two hundred patients enrolled and received CP601B, including one patient who enrolled twice; these 200 patients made up the intent-to-treat group.

CP601B contains 20 mg testosterone USP/g gel. A total of 3g of gel (60 mg testosterone) was applied once daily in the morning after the only bath or shower allowed each day. Half the dose (1.5g gel; 30 mg testosterone) was rubbed on a 150 cm^2 area of skin on one anteromedial thigh, and half on the contralateral thigh. Patients whose doses were decreased to 2g of gel once daily applied 1g (20 mg testosterone) on each thigh. Patients whose doses were increased to 4g gel once daily applied 2g (40 mg testosterone) on each thigh. For all dose levels, 1g of gel was applied over a 100 cm^2 area of skin. Following approval of amendment 1, patients were requested to change the location of the application sites on the anteromedial thighs (not lateral thighs or scrotum) in an attempt to minimize potential irritation from daily applications to the same site. The patient was instructed to wash his hands with soap and hot water after applying the gel.

Efficacy of CP601B was determined through measurement of serum testosterone concentrations. Bioactive testosterone (BAT), dihydrotestosterone (DHT), sex hormone binding globulin (SHBG), estradiol (E_2), follicle stimulating hormone (FSH), and luteinizing hormone (LH) were also measured. In a subset of patients who had not been treated previously with testosterone products and who were evaluated at sites with the appropriate equipment, bone mineral density (BMD) of the hip and lumbar spine was measured at baseline and after 182 days of treatment.

Safety was evaluated by adverse events, protocol-specified assessment of application site reactions, measurements of vital signs, clinical laboratory test results, physical examination findings, and EKG's.

At each visit to the study site, the investigator was to grade the sites of CP601B applications as follows:

Grade	Description of Application site
0	Normal skin; no erythema
1	Questionable erythema not covering entire site
2	Definite erythema covering entire area
3	Swelling or induration and definite erythema
4	Blister formation and/or necrosis

Blood and urine samples were to be obtained during the screening period and at the Day 92 and Day 182 visits. Hematology tests included hemoglobin, hematocrit, WBC count and platelet count. Chemistry tests included creatinine, uric acid, total cholesterol, LDL cholesterol, VLDL cholesterol, HDL cholesterol, alkaline phosphatase, BUN, chloride, glucose, potassium, sodium, SGOT, and SGPT. A PSA and urinalysis were also obtained. Hematocrit concentrations were also to be measured prior to each 24-hour pharmacokinetic profile. A 12-lead EKG was performed at screening and at Day 182.

Inclusion/exclusion criteria: Important inclusion criteria included 1) men aged 18 to 75 years and 2) primary or secondary hypogonadism, defined as a serum testosterone concentration <250 ng/dL in a single blood sample or <300 ng/dL in two consecutive samples obtained at least one week apart during the screening period.

B. Efficacy:

Primary and secondary endpoints:

Primary endpoint: The primary efficacy variable is the proportion of patients with both C_{min} and C_{avg} within the physiologic range (300 to 1140 ng/dL) on Day 42/56.

Secondary endpoints: Secondary efficacy variables included:

1) proportion of patients with C_{avg} within the physiologic range (300 to 1140 ng/dL on Day 42/56
2) proportion of patients with both C_{min} and C_{avg} within the physiologic range (300 to 1140 ng/dL) on Day 182
3) proportion of patients with C_{avg} within the physiologic range (300 to 1140 ng/dL) on Day 182

Two efficacy analysis populations were defined for the primary efficacy analysis on Day 42/56. The ITT population (N=200) included all patients who were enrolled and received study drug and the EE population (N=89) included patients who met key enrollment criteria and were compliant with study requirements. The EE population was defined as those patients who: 1) used at least one dose of study drug 2) met the criterion for hypogonadism based on serum testosterone levels at screening 3) had no more than one missing time point on Day 1 and full PK profiles for the other two 24-hour PK evaluations (Days 14 and 42/56) during the treatment period without loss of a sample 4) had an adjustment to study drug dose in accordance with the protocol-specified criteria 5) used at least 70% but no more than 130% of the prescribed amount of study drug between Day 1 and Day 42/56 and 6) did not use prohibited concomitant medications **The EE population was defined by the sponsor as the primary analysis population.** Because of the strict definition of the EE, a large number of patients were excluded, many with only minor deficiencies (e.g. missing one sample from a 24- hour PK analysis). The sponsor believes that there is need for a population that would not include patients

who discontinued prior to Day 42/56, yet would be less restrictive than the EE population. Consequently, a MITT (modified ITT) population (N=163), which "was composed of all patients who participated in the study up to the Day 42/56 assessment, regardless of any other criteria." The MITT group is defined in the protocol as "all subjects who used at least one dose of study drug and had more than one PK sample obtained during the 24-hour PK profile on Day 42/56." The sponsor believes that this MITT group provides a more accurate assessment of the success of the dose-adjustment scheme than allowed by the ITT population.

Primary efficacy analysis:

Of the 89 EE patients, 37 (41.6%) had testosterone concentrations on Day 42/56 which met the criterion specified for the primary endpoint, i.e., C_{avg} and C_{min} within the physiologic range of 300-1140 ng/dL. The sponsor notes that "this rate was higher than the historical point estimate (35%) selected for this analysis." Additionally, the lower bound of the 95% CI (31.3, 51.8) was higher than the CI lower bound for the historical point estimate (20%).

When the analysis is based on the MITT population (N=163), 68 (41.7%) met the primary endpoint. The 95% CI was 34.1%-49.3%. The lower bound was higher than the 20% historical point estimate.

For the ITT population (N=200), 34% of patients met the primary endpoint. The lower bound of the 95% CI was 27.4%.

Secondary efficacy endpoints:

C_{avg} within the physiologic range at Day 42/56: Eighty of the EE patients (89.9%) had C_{avg} values within the physiologic range on Day 42/56. The 95% CI was 83.6%-96.2%. In the MITT population, 150 of 163 patients (92%) had C_{avg} within the physiologic range. In the ITT population, 75% of patients met this criterion with a lower bound of the 95% CI of 69%.

Proportion of patients with both C_{avg} and C_{min} within the physiologic range on Day 182: Fifty percent of the 62 EE patients had both C_{avg} and C_{min} in the normal range on day 182. Corresponding percentages for the MITT and ITT populations were 40.5% and 28.1%. The lower bound of the 95% CI for the ITT population was 21.3%.

Proportion of patients with C_{avg} within the physiologic range on Day 182: Fifty-nine of the 62 EE patients (95.2%) and 109 of the 116 MITT patients had C_{avg} within the physiologic range on Day 182. In the ITT population, 65.3% of patients had C_{avg} within the normal range and the lower bound of the 95% CI was 58.0%.

Efficacy summary: The agreed upon primary endpoint was achieved in the phase 3 trial. Cavg values within the normal range were achieved by approximately 90% of patients and varied slightly between the variously defined patient populations. I

believe that Fortigel is effective for the treatment of men with primary or secondary hypogonadism.

5. Safety Summary:

A. Extent of Exposure

Data presented in the Integrated Summary of Safety is drawn from a total of 325 patients enrolled in 6 completed studies (the single phase 3 pivotal study and 5 completed Phase 1/2 studies, all open-labeled) conducted in the United States. The 325 patients included 18 in a non-vehicle-controlled, randomized, 7 treatment regimen, 3-way, 3-period, matrix-type crossover study (T 98-02-01), 7 in a non-vehicle-controlled, randomized, 2-treatment, 2-period crossover study (T 00-02-03), 12 in a non-vehicle-controlled, randomized, 3-treatment with different area sizes, 3-period crossover study (T 00-02-07), 15 in a non-vehicle-controlled, randomized, 3-treament with different locations, 3-period, crossover study (T 00-02-08), 72 in randomized, 3-treatment with vehicle only, parallel groups study (T 00-02-09), and 201 in the pivotal Phase 3 study (T 00-02-01). The patient population in the single phase 3 trial reflects the probable marketing exposure. The extent of exposure is shown in Table 3.

Table 3 Extent of Exposure to CP601B by dose level for Phase 3 and Phase 1 / 2 studies: All enrolled patients

	Phase 3 study CP601B			Phase 1 / 2 study CP601B			
	40 mg T in 2g 2% gel	60 mg T in 3g 2% gel	80 mg T in 4g 2% gel	10 mg T in 1g 1% gel	20 mg T in 2g /1g 1%/2% gel	40 mg T in 2g 2% gel	60 mg T in 3g 2% gel
Days on therapy							
1-7 (WK 1)	0	8	0	13	7	9	9
8-14 (WK 2)	0	5	0	2	9	0	7
15-21 (WK 3)	0	5	0	0	0	0	0
22-28 (WK 4)	0	4	0	0	0	12	12
29-60 (Mon. 2)	1	13	6	0	0	0	0
61-90 (Mon. 3)	2	2	1	0	0	0	0
91-120 (Mon. 4)	1	2	1	0	0	0	0
121-150 (Mon. 5)	1	5	2				
151-186 (Mon. 6)	15	46	42	0	0	0	0
187-223 (Mon. 7+)	12	13	17	0	0	0	0
Total patients	32	201	69	15	16	21	28
Mean±SD	173.1±40.9	126.8±74.5	168.7±42.8	7.5±2.86	10.8±3.49	16.7±8.62	16.0±7.52
Median	184.5	180.5	183.6	7.0	12.5	24.0	14.0
Range	43.0±223.0	1.0-211.0	37.0-207.0	3.0-14.0	7.0-14.0	7.0-24.0	7.0-24.0
Missing	0	3	0	0	0	0	0
Amount of CTM (g of Gel)							
N	32	99	68	13	13	42	51
Mean±SD	340.1±99.8	317.±203.2	548.±173.7	6.1±1.28	8.6±3.32	14.1±3.05	20.9±7.83
Median	354.3	375.0	586.1	6.2	6.4	13.2	18.4
Range	92.6-495.0	2.8-764.6	86.6-994.2	2.2-7.2	5.7-13.4	11.0-25.4	7.2-43.0
Missing	0	4	1	0	0	0	0

B. Safety evaluation of single phase 3 study (T 00-02-01):

The only relatively long term safety data of particular relevance to a testosterone gel preparation is contained in Trial 00-02-01 and its extension Trial 00-03E-01.

Extent of exposure in Trial 00-02-01:

The ITT population in Trial 00-02-01 consisted of 200 patients (this number is also reported at times to be 201 because one patient actually was enrolled twice). The mean pre-treatment serum testosterone concentration was 204.0±118.68 ng/dL. Demographic characteristics of the patients are shown in Table 4.

Table 4. Demographic and baseline characteristics (Study T 00-02-01)

	Day 42/56 ITT (N=201)	Day 42/56 MITT (N=163)	Day 42/56 EE (N=89)
Age			
< 55	112 (55.7)	92 (56.4)	53 (59.6)
≥ 55	89 (44.3)	71 (43.6)	36 (40.4)
Mean±SD	53.2±11.47	53.2±11.22	51.8±11.52
Median	53.0	53.0	53.0
Range	19.0-74.0	19.0-74.0	19.0-74.0
Race			
Caucasian	169 (84.1)	135 (82.8)	77 (86.3)
Black	27 (13.4)	24 (14.7)	10 (11.2)
Asian	1 (0.5)	1 (0.6)	1 (1.1)
Hispanic	4 (2.0)	3 (1.8)	1 (1.1)
Other	0 (0.0)	0 (0.0)	0 (0.0)
Weight (kg)			
Mean±SD	102.2±21.56	102.5±22.42	101.2±22.11
Median	99.9	99.9	98.1
Range	56.8-202.9	56.8-202.9	64.1-202.9

The number of patients using the three dose levels at each evaluation time is shown in Table 5.

Table 5. Number of patients in each dose level by time point

Time point	40 mg T	60 mg T	80 mg T	All
Day 1	0	201	0	201
Day 14	0	188	0	188
Day 28	32	76	69	177
Day 42/56	30	71	63	164
Day 70	28	65	50	153
Day 98	26	59	42	127
Day 140	26	56	36	118
Day 182	24	53	36	113
Total patients at any time point	32	201	69	201

The mean duration of exposure was 131.8 days. The duration of exposure was highest among those patients using a final dose of 2g (166.8 days). The mean duration of exposure was 122.3 days for the 3g group and 129.1 days for the 4g group.

Patient withdrawal

Thirty-four of the 253 subjects (13.4%) in the safety population discontinued study drug due to a treatment-emergent adverse event. Thirty-three patients (33/201, 16.4%) from the pivotal Phase 3 study and 1 in the Phase 1/2 studies were withdrawn. Application site reactions (ASRs) accounted for 20 (20/33, 61%) of the discontinuations in the phase 3 study and consisted of erythema (11 patients), pruritis (11 patients), xerosis (6 patients), rash (5 patients), and paresthesia (4 patients). None of the ASRs were assessed as serious. Most of the patients withdrawn for application site reactions were discontinued during the first month of therapy. The non-application site reactions most commonly leading to discontinuation were cardiac-related (4 patients). In addition, three patients discontinued due to erythrocytosis.

Serious adverse events:

Deaths: No deaths occurred during the study.

Serious adverse events: Eleven patients in Trial 00-02-01 experienced serious adverse events. Two of these patients had SAE's which occurred either before administration of study medication or more than 14 days after completion of the study. Narratives for the remaining 9 patients with SAE's are as follows:

Patient 010-103 (dyspnea, chest pain, right heart failure, and arrhythmia) This 64-year-old man had a history of rheumatic fever followed by CHF, depression, hypertension, erectile dysfunction and seasonal allergies. He began 3g testosterone/day on September 18, 2000. On (b) (6), he experienced shortness of breath. A chest x-ray was consistent with CHF. He was admitted to the hospital. The event resolved. The investigator believed the event to be possibly related to study medication. Medications included naproxen, lisinopril, paroxetine, and aspirin. On Day 42, the testosterone C_{max} was 2453 ng/dL. I agree that relationship to study drug is possible.

Patient 011-109 (apnea, dehydration, pain) This 63-year-old man had a history of mild obstructive sleep apnea. He had been administering study medication (40 mg/day) beginning August 26, 2000. On (b) (6), he experienced dehydration and pain following planned surgery for sleep apnea. The events resolved and he continued on study medication. The testosterone C_{max} on Day 56 was 1664 and on Day 182 was 1618 ng/dL. The investigator believed that the events were not related to study medication. I agree that the event is not related to study medication. Sleep apnea is associated with testosterone administration.

Patient 014-106 (abdominal pain) This 46-year-old man had no significant past medical history. He had been receiving study drug beginning August 24, 2000. On (b) (6) he was hospitalized with a 4 day history of diarrhea and abdominal pain. A diagnosis of diverticulitis was made on CT scan. The testosterone C_{max} on Day 42 was 1670 and on Day 182 was 1042 ng/dL. The event resolved and the investigator believed that it was not related to study medication and I agree.

Patient 014-114 (chest pain) This 54-year-old man had a history of hyperlipidemia, myocardial infarction, and quadruple bypass surgery. He had been on 60 mg study drug since September 1, 2000. On (b) (6), he was hospitalized with chest and shoulder pain. Cardiac catheterization and stent placement was performed on (b) (6) The event resolved and the patient was withdrawn from the study. The testosterone C_{max} on Day 42 was 2270 ng/dL. The investigator believed that the event was not related to study medication. I believe this event is unlikely due to study medication.

Patient 014-118 (blood dyscrasia) This 63-year-old man had no significant past medical history. He began 60 mg study drug on September 16, 2000. On March 20, 2001, at the week 26 visit, his hemoglobin/hematocrit were 18.4 and 56.9. Study medication was withheld and he was placed on aspirin. Subsequent laboratory tests showed a H/H of 18.3/53.5 on March 30 and 17.1/53.5 on April 23, 2001. The testosterone C_{max} on Day 42 was 1092 and on Day 182 was 729 ng/dL. The investigator believed that the event was "possibly" related to study drug. I believe that this event is probably related to study drug.

Patient 014-137 (blood dyscrasia) This 54-year-old man had no significant past medical history. He had been administering 80 mg of study drug beginning January 13, 2001. On April 18, 2001, (week 14), his H/H were 18.2/54.0. Study medication was withdrawn and he was placed on aspirin. He was withdrawn from the study and the outcome of the event is unknown. The testosterone C_{max} on Day 42 was 629 ng/dL. The investigator considered the event as "possibly" related to study medication. He was taking no concomitant medications. I believe that this event is probably related to study drug.

Patient 014-141 (dyspnea) This 41-year-old man had a history of hypertension, CHF, myocardial infarction, and double bypass cardiac surgery. He began 60 mg study drug on January 5, 2001. On (b) (6), he was hospitalized with shortness of breath and was diagnosed with congestive heart failure. He improved, but was discontinued from the study. Testosterone C_{max} on Day 14 was 491 ng/dL. The investigator rated the event as "not related" to study drug. Concomitant medications included digoxin, furosemide, auinapril, omeprazole, spironolactone, atorvastatin, and glyburide/metformin. I believe that relationship to study drug is possible.

Patient 020-110 (kidney tubule disorder) This 66-year-old man had a history of hypertension. He had administered study drug (3g) for 4 weeks and then 4g beginning December 11, 2000. On (b) (6), he experienced a lacerated artery with peritoneal bleeding during outpatient stent placement to correct renal artery stenosis. Emergency surgery to repair the renal artery was performed. The event resolved. Study drug was withheld from May 3, 2001 and restarted on May 11, 2001. Testosterone C_{max} was 914 on Day 56 and 935 ng/dL on Day 182. The investigator considered the event to not be related to study drug and I agree.

Patient 022-103 (erythrocytosis) This 60-year-old man had a medical and surgical history of vertigo, tinnitus, back pain, seasonal allergies, impotence and decreased libido, obesity, cholecystitis, nocturnal enuresis, headache and numerous surgeries. He

had been administering study drug (4g) since 10/15/2001. Concomitant medications included acetaminophen and diphenhydramine. Serial hemoglobin (14.0-18.0 g/dL normal range) and hematocrit (42-52%) values were as follows:

Assessment	Hemoglobin (g/dL)	Hematocrit (%)
Baseline (09/14/2001)	15.7	48.0
Week 14 (01/31/2002)	18.9	56.7
Week 14 repeat (02/05/2002)	19.1	58.4
Week 26 (04/24/2002)	18.2	53.7
Follow-up (/5/10/2002)	15.4	Not reported

He completed the 6-month study and entered the extension phase on 04/26/2002. Polycythemia was diagnosed on 04/30/2002. Study drug was discontinued on 05/02/2002 and phlebotomy was performed on 04/30/2002 and again on 05/03/2002. Hemoglobin and hematocrit returned to normal on 05/10/2002 at follow-up. The testosterone C_{max} was 2913 ng/dL on Day 56. The investigator considered the event to be "possibly" related to study drug. I believe that the event is probably related to study drug.

The following additional 5 subjects experienced serious adverse events during the extension phase of the phase 3 trial:

Patient 001-131 (bowel obstruction) This 74-year-old Caucasian man had a medical and surgical history of colitis, colon polyps, hives, gout, ED and appendectomy. He began treatment with study medication in the extension phase on 08/18/2001. The dose of study drug at onset of the SAE was 3 g. Concomitant medications included probenecid, colchicine, and sildenafil. About (b) (6) after starting study medication in the extension phase (b) (6), he experienced sudden onset of severe, left lower abdominal pain accompanied by nausea and vomiting. He was admitted to the hospital and CT scan was consistent for small bowel obstruction. The plain film the next day excluded the possibility of an obstruction. He was treated with intravenous medication and discharged on the same day. The event was considered resolved. Study drug was withheld during the 2-day hospitalization and restarted at the previous dose. Testosterone C_{max} was 2189 on Day 42 and 1921 ng/dL on Day 182.The investigator considered the event to not be related to study drug and I agree.

Patient 002-105 (deep vein thrombosis) This 74-year-old Caucasian male had a history that included hypertension, panhypopituitarism, and scoliosis. He began treatment with study medication in the extension phase on 08/08/2000 with dose of 2g gel. Concomitant medications included potassium, hydrochlorothiazide, and lisinopril. The patient developed a DVT in the left leg in Dec. 2000 (approximately 5 months after entering the extension phase) which did not required hospitalization. On (b) (6) he experienced pain and warmth in his right leg, was diagnosed with DVT, and hospitalized. The hematocrit was 52.4% in the ER compared with 48.7% 7 months earlier (02/10/2001). The DVT improved by

subcutaneous enoxaparin and oral warfarin and he was discharged. Study medication was discontinued due to the event on 09/20/2001. The testosterone C_{max} was 3416 on Day 56 and 1882 ng/dL on Day 182. The investigator considered the DVT to be severe in intensity and possibly related to the study medication and I agree.

Patient 006-116 (myocardial infarction) A 51-year-old Caucasian male had a medical and surgical history of type 2 diabetes mellitus, hypertension, hyperlipidemia, seasonal allergies, depression, alcoholism, subdural hematoma, testicular surgery, and appendectomy. He had been administering study drug with a dose of 3g in the extension study since 09/24/2001. Concomitant medications included pioglitazone, rosiglitazone, loratadine, metformin, and paroxetine. (b) (6) days after starting study drug (b) (6), he experienced chest pain and the ECG confirmed a myocardial infarction. He was hospitalized and underwent stent implantation. He was discharged (b) (6). Study medication was withheld during hospitalization and then resumed. Testosterone C_{max} on Day 182 was 915 ng/dL. The investigator considered the MI to be mild and unrelated to study medication and I believe that relationship to study drug is unlikely.

Patient 014-133 (back pain, difficulty walking) This 53-year-old Caucasian male had a medical and surgical history including spinal fusion back surgery, renal transplantation, hypertension, coronary artery bypass graft, diabetic dermopathy, stasis dermatitis, hypercholesterolemia, hypertriglyceridemia, diabetes, obesity, gastroesophageal reflux, nephropathy, right great toe amputation, below the knee amputation (left leg), carpal tunnel syndrome, gout, peripheral neuropathy, glaucoma, and retinopathy. He had been administering study drug (3g) in the extension phase since 12/02/2000. Concomitant medications included aspirin, atorvastatin, azathioprine, cyclosporin, dorzolamide/timolol ophthalmic solution, furosemide, gemfibrozil, insulin, latanoprost, losartan, prednisone, ranitidine and TMP/SMZ. At an unspecified time during the study period, he had complaints of back pain and difficulty walking. An MRI indicated the presence of a herniated disc. He was admitted to the hospital for a lumbar fusion and discharged 5 days later with improvement. He continued on study medication. Testosterone C_{max} on Day 182 was 401 ng/dL. The investigator believed that the events were severe but not related to study medication and I agree.

Patient 021-105 (*Staph* infection to wound of right foot) This 49-year-old Caucasian male had a history of type 2 diabetes mellitus, diabetic nephropathy, diabetic neuropathy, diabetic retinopathy, hypertension, hyperlipidemia, coronary artery disease, coronary artery bypass graft, systolic murmur, impotence, bilateral Dupuytren's contractures, trace edema, generalized muscle aches, uvulopalatopharyngoplasty, and sleep apnea corrected by surgery. He had been administering study drug (3g) since 12/15/2000. Concomitant medications included quinapril, aspirin, hydrochlorothiazide, gemfibrozil, simvastatin, glimepiride, and ibuprofen. More than 7 months after starting the extension phase (01/22/2002), a blister formed on the patient's right foot (between 4th an 5th toes) and ruptured (b) (6) with drainage from the site. The patient's right lower leg, ankle, and foot were red and swollen the next day and further deteriorated over the next 2

days. He was hospitalized (b) (6) and treated and the event resolved. The culture from the wound grew Staphylococcus. Study drug was withheld starting 01/30/2002 and then resumed 02/13/2002. Testosterone C_{max} was 1554 on Day 42 and 960 ng/dL on Day 182. The investigator believed the event to be severe but not related to study drug and I agree.

Frequent adverse events:

One hundred sixty of the 201 patients (80%) experienced at least one AE at some time during the study. The maximum severity of any event was mild or moderate in 92% of those patients with adverse events and severe in 8% of patients. The most commonly occurring AE's were application site reactions which were reported for 49.8% of patients. The other adverse events which occurred in >5% of patients were infection (8.0%), flu syndrome (6.5%), headache (5%), sinusitis (8.5%), pharyngitis (7.0%), peripheral edema (5.5%), and hypertension (5.0%).

Adverse events which occurred in between 2% and 5% of patients were: accidental injury, pain, back pain, asthenia, chest pain, rhinitis, hyperglycemia, gynecomastia, prostatitis, increased PSA, depression, diarrhea, nausea, diarrhea, dizziness, and erythrocytosis. One patient developed deep vein thrombophlebitis.

Besides application site reactions, those events considered by the investigator as being related to study drug in > 1% of patients were: hypertension (3%), asthenia (2%), blood dyscrasia (2%), gynecomastia (2%), eosinophilia (1.5%), headache (1.5%), peripheral edema (1.5%), hirsutism (1.0%), insomnia (1.0%), nervousness (1.0%), PSA increased (1.0%), and xerosis not at the application site (1.0%).

Adverse events known to be related to testosterone administration:

Gynecomastia: Four patients developed gynecomastia or breast tenderness. Two patients developed gynecomastia (1 taking 60 mg and 1 taking 40 mg T) and one patient experienced worsening previous gynecomastia (40 mg T). One patient taking 60 mg T developed left breast tenderness. None of these patients had persistently high estradiol levels, but 3 of them were obese.

Erythrocytosis: Five patients had elevated hematocrit levels (014-118 and 014-137), elevated hemoglobin levels (002-115), or both (018-115 and 022-103) which were reported as adverse events by the investigator. Patients 018-115 and 022-103 had testosterone C_{max} levels of 2436 and 2913 ng/dL , respectively, on Day 182. Patient 014-137 had a baseline hematocrit of 53.3% which was above the upper limit of normal. The onset of elevated hemoglobin and/or hematocrit occurred anytime from Day 36 to Day 186 while the patients were using either 3g gel (3 patients) or 4g gel (2 patients). None of the patients reported symptoms associated with the increased hemoglobin/hematocrit. Three patients were discontinued from the trial because of elevated hemoglobin/hematocrit levels. The outcome of the 5 patients was resolution in 2, unchanged in 2 and the other patient was lost to follow-up. The highest recorded hematocrit in these 5 patients was 58.6 % (#018-115). None of the participants reported neuro-occlusive symptoms in association with the increase in hematocrit. The sponsor

further reported that 12 other patients had increased hematocrit or increased hemoglobin level above the ULN at the end of treatment but these were not considered to be adverse events.

Hemoglobin levels in patients treated with CP601B for 6 months increased by 0.5±1.3 g/dL (3.3%). Only 2 patients (2/190, 1.1%) with Hb concentrations within the normal range at baseline developed treatment-related Hb concentrations above the upper limit of normal (ULN). Of these 2 patients, 1 had a C_{max} > 1140 ng/dL, and the other did not. The sponsor concluded that these limited data suggest that elevation of peak testosterone concentrations are not related to elevations of serum hemoglobin. The mean hematocrit in patients in T 00-02-01 increased from 44.0±4.2% at baseline to 46.0±4.5% at Day 182. The 6.5% (9/139) of patients reported by the sponsor who developed hematocrit levels above the ULN was higher than the percentage of patients that developed hemoglobin levels above the ULN. In a review of the line listings, the primary medical reviewer found 15 subjects with recorded hematocrit levels above normal (Table 6):

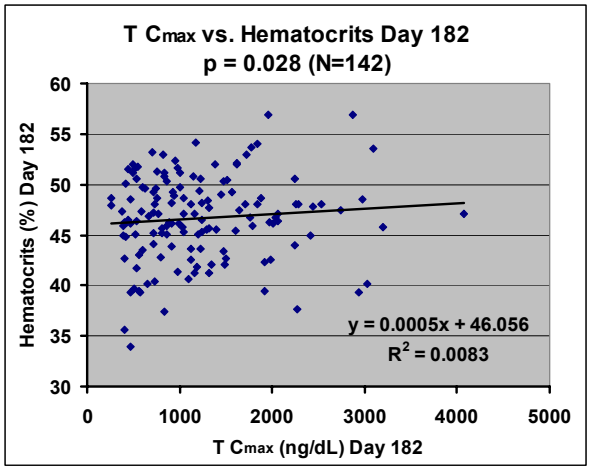
Table 6 Erythrocytosis (15 subjects had hematocrit values ranging from 52.9% to 58.6%) (#002-115, hemoglobin alone increased, is not listed)

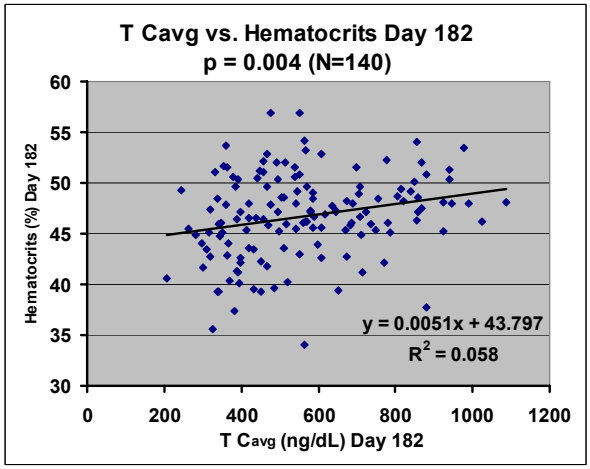
I.D.	Dose	Hematocrit (%)			Day 14		Day 42/56		Day 182		Day 1	
		Base	Day 98	Day 182	C_{max}	C_{avg}	C_{max}	C_{avg}	C_{max}	C_{avg}	C_{max}	C_{avg}
001-126	60 mg	42.4	50.0	53.5	2770	533	3713	863	3098	978	1201	580
002-104	60 mg	49.3	50.7	54.0	1255	679	1326	732	1843	856	285	235
006-100	60 mg	48.3	53.7	ND	804	413	1366	556	1378	577	248	202
006-117	60 mg	49.7	56.7	51.6	3684	920	3917	1251	1964	700	2440	824
007-106	60 mg	46.0	49.8	52.3	1655	511	1361	617	2259	778	414	327
014-106	60 mg	40.3	54.3	49.0	1965	720	1670	664	1042	587	530	365
014-118	60 mg	49.0	50.7	56.9	963	475	1092	434	729	477	156	121
014-137	80 mg	51.2	54.0	54.3	629	285	483	387	Lost follow-up		329	264
014-154	40 mg	49.3	49.4	52.9	2184	836	1123	482	1610	608	1996	781
017-129	80 mg	48.0	53.4	48.2	758	400	1375	570	1475	672	410	331
018-115	60 mg	47.8	54.8	58.6	2461	580	2259	613	Withdrawn?		3162	691
020-102	80 mg	50.3	50.5	54.2	470	361	1679	566	721	565	231	196
020-123	80 mg	44.7	48.7	53.2	1026	412	1466	631	1230	567	840	462
022-103	60 mg	48.0	58.4	53.7	398	298	2913	719	884	360	374	274
023-110	80 mg	48.6	53.0	52.9	814	360	816	448	723	468	352	260

Of the fifteen patients with increased hematocrits, 11/15 (73%) had Day 42/56 C_{max} > 1140 ng/dL and 8/13 (62%) had Day 182 C_{max} > 1140 ng/dL (#018-115 withdrew and #014-137 was lost follow-up)

In the extension study, 5/15 (33.3%) patients with C_{max} >1800 ng/dL on Day 182 had their hematocrits increased from normal to high, while similar changes in hematocrits occurred in only 6/46 (13%) patients with $C_{max} \leq 1800$ on Day 182.

The following two figures show analyses performed by the medical and clinical pharmacology reviewers and demonstrate that hematocrit levels on Day 182 and in the extension study were statistically significantly correlated with C_{max} (and nearly significant for C_{avg}) on Day 182.





These analyses show that hematocrit levels are statistically correlated with the C_{max} levels of testosterone. Although the true clinical relevance of this association is not clear, it is, in my opinion, a signal that high levels of C_{max} may produce adverse events.

Prostate disease and elevations of PSA: Nine patients had an adverse event associated with the prostate. Five patients experienced prostatitis. Two of these 5 patients with prostatitis also had elevated PSAs. Increased PSA was reported in another 2 patients; one had an enlarged prostate gland and the other had an indurated prostate noted on his exit physical examination. This patient was diagnosed with prostate carcinoma even though he had normal PSA levels. Two of these 9 patients withdrew from the study due to their events including the patient with prostate cancer. The other patient who withdrew had an elevated PSA of 20 ng/mL after 1 month of administering 3g CP601B and the event resolved (PSA fell to 0.9 ng/mL) 3 months after discontinuing treatment. The prostate –related events were classified as mild to moderate in the remaining 7 patients. In 3 patients, the

events (prostatitis, enlarged prostate with increased PSA, and indurated prostate) occurred at the end of the study, and the patients are undergoing evaluation and follow up. The other 4 cases were reported as mild and resolved with continued CP601B treatment; prostatitis was treated with antibiotics in 3 of these patients. All patients who had increased PSA levels had their PSA's return to normal by the end of the study. For the prostate carcinoma case, the investigator assessed the event as severe in intensity and possibly related to CP601B gel administration and I agree. The patient had received intramuscular testosterone for hypogonadism before participating in the study.

Additional analyses performed by the Division of changes in PSA (delta PSA) vs. serum testosterone C_{max} and C_{avg} on Day 182 did not demonstrate a statistically significant relationship between changes in PSA and either C_{max} or C_{avg} on Day 182

Changes in HDL

HDL changes are summarized in Table 7.

Table 7. Changes in HDL

	Age	Wt. 1	Wt. 2	Baseline HDL	C_{max} 42/56	C_{avg} 42/56	HDL Day98	C_{max} 182	C_{avg} 182	HDL 182	Δ HDL 182
Mean	52.9	223	223	41.03	1562	826	36.51	1218	715	37.99	-3.04
SD	10.8	44.7	42.5	12.89	927	348	10.30	722	319	10.61	9.03

Δ HDL 182 = HDL Day 182 – HDL baseline

In study T 00-02-01, the mean HDL-C concentrations were decreased by 8% (from 41.0±12.9 at baseline to 38.0±10.6 mg/dL at Day 182). The decrease (ΔHDL) was more commonly seen in those patients whose testosterone C_{max} was > 1140 ng/dL (22.8%) than those below 1140 ng/dL (15.8%). Forty percent of patients with C_{max} > 1140 ng/dL in the 12-month extension study had a decrease in HDL. A statistically significant negative relationship between HDL and testosterone C_{max} and C_{avg} was demonstrated at Day 182. As with the correlation between C_{max} and hematocrit values, the clinical significance, particularly as it relates to cardiovascular disease, of the correlation between C_{max} and HDL is not known.

Application site reactions

In the phase 3 study, patients applied the gel to the same site on the inner thighs once daily. One hundred nine of the 200 patients (54.2%) reported one or more application site reactions which were judged as possibly related or related to the testosterone gel. Twenty patients discontinued the trial due to application site reactions. Seventeen of the 20 reported the first onset of application site reaction on or before Day 28 and discontinued by Day 56. The most frequently reported application site reactions were erythema, paresthesia, pruritis, rash, and xerosis. Most of the application site reactions were classified as mild or moderate in intensity. There were no reports of skin reactions beyond the border marked by the template used to define the application area.

The severity of the application site reactions is shown in Table 8.

Table 8. Severity of application site reactions.

Preferred term	Mild	Moderate	Severe
Erythema N (%)	26 (13%)	39 (19.5%)	1 (0.5%)
Paresthesia N (%)	15 (7.5%)	6 (3.0%)	0
Pruritis N (%)	22 (11.0%)	10 (5.0%)	2 (1.0%)
Rash	6 (3.0%)	14 (7.0%)	0
Xerosis	39 (19.5%)	6 (3.0%)	1 (0.5%)

There were 4 reports of "severe" application site reactions. In 2 of the 4 patients, the adverse event resolved within 3 weeks despite continuous daily application. One of these patients had severe itching on Day 13 which resolved in 2 weeks. Another patient developed severe urticaria on both thighs that resolved in 13 days. Two other patients with "severe" reactions discontinued the study. One of these patients had severe erythema on Day 2 and discontinued 10 days later. Another patient reported severe dry skin on the application site on Day 28 and discontinued from the study.

In an attempt to reduce the incidence of application site reactions, patients were requested to rotate the application site around the inner thigh, although considerable overlap was inevitable (Protocol Amendment 1). Sixty-three patients were enrolled after the implementation of Amendment 1. The patients enrolled after Amendment 1 had a lower incidence of application site reactions than did those patients enrolled before amendment 1 (42.9% versus 55.5%). This difference is not statistically significant.

In summary, 20 of the original 200 patients who enrolled discontinued the trial because of an application site skin reaction and 4 of these reactions were rated as "severe."

6. Comments from the Office of Drug Safety and the Division of Drug Marketing, Advertising, and Communications:

The sponsor initially submitted the tradename Tostrex. DMETS did not recommend use of the proprietary name Tostrex (b) (4) The name Tostran was also not recommended for the same reasons. The sponsor then proposed the tradename Fortigel. DMETS had no objection to the use of this name and DDMAC found the proprietary name Fortigel acceptable from a promotional perspective. (b) (4)

7. Clinical Inspection Review (DSI):

Overall, "the data submitted in support of the NDA by Drs. McDavid, Meikle, and Pino appear acceptable."

Three clinical sites were inspected. At site #1, the inspection found issues related to inadequate informed consent, protocol deviation, and inadequate and inaccurate record

keeping. The inspector did not think that these observations had a significant impact upon the acceptability of the data. At site #2, no significant problems were found. At site #3, 7 patients were enrolled into the extension study before each patient completed the efficacy study and 4 patients were enrolled into the extension study before an IRB approved consent form was available at the site.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

George Benson
7/3/03 11:28:35 AM
MEDICAL OFFICER
Team leader memo

Donna Griebel
7/3/03 04:01:26 PM
MEDICAL OFFICER

NDA 21,463

Date submitted:	May 31, 2002
Date received:	June 3, 2002
PDUFA date:	July 3, 2003
Draft review completed:	June 25, 2002
Review completed:	June 30, 2003

Medical Officer Review

Sponsor:	Cellegy Pharmaceuticals Inc. 349 Oyster Point Blvd., Suite #200 South San Francisco, CA 94080
Drug Name:	**Generic:** Testosterone gel (2%) **Trade:** Fortigel™ 2% gel
Pharmacologic category:	Androgen steroid
Route of administration:	Transdermal
Dosage form:	2% gel
Strength:	20 mg testosterone USP / gm gel
Proposed indication:	Replacement therapy in men with primary or secondary hypogonadism
Related INDs:	(b) (4) [redacted]

Guodong Fang, MD
Medical Officer _____

George Benson, MD
Urology Team Leader _____

Executive Summary

I. Recommendations

A. Recommendation on Approvability

In the opinion of this reviewer, from a clinical perspective, Fortigel ™ (testosterone gel) 2% gel applied transdermally once/day should not be approved for the indication of "replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone." This recommendation is based on CFR 314.125 (b)(4): there is insufficient information about the drug to determine whether the product is safe for use under the conditions prescribed, recommended, or suggested in its proposed labeling.

This opinion is based on the fact that high maximal (C_{max}) serum T levels (observed in a significant percentage of patients) are achieved with the use of this product. Furthermore, within the scope of the limited Phase 3 clinical trial, elevated serum C_{max} T levels were statistically significantly correlated with a decrease in HDL and increasing hematocrits.

B. Recommendation on Phase 4 Studies and/or Risk Management Steps

None.

II. Summary of Clinical Findings

A. Brief overview of clinical program

Fortigel ™ 2% (testosterone gel) supplied in a 60 gram metered dose canister, is a transdermal preparation and indicated for testosterone replacement therapy in male hypogonadism, either primary (abnormalities of testicular function) or secondary (abnormal hypothalamic or pituitary regulation of testicular function). Fortigel was demonstrated to be effective for the treatment of hypogonadism and restored average serum testosterone (T) concentration (C_{avg}) to 300-1140 ng/dL in men.

Since first pass metabolic inactivation of testosterone occurs in the liver after oral administration, testosterone esters given by intramuscular administration have until recently been the mainstay of testosterone replacement therapy. Significant amounts of testosterone are absorbed and enter the systemic circulation following application to the skin in an appropriate vehicle. This observation is the basis for the development of testosterone patches and gels including Fortigel.

Overall data: The efficacy evaluation is based on one pivotal Phase 3 trial (Protocol **T-00-02-01**) described below. The safety evaluation is based on:

- One pivotal Phase 3 trial (Protocol **T-00-02-01**)
- Five completed Phase 1 /2 studies
    - Non-vehicle-controlled, randomized, 7 treatment regimen, 3-way, 3-period, matrix-type crossover study (T 98-02-01)
    - Non-vehicle-controlled, randomized, 2-treatment, 2-period crossover study (T 00-02-03)
    - Non-vehicle-controlled, randomized, 3-treatment with different area sizes, 3-period crossover study (T 00-02-07)
    - Non-vehicle-controlled, randomized, 3-treatment with different locations, 3-period, crossover study (T 00-02-08)
    - Randomized, 3-treatment with vehicle only, parallel group study (T 00-02-09)

- One transfer study (T 01-02-02)

Pivotal Phase 3 study design: In support of NDA 21,463, the sponsor submitted a single pivotal Phase 3 trial (Protocol **T-00-02-01**) conducted entirely in the United States. The study was an open label, non-placebo controlled trial which allowed dosage adjustment based on a 24-hr serum T concentration-time profile obtained following 14 days of continuous treatment. According the protocol, all patients began treatment using a once daily 3 g dose of Fortigel 2% gel (60 mg testosterone applied to the skin) for 14 days. A 24-hr pharmacokinetic (PK) profile including, minimum T concentration (C_{min}), average T concentration (C_{avg}) and maximum T concentration (C_{max}) was obtained after application of the first dose and on Day 14. Based on the testosterone (T) concentrations measured on Day 14, the patients dose was either modified to 2 g gel (40 mg T) or 4 g gel (80 mg T) on Day 28 or the dose remained unchanged. The patient continued once daily application of the dose assigned on Day 28 for the remainder of the study. Follow-up visits occurred on Days 42, 56, 70, 98, 140, and 182. The 24 hour PK profile was repeated on Day 42 for patients who continued using 3 g gel after the Day 28 visit, or on Day 56 for patients who began using 2 or 4 g gel on Day 28 (Day 42/56). A final 24 hour PK profile was performed on Day 182. Upon successful completion of the T-00-02-01 trial, all subjects were permitted to continue treatment with Fortigel in the 6 to 12-month, open label extension study (T-00-02E-01).

This NDA submission contains the 120 day safety update including final data for the 6-month primary efficacy and safety endpoints for all subjects (Day 182) and an interim abbreviated report for ongoing 12-month therapy extension.

B. Efficacy

The efficacy is based on single pivotal study T-00-02-01.

The primary efficacy endpoint in the pivotal Phase 3 trial was the proportion of subjects with both average and minimum serum testosterone concentrations (C_{avg}, C_{min}) within the physiologic range (PR) (C_{min} >300 ng/dL and C_{avg} 300-1140 ng/dL) on Day 42/56. To meet the primary endpoint, the results should exceed the lower bound of the 95% confidence interval (CI) of 20%, 15% lower than the historical point estimate of 35%. The secondary endpoints included proportion of subjects with C_{avg} within PR on Day 42/56, proportion of subjects with both C_{avg} and C_{min} within the PR on Day 182, and proportion of subjects with C_{avg} within the PR on Day 182.

To analyze the primary efficacy endpoint, the sponsor defined three different populations on Day 42/56: the Day 42/56 EE (efficacy evaluable) population: subjects who met key enrollment criteria and were compliant with study requirements, N=89; the Day 42/56 MITT (modified intend to treat) population: subjects who participated in the study up to the Day 42/56 assessment, regardless of any other criterion, N=163; the Day 42/56 ITT (intent to treat) population, all subjects enrolled who received Fortigel, N=201. **The Day 42/56 EE population was defined as the primary analysis population** since the efficacy of this study is predicated upon PK results. Because of the strict definition of EE, a large number of patients were excluded. Consequently, a MITT (modified ITT) population was defined as subjects who participated in the study up to the particular Day for assessment, regardless of any other criterion and the sponsor believes that this MITT group provides a more accurate assessment of the success of the dose-adjustment scheme than allowed by the ITT population.

Primary endpoint: The results showed that 42.7% (38/89) of the Day 42/56 EE subjects, 41.7% (68/163) of the Day 42/56 MITT, and 33.8% (68/201) of the ITT population had both C_{avg} and C_{min} within the PR of 300-1140 ng/dL. The lower bound of the 95% CI for the percentage of subjects with both C_{avg} and C_{min} within the PR was above the 20% non-inferiority margin in all three patient populations on the primary efficacy day.

Table 1 C_{avg}, and C_{min} on PK profile Day 42/56: Day 42/56 EE, MITT, and ITT population

Day 42/56 Population / Criterion	N	%	95% Conf. Int.
Efficacy evaluable population (EE, N=89)			
Patients with C_{avg} in [300 ng/dL, 1140 ng/dL] and $C_{min \geq}$ 300 ng/dL	38	42.7	(32.4, 53.0)
MITT population population (N=163)			
Patients with C_{avg} in [300 ng/dL, 1140 ng/dL] and $C_{min \geq}$ 300 ng/dL	68	41.7	(34.1, 49.3)
ITT population (N=201)			
Patients with C_{avg} in [300 ng/dL, 1140 ng/dL] and $C_{min \geq}$ 300 ng/dL	68	33.8	(27.3, 40.4)

Secondary endpoints:

1) 92% of the EE, 92% of the MITT and 75% of the ITT population had C_{avg} within the PR on the Day 42/56, the lower bound of the 95% CI for this percentage was above the 65% non-inferiority margin selected for significance in all three populations.

Table 2 C_{avg} on PK profile Day 42/56: Day 42/56 EE, MITT, and ITT population

Day 42/56 Population / Criterion	N	%	95% Conf. Int.
Efficacy evaluable population (EE, N=89)			
Subjects with C_{avg} in [300 ng/dL, 1140 ng/dL]	82	92.1	(86.5, 97.7)
MITT population population (N=163)			
Subjects with C_{avg} in [300 ng/dL, 1140 ng/dL]	150	92.0	(87.9, 96.2)
ITT population [a] (N=201)			
Subjects with C_{avg} in [300 ng/dL, 1140 ng/dL]	150	74.6	(68.6, 80.6)

2) 48.8% of the Day 182 EE, 42.5% of the Day 182 MITT and 30.8% of the ITT had both C_{avg} and C_{min} within the PR on Day 182, and the lower bound of the 95% CI for the percentage of subjects with both C_{avg} and C_{min} within the PR on Day 182 was above the 20% non-inferiority margin in all 3 populations.

Table 3 C_{avg} and C_{min} on PK profile Day 182: Day 182 EE, MITT, and ITT population

Day 182 Population / Criterion	N	%	95% Conf. Int.
Efficacy evaluable population (EE, N=84)			
Subjects with C_{avg} in [300 ng/dL, 1140 ng/dL] and $C_{min \geq}$ 300 ng/dL	41	48.8	(38.1, 59.5)
MITT population (N=146)			
Subjects with C_{avg} in [300 ng/dL, 1140 ng/dL] and $C_{min \geq}$ 300 ng/dL	62	42.5	(34.4, 50.5)
ITT population (N=201)			
Subjects with C_{avg} in [300 ng/dL, 1140 ng/dL] and $C_{min \geq}$ 300 ng/dL	62	30.8	(24.5, 37.2)

3) Over 96% of the Day 182 EE, 95% of the Day 182 MITT and 69% of the ITT subjects had C_{avg} values within the PR on Day 182. The lower bound of the 95% CI was above the 65% non-inferiority margin selected for comparison in both the Day 182 EE and MITT populations (it was below in the ITT population).

Table 4 C_{avg} on PK profile Day 182: Day 182 EE, MITT, and ITT population

Day 182 Population / Criterion	N	%	95% Conf. Int.
Efficacy evaluable population (EE, N=84)			
Subjects with C_{avg} in [300 ng/dL, 1140 ng/dL]	81	96.4	(92.5, 100.4)
MITT population (N=146)			
Subjects with C_{avg} in [300 ng/dL, 1140 ng/dL]	139	95.2	(91.7, 98.7)
ITT population (N=201)			
Subjects with C_{avg} in [300 ng/dL, 1140 ng/dL]	139	69.2	(62.8, 75.5)

All the primary and secondary endpoints were satisfied except the proportion of the ITT population with C_{avg} in PR on Day 182. Overall, Fortigel at doses of 40 mg, 60 mg and 80 mg was effective in producing C_{avg} within the normal range in the majority of hypogonadal men studied. There was some evidence that clinical parameters consistent with hypogonadism, such as bioactive testosterone (BAT), dihydrotestosterone (DHT), sex hormone binding globulin (SHBG), estradiol (E_2), follicle stimulating hormone (FSH), and luteinizing hormone (LH) and bone mineral density (BMD) of the hip and lumbar spine also improved.

C. Safety

Safety data are drawn from a total of 325 patients enrolled in the single Phase 3 pivotal study (201 ITT patients) and 5 additional completed Phase 1 / 2 studies (all are open-labeled) (124 patients) in the US. The 325 patients included 18 in a non-vehicle-controlled, randomized, 7 treatment regimen, 3-way, 3-period, matrix-type crossover study (T 98-02-01), 7 in a non-vehicle-controlled, randomized, 2-treatment, 2-period crossover study (T 00-02-03), 12 in a non-vehicle-controlled, randomized, 3-treatment with different application area sizes, 3-period crossover study (T 00-02-07), 15 in a non-vehicle-controlled, randomized, 3-treament with different locations, 3-period, crossover study (T 00-02-08), 72 in a randomized, 3-treatment with vehicle only, parallel groups study (T 00-02-09), and 201 in the pivotal Phase 3 study (T 00-02-01). The patient population in the clinical trials reflects the probable marketing exposure.

Reviewer's Comments: These studies did not provide sufficient data to make a conclusion about the safety of the product.

In the development program for Fortigel, 2 formulations were utilized, CP601 and CP601B; the difference between the 2 formulations is the use of different carbomers. CP601 included carbomer 1342 while CP601B included carbomer 1382. One of the studies (T 98-02-01) evaluated CP601 1% and 2% gel formulations; 4 other studies evaluated the CP601B 2% testosterone gel formulation (T 00-02-01, T 00-02-03, T 00-02-07, T 00-02-08). Study T 00-02-09 evaluated the vehicle component of Fortigel only without active drug.

Reported significant adverse events (AEs) included a large number related to application site reactions (ASRs). Over half (54%) of the subjects experienced ASRs in the 6 month pivotal trial (T-00-02-01). Body as a whole was the second most frequent category of AEs (27.3%) of subjects. Adverse events of special interest in patients using testosterone preparation such as Fortigel are shown in Table 5

Table 5 Adverse events (AEs) of special interest in safety population of Phase 3 and Phase 1 / 2 studies

Body system / preferred term	Number of subjects					
	Phase 3 study (N=201)[a]		Phase 1 / 2 study (N=52)		Total subjects (N=253)[b]	
	n	(%)	n	(%)	n	(%)
Subjects who died	0	(0.0)	0	(0.0)	0	(0.0)
Subjects with adverse events	160	(79.6)	26	(50.0)	186	(73.5)
Application site reactions (ASRs)	109	(54.2)	17	(32.7)	126	(49.8)
Body as a whole	63	(31.3)	6	(11.5)	69	(27.3)
Respiratory system	40	(19.9)	2	(3.8)	42	(16.6)
Hyperlipemia	4	(2.0)	0	(0.0)	4	(1.6)
Gynecomastia	5	(2.5)	0	(0.0)	5	(2.0)
PSA ↑	4	(2.0)	0	(0.0)	4	(1.6)
Hypertension	10	(5.0)	2	(3.8)	12	(4.7)
Erythrocytosis	5	(2.5)	0	(0.0)	5	(2.0)

[a] 3 subjects in study T 00-02-01 were enrolled twice, adverse events were consolidated for these subjects; therefore, the incidence of adverse events is based on the total number of unique subjects (N=201).

[b] Since subjects may be counted under more than one column, the sum of columns counts may exceed the total.

Treatment-related adverse events: The majority of the application site reactions (ASRs) (124/126, 98.4%) reported in all 5 clinical studies was assessed by the investigator as related to study drug (1% or 2% testosterone gel) administration. In contrast, the majority of treat-emergent AEs for the other body systems (155/224, 69.2%) were assessed by the investigator as unrelated to study drug application.

Reviewer's comments: **The risks of testosterone administration in hypogonadal men include erythrocytosis, induction or exacerbation of sleep apnea, breast tenderness or enlargement, liver toxicity, and acne. In addition, 2 major areas of concern and uncertainty in older men with aging-associated decline in serum testosterone are the effects of long-term testosterone administration on the risk of prostate cancer and progression of atherosclerotic heart disease. These concerns exist regarding potential adverse events in patients taking Fortigel 2% gel.**

The most common non-ASRs assessed by the investigator as treatment-related in the pivotal Phase 3 study and other clinical Phase 1 /2 studies were hypertension (12 subjects, 4.7%), erythrocytosis (6 subjects, 2.0%) and serum HDL-cholesterol reduction (29 subjects in T-00-02-01, 20.9%). All of these events are recognized potential consequences of testosterone replacement. The incidence rate of gynecomastia or breast tenderness associated with application of Fortigel (5 subjects, 2.0%) is similar to previous experience with other testosterone formulations. There were 3 patients with an elevated PSA level on Day 42/56 and one on Day 182 in the pivotal study. One patient developed prostate cancer.

In the extension safety study (T 00-02E-01) of Phase 3 trial (T 00-02-01), 34 of the 82 subjects (41.5%) experienced at least one adverse event at some time during the study period. The maximum severity of these events was mild or moderate in 26 subjects (76.5%), and severe in the other 8 subjects (23.5%) (treatment-emergent in 5 subjects). These severe events were considered unrelated to Fortigel in 5 subjects and drug-related in 3 subjects (2 with erythrocytosis and 1 with deep vein thrombosis [DVT, thrombophlebitis]) by the investigator. 14 subjects (17.1%) reported at least one treat - emergent event considered related to Fortigel during the extension study. Two subjects (2.4%) were withdrawn from the 1-year extension study because of adverse events (one with elevated hematocrits and one developed DVT).

Table 6 Summary of treat-emergent adverse events (Study T 00-02E-01)

	No. of subject (N=82)	
	n	(%)
Subjects who died[a]	0	(0.0)
Subjects with at least 1 serious treatment-emergent AE[a]	5	(6.1)
Subjects with at least 1 adverse event[a]	34	(41.5)
Subjects with at least 1 drug related adverse event[a]	14	(17.1)
Maximum AE severity reported per subject for AE (including application site reactions)[b]		
Mild	10	(29.4)
Moderate	16	(47.1)
Severe	8	(23.5)
Subjects with at least 1 application site reaction[a]	6	(7.3)
Strongest AE relation to CTM reported per subject[b]		
None	20	(58.8)
Possibly	7	(20.6)
Related	7	(20.6)
Number of subjects discontinued due to adverse event[a,c]	2	(2.4)
Numbers of subjects discontinued due to application site reaction[a]	0	(0.0)

[a] Percentage based on number of subjects in the safety population.

[b] Percentage based on number of subjects reporting adverse events.
[c] Includes subjects who discontinued due to treat-emergent adverse events.

In contrast to the initial 6-month study, only 6 subjects (7.3%) experienced treat-emergent application site reactions (ASRs). There was no apparent relationship between the incidence of ASRs and the amount of gel or testosterone applied, although the number of subjects with ASRs was small. In addition, there were no reports of the reaction spreading beyond the area of application, and more than 75% were of mild or moderate severity, and none were of significant consequence. None of the subjects discontinued therapy due to an ASR in the extension study. One subject had a significantly increased PSA value at the end of the study and was associated with prostatitis. There were 10 patients with at least one serum T concentration > 1140 ng/dL. Among these 10 patients, 40% had increased hematocrits, reduced HDL-C, increased LDL or VLDL, and increased AST or ALT. Four of them had hypertension.

High Exposure:

One of major concerns regarding potential risks in patients using Fortigel 2% gels is **high exposure**. Based on results of the pivotal Phase 3 study, this product was found to result in supraphysiologic C_{max} serum T levels in a significant proportion of the study population (normal serum total T level is 300 - 1140 ng/dL):

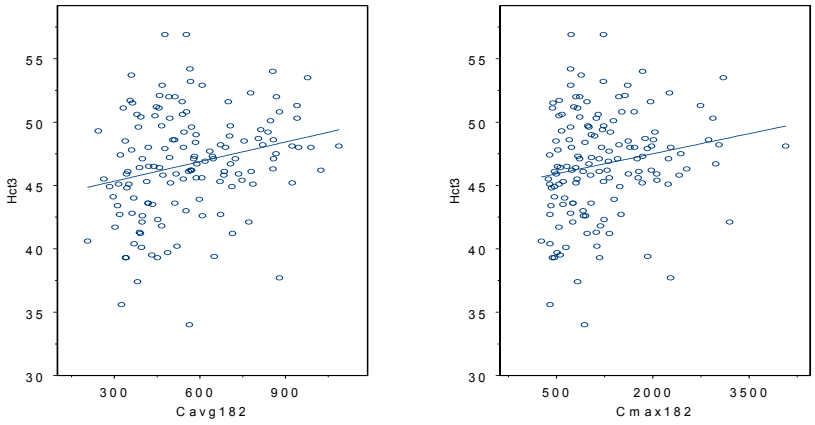
- On Day 42/56 (1 month at final dosing regimen), 5/165 (3%) patients had $\mathbf{C_{avg}}$ values > 1140 ng/dL and 1 among them had C_{avg} values > 1700 ng/dL
- On Day 42/56, 23/165 (14%) patients had C_{max} values between 1500 - 1800 ng/dL; 28/165 (17%) had C_{max} values between 1800 - 2500 ng/dL and 26 (16%) had C_{max} values between 2500 - 5311 ng/dL (3 values were > 4000).
- On Day 182, 13/147 (8.8%) patients had C_{max} values between 1500 - 1800 ng/dL; 20 (14%) had C_{max} values between 1800 - 2500 ng/dL, and 9(6%) had C_{max} >2500 ng/dL with 1 value > 4000.

Exposure – Response:

The hematocrits (Hct.) and the changes of HDL-C (ΔHDL) of patients were statistically significantly correlated with serum T C_{max}, and C_{avg} concentrations on Day 182.

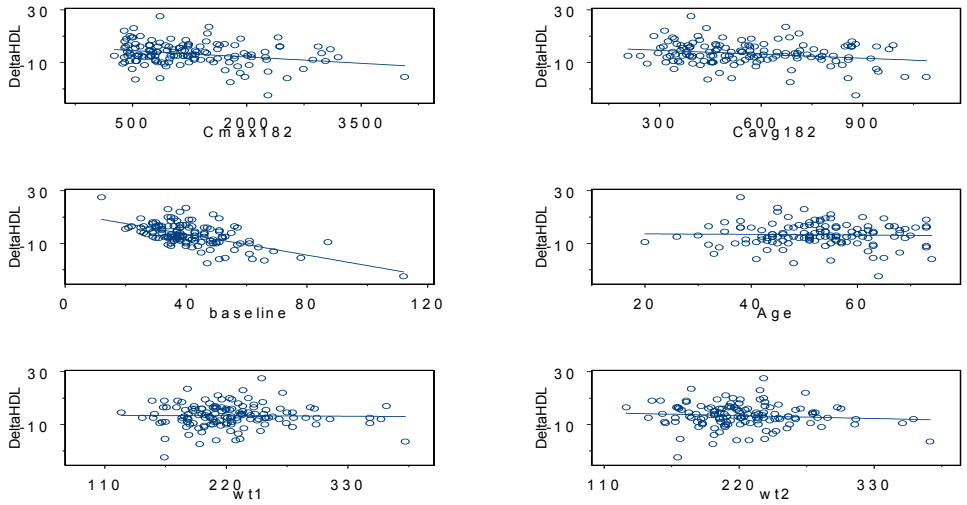
Hematocrit: There was a statistically significant trend of increasing Hct values with both increase in serum T C_{avg} ($p = 0.0042$) and C_{max} ($p = 0.0303$).

- A positive slope was found in the relationship between hematocrit and T concentration indicating increased hematocrits corresponding to an increasing T concentration C_{avg} and C_{max}) as shown below.



The changes of HDL-C (ΔHDL)

- A negative correlation between ΔHDL (defined as HDL on measurement day – baseline HDL) and T concentrations (C_{avg} or C_{max}) was apparent, a decrease in HDL corresponding to an increase in serum T concentrations.
- Regression analyses show that ΔHDL is significant in patients with higher HDL baseline values ($p<0.0001$). Statistically, body weight (at 6 months) was also correlated with a decrease in HDL.



D. Dosing, Regimen and Administration

The initial [redacted] (b) (4) of Fortigel 2% gel and dosage adjustment on [redacted] (b) (4) was selected based on results from pilot Phase 1 /2 studies. The recommended starting dose in the labeling is the same as in the pivotal Phase 3 study, but the basis for dose modification is changed to serum T concentration 2-hour post dosing (C_2) instead of [redacted] (b) (4). Despite dose adjustment, 25.3% (24/95) of patients whose dose were adjusted to either 40 mg or 80 mg have C_{max} testosterone levels > 1500 ng/dL at Day 182.

The application site of Fortigel should be allowed to dry. Hands should be washed thoroughly with soap and water immediately after Fortigel has been applied. The transfer study showed that once the hands are washed and the application site is covered with clothing, there is little risk of transferring Fortigel to someone else due to bodily contact. However, to assure adequate absorption of the testosterone, the application site should not be washed for at least two hours after gel administration.

E. Drug-drug interactions

There is no known effect of concomitant medications on the efficacy of Fortigel. No special drug-drug interactions studies were performed by the sponsor.

F. Special Populations

Gender differences: Fortigel is indicated for testosterone replacement therapy in men for conditions associated with deficiency or absence of endogenous testosterone. The drug is contraindicated in women.

Racial differences: The effect of race of pharmacokinetics has not been studied. The number of non-Caucasian patients in the clinical trials is too small (13.1%, including 10.7% for Black, 2.0% for Hispanic, and 0.4% for Asian) to draw meaningful conclusions.

Issues with elderly: The pharmacokinetics and pharmacodynamics were evaluated in pivotal Phase 3 study T 00-02-01 in 201 patients including 89 patients with age ≥ 55 (44.3%). Exposure to testosterone, represented by AUC and C_{max}, was not statistically different between age groups. The incidence of major adverse events appeared to be no different between age groups. The two main areas of concern and uncertainty in older men with aging-associated decline in serum testosterone are the effects of long-term testosterone administration on the risk of prostate cancer and progression of atherosclerotic heart disease, especially, in older men with high testosterone C_{max} levels.

Fortigel did not significantly affect PSA levels during the 6-month Phase 3 study, as only one patient had an increased PSA level at the end of the study. Increased PSA levels were also observed in 6 patients during clinical chemistry studies on Day 98 or other times. These increases were associated with prostatitis in 2 patients and PSA returned to pretreatment levels following resolution of the infection without stopping CP601B administration. Two others returned to normal upon repeat examination and the remaining 2 are still being evaluated.

Many older men have microscopic foci of cancer in their prostate glands. There are no data to clarify whether testosterone administration will make these subclinical foci of cancer grow and become clinically overt. Testosterone administration is contraindicated in men with a history of prostate cancer.

Renal/Hepatic impairment: The effect of renal or hepatic impairment on Fortigel pharmacokinetics was not evaluated.

Pediatric issues: Fortigel has not been evaluated in males less than 18 years of age. The sponsor requested a pediatric deferral until appropriate studies can be planned and completed in the pediatric population.

Pregnancy use information: Fortigel is contraindicated in women. Since testosterone may cause fetal harm, pregnant women are contraindicated to have skin contact with Fortigel application sites in men.

Clinical Review **Page**

Clinical Review

I. Introduction and Background

A. Drug Action and State of Armamentarium for Drug Therapy of Hypogonadism

Fortigel™ brand 2% Gel (testosterone gel) (CP601B 2% testosterone gel) belongs to the pharmacological class of androgenic hormones. A metered dose pump comprised of (b) (4) canister and a fixed volume pumping mechanism. The 60-g canister dispenses 500 µL of testosterone gel/pump depression. The initial dose is (b) (4) of gel, corresponding to (b) (4) of testosterone. The formulation contains eight excipients in addition to the 2% testosterone. All excipients have USA/NP monographs.

The proposed indication is "testosterone replacement therapy in male hypogonadism." The recommended dose is 2 (b) (4) g containing approximately 40, (b) (4) mg of testosterone respectively to be applied to the skin. Approximately 12% of the applied testosterone is absorbed across skin of average permeability during a 24-hr period, providing an average systemic input of approximate 7 mg testosterone per day.

B. Milestones in Drug Development

Regulatory history: IND (b) (4) (Fortigel testosterone gel) was originally filed on August 24, 1998. The clinical pre-NDA meeting was held on October 29, 2001. The NDA was filed on June 3, 2002. The goal date was extended for three months because of a major amendment received on January 30, 2003

Clinical background and important milestones in product development: Endogenous androgens, including testosterone (T) and dihydrotestosterone (DHT), are responsible for the normal growth and development of the male sex organs and for the maintenance of secondary sex characteristics. Male hypogonadism is a multi-system syndrome associated with impaired androgen production or action. Androgen deficiency can result from abnormalities of testicular function (primary hypogonadism) or hypothalamic or pituitary regulation of testicular function (secondary hypogonadism) or from impairment of androgen action at the target tissue (androgen resistance). Patients with classic primary or secondary hypogonadism are characterized by low serum testosterone concentrations (< the lower limit of the physiologic range, 300 ng/dL). Symptoms of male hypogonadism include impotence and decreased sexual desire, fatigue and loss of energy, mood depression and regression of secondary sexual characteristics. Hypogonadism is also a risk factor for osteoporosis in men. Testosterone replacement in men with primary or secondary hypogonadism is important because failure to treat androgen deficiency can have significant health consequences.

Hypogonadism has been treated with administration of exogenous testosterone since it was first synthesized approximate 60 years ago. Since marked first pass metabolic inactivation of testosterone occurs in the liver after oral administration, testosterone esters by intramuscular (I.M) administration have until recently been the mainstay of replacement therapy. Significant amounts of testosterone are absorbed and enter the systemic circulation when applied to the skin in an appropriate vehicle. This observation led to the development of testosterone patches to deliver the hormone to scrotal and non-scrotal skin, and more recently, by the use of topical testosterone gels. Theoretically, upon applying the gel to the skin, the excipients evaporate and the testosterone penetrates into the epidermis. However, the skin in general is quite variable in its transdermal delivery of the drugs to the systemic circulation. For this reason, the development of CP601B included establishing a method to allow dosage adjustment to compensate for the variability in transdermal delivery and other factors, such as body size and rate of elimination.

C. Foreign Market History

Fortigel has not been marketed outside of the United States.

D. Important Issues with Pharmacologically Related Agents

The two other pharmacologically related topical and transdermal gels approved for the treatment of male hypogonadism are

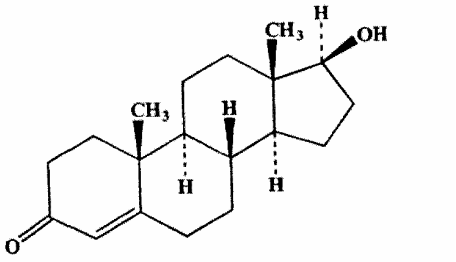
- AndroGel™- a transdermal testosterone gel
- Testim™- 1% transdermal testosterone gel

These drugs are contraindicated in women. Since testosterone may cause fetal harm, pregnant women are contraindicated to have skin contact with topical or transdermal application sites in men. The risks of testosterone administration in hypogonadal men include erythrocytosis, induction or exacerbation of sleep apnea, breast tenderness or enlargement, and acne. In addition, two major areas of concern and uncertainty in older men with aging-associated decline in serum testosterone are the effects of long-term testosterone administration on the risk of prostate cancer and progression of atherosclerotic heart disease. These concerns exist regarding potential adverse events in patients using testosterone medications.

II. Clinically Relevant Findings from Chemistry, Animal Pharmacology and Toxicology, Microbiology, and Statistics

There is no unresolved chemistry, microbiology, or statistical issues (see each discipline's complete review).

CAS number: 58-22-0
Molecular Weight: 288.42
Molecular Formula: $C_{19}H_{28}O_2$
Structural Formula:



DRUG PRODUCT COMPOSITION

INGREDIENT	% (w/w)
Testosterone, USP	2.0
Propylene Glycol, USP	(b) (4)
Ethyl Alcohol, (b) (4)	
Isopropyl Alcohol, USP	
Oleic Acid, NF	
Carbomer 1382	
Trolamine, NF	
Butylated Hydroxytoluene, NF	
Purified Water, USP	

The pharmacology / toxicology reviewer has no concerns regarding the safety of the proposed testosterone gel: "There is no safety concern for testosterone which has been approved as testosterone injection products (testosterone enanthate, testosterone cypionate); as testosterone transdermal systems (Androderm and Testoderm patches); and as topical gel (Androgel). All other components of the formulation have been used before in approved products." "Labeling review: The label is essentially similar to that of AndroGel except that results of the potential of testosterone transfer study are to be added."

III. Human Pharmacokinetics and Pharmacodynamics

The pivotal study T 00-02-01 was designed as a pharmacokinetic/exposure study that evaluated the serum T concentration-time course over a 24-hr dosing interval on Day 1 (first dose), Day 14 (steady state), Day42/56 (28 days after dosage titration) and Day 182 (after 6 months of replacement therapy). Other studies were designed to determine similar 24-hr T PK profiles following different sites of application, different surface areas of application, and showering 2 hrs after application, as well as possible transference of Fortigel to another person.

Pharmacokinetics Studies

Study name	T 98-02-01	T 00-02-03	T 00-02-07	T 00-02-08	T 01-02-02
No. subjects	18	7	12	15	16 (8 couples)
Purpose: to determine	the PK & tolerability of a single & multi. doses via different sites, doses & doing intervals	the effects of showering on the PK	1) the effects of the surface area; 2) the tolerability of multi. application	1) the PK after applying to the thighs, abdomen or upper arms; 2) tolerability of multi. doses to different sites	1) the PK of the transfer to another person after applying to the thighs, abdomen or upper arms
Type of study	**PK**, open-label, non-vehicle-controlled, 7-trt, 3-per. cross-over, matrix-type	**PK**, open-label, non-vehicle-controlled, randomized, 3-trt, 3-per. crossover	**PK**, open-label, non-vehicle-controlled, randomized, 3-trt (200, 400 or 800 cm^2), 3-per. crossover	**PK**, open-label, non-vehicle-controlled, randomized, 7-trt, 3-way, 3-per. matrix-type crossover	**PK**, open-label, non-vehicle-controlled, randomized, 7-trt, 3-way, 3-per. matrix-type crossover
Duration	7 days/dose regimen, up to 21 days total	7 days/dose regimen, up to 21 days total	8 days/dose regimen, up to 24 days total	8 days/dose regimen, up to 24 days total	3 phases (baseline, uncovered and covered exposure)

Dose selection

Based on the results of study T 98-02-01, the sponsor elected to use a regimen consisting of once-daily application of 3g Fortigel (CP601B) per 300 cm^2 as initial dose for the pivotal Phase 3 study.

Reviewer's comments: This dose finding study was *complicated in design with a small number of patients on each dose/regimen. C_{max} in eight of sixteen subjects was as high as 2500-5000ng/dL. Based on data from this as well as an in vitro study, this reviewer believes that the sponsor did not optimize the dose.*

No information is available concerning the pharmacokinetics of Fortigel in renal or hepatic impaired patients. Information regarding drug-drug interactions is limited. No drug-drug interaction studies based upon metabolic pathways have been conducted.

IV. Description of Clinical Data and Sources

The following materials were reviewed:

1) Overview section, integrated summary of safety (ISS), and the integrated summary of efficacy (ISE) from NDA
2) The pivotal 6-month phase 3 study (T 00-02-01) "A phase 3 evaluation of CP601B in hypogonadal males" with study report 00-03-01
3) A 12-month extension to the pivotal phase 3 study (T 00-02-01) with study report 00-03E-03
4) Three randomized crossover studies with evaluation of the effects of site of application (T 00-02-08), surface area of application site (T 00-02-07), and effect of showering (T 00-02-03)
5) A clinical pharmacology study (T 00-02-09) evaluating the effect of site of application and surface area of application on the incidence of CP601B vehicle-induced application site reaction (ASRs) in healthy, non-hypogonadal male and female volunteers
6) Phase 1 / 2 randomized, open-label, non-vehicle-controlled, 7 treatment regimen, 3-way, 3-period, matrix-type crossover study (T 98-02-01) (Treatment G added by amendment)
7) Sponsor submission to requests for information related to high C_{max} values (received on October 22, 2002 and May 29, 2003)

V. Clinical Review Methods

The pivotal 6-month trial and its 12-month extension trial were reviewed in detail

Adequate documentation was submitted to comply with financial disclosure. The sponsor performed adequate "due diligence" to obtain documentation from non-compliant investigators. The Phase 3 pivotal study was a multi-center (19 sites) study, with no single center enrolling significantly more patients in the study than the others. It is unlikely that the study was biased.

VI. Integrated Review of Efficacy

A. Brief statement of conclusions: The sponsor has demonstrated in the only but adequate, well-controlled pivotal study that CP601B (transdermal 2% testosterone gel) significantly increases both average and minimum serum testosterone concentrations (C_{avg}, C_{min}) (C_{min} >300 ng/dL and C_{avg} 300-1140 ng/dL) on Day 42/56 (one month after dose titration) and on Day 182 (6 months of therapy) in patients with hypogonadism. The primary and secondary endpoints are currently accepted for the Phase 3 pivotal study evaluating drug therapy for primary and secondary hypogonadism.

B. Approach to Review of Drug Efficacy

The efficacy data base consists of single pivotal Phase 3 study.

Table 7 : An Overview of Pivotal Efficacy Study

Protocol No. (Sponsor)	T 00-02-01
Investigator (s) (Country)	Multicenter – 19 sites (USA)
Start date	06/13/00
Study design	Open-label, non-vehicle-controlled
Treatment Regimen (Dose0	3g of CP601B (60 mg T applied to the skin) q.d., for 182 days; the dose might be modified at Day 29 (↑ to 4g gel [80 mg T/day] or ↓ to 2g gel [40 mg T/day]) depending on serum T concentration measured on Day 14.
Patients enrolled	204*
% Patients by sex (M/F)	100% / 0%
% Patients by race (C/B/Other)	84.1% / 13.4% / 2.5%
Mean age (Range)	53.2 (19-74)

* 3 patients enrolled twice into the study

C. Review of Clinical Trials

The pivotal Phase 3 trial was an open-label, non-vehicle-controlled, 6-month study of the efficacy and safety of 3g 2% Fortigel gel (CP601B) administered once daily in the treatment of hypogonadism. The study could extend to 12 months. Dosage adjustment on Day 29 was based on pharmacokinetic results on Day 14.

All patients started on a once daily 3 g dose of Fortigel 2% gel (60 mg testosterone applied to the skin) for 14 days. On Day 14, a 24-hour serum testosterone (T) concentration-time PK profile was obtained from each patient. Based on this profile, the final dose for each patient was determined. On Day 14:

- If C_{min} < 300 ng/dL & C_{max} < 1000 ng/dl, increase to 4 g (80 mg T)
- If C_{min} > 400 ng/dL & C_{max} > 1000 ng/dl, decrease to 2 g (40 mg T)
- If C_{min} > 300 ng/dL & C_{max} < 1140 ng/dl, continue at 3 g (60 mg T)

If the testosterone concentrations did not meet any of these criteria, a Cellegy Medical Monitor would make a decision about the dose adjustment.

Following dose adjustment (on Day 29), and after patients were treated for at least 28 days on their final dose adjustment, 2 additional PK profiles were obtained on Day 42/56 and Day 182.

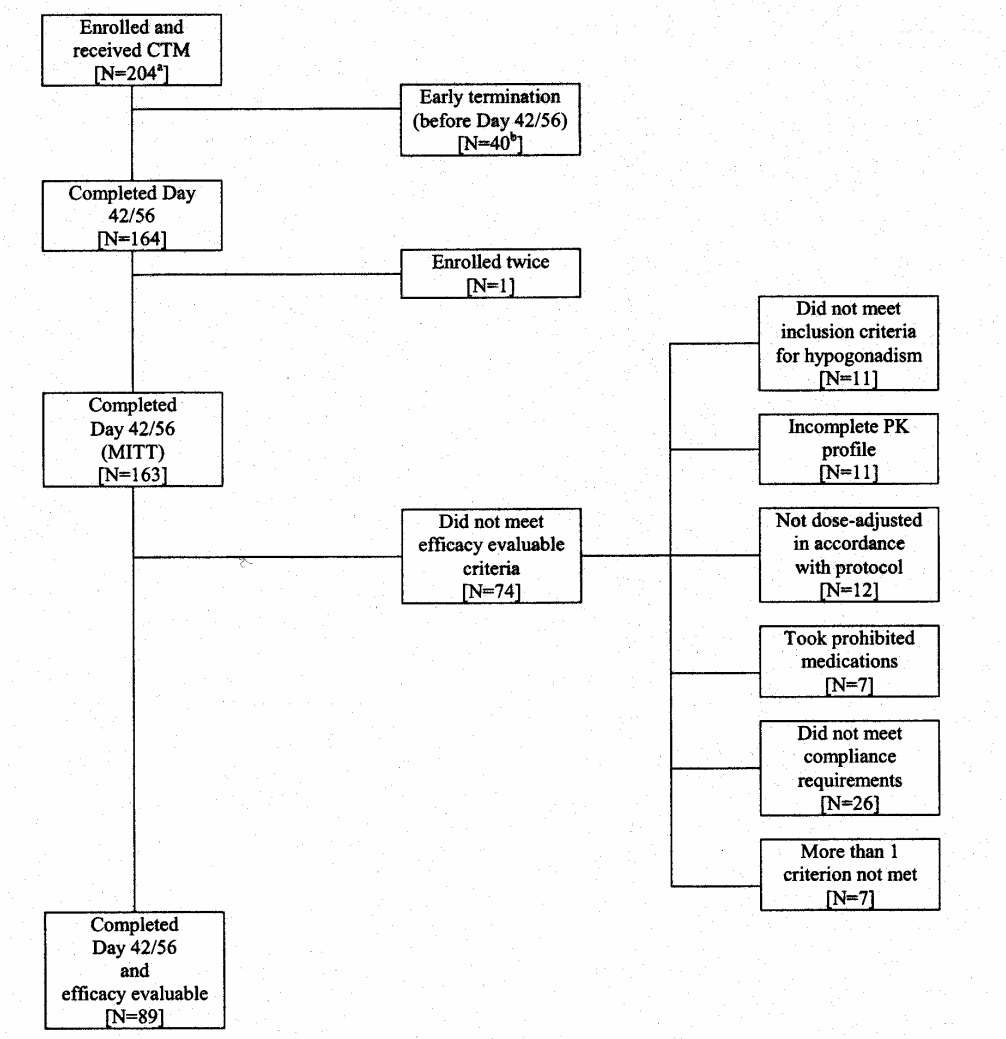
The patient continued once daily application of the dose assigned on Day 28 for the remainder of the study. Follow-up visits occurred on Days 42, 56, 70, 98, 140, and 182. The 24 hour pharmacokinetic profile was repeated on Day 42 for patients who continued using 3 g gel after the Day 28 visit, and on Day 56 for patients who began using 2 or 4 g gel on Day 28. A final 24 hour pharmacokinetic profile was performed on Day 182. Patients who completed the study through Day 182 could participate in a 12-month extension study to assess long-term safety.

Analysis populations

Table 8 Analysis populations

	No. (%) of patients	
	N	(%)
Screened	477	
Enrolled and received CTM	204*	
Completed study	146*	(71.5)
Discontinued	58	(28.4)
Analysis of efficacy – Primary efficacy Day (Day 42/56)		
Intent-to-treat (ITT) population	201	(98.5)
Day 42/56 Modified ITT (MITT) population	163	(79.9)
Day 42/56 Efficacy evaluable (EE) population	89	(43.6)
Analysis of efficacy – Secondary efficacy Day (Day 182)		
Intent-to-treat (ITT) population	201	(98.5)
Day 182 Modified ITT (MITT) population	146	(71.5)
Day 182 Efficacy evaluable (EE) population	84	(41.1)
Analyzed for safety	204	(100.0)

*3 patients enrolled twice. Other summaries and incidence of AEs are based on a total of 201 patients.
Percents are the percents of the patients who were enrolled and received CTM.



Compliance / Withdrawal

Table 9 Summary of Study Completion / Withdrawal

	Efficacy						Day 42/56 Safety	
	ITT		Day 42/56 MITT		Day 42/56 EE			
	N	(%)	N	(%)	N	(%)	N	(%)
No. of patients enrolled and received CTM	201		163		89		204	
No. of patients completing 6-month study	145	(72.1)	145	(89.0)	82	(92.1)	146	(71.6)
No. of pts prematurely withdrawn from 6-M study	56	(27.9)	18	(11.0)	7	(7.9)	58	(28.4)
Reason for prematurely withdrawal								
Adverse event	32	(15.9)	7	(4.3)	3	(3.4)	33	(16.2)
Protocol violation	4	(2.0)	0	(0.0)	0	(0.0)	5	(2.5)
Non-compliance	7	(3.5)	5	93.1)	2	(2.2)	7	(3.4)
Patient choice	7	(3.5)	2	(1.2)	0	(0.0)	7	(3.4)
Lost to follow-up	1	(0.5)	1	(0.6)	1	(1.1)	1	(0.5)
Other	5	(2.5)	3	(1.8)	1	(1.1)	5	(2.5)

Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
1) primary or secondary hypogonadism, defined as a serum testosterone concentration <250 ng/dL in a single blood sample or <300 ng/dL in two consecutive samples obtained at least 1 wk apart during the screening period 2) male aged 18-75 years 3) was deemed healthy based on medical history, physical examination, ECG, serum biochemistry, hematology, urinalysis, and serology 4) had non-fasting screening results for hematology, clinical chemistry, urinalysis and serology (PSA) that were within the established range for normal values, unless abnormal values were deemed acceptable by the investigator 5) was willing to discontinue use of current testosterone medication until the serum testosterone concentration was < 300 ng/dL	1) was currently receiving testosterone by any route of administration for treatment of hypogonadism and was unwilling to discontinue use of current treatment until the serum concentration was < 300 ng/dL 2) had significant dermatitis precluding sufficient normal skin at the gel application sites, or was being treated with topical preparations of any kind for any skin disorder 3) had a history of "sensitive" skin and/or atopic reactions to topically applied products. Subjects with a history of asthma, hay fever, or allergic rhinitis were to be questioned carefully regarding a history of atopy 4) allergy to testosterone, topically applied alcohols, or any of the components of the delivery system 5) abnormal clinical laboratory test results unacceptable to the investigator 6) uncontrolled diabetes 7) history of malignancy (except basal cell carcinoma) 8) marked benign prostatic hypertrophy 9) receiving finasteride, androgens, or alpha-adrenoreceptor antagonists for difficulty urinating 10) sleep apnea.

Reviewer's comments: These eligibility and exclusion criteria are considered adequate and appropriate.

Primary endpoint: The primary efficacy variable is the proportion of patients with both C_{min} and C_{avg} within the physiologic range(PR) (300 – 1140 ng/dL) on Day 42/56.
Secondary endpoints: Secondary efficacy variables included:
1) proportion of patients with C_{avg} within the PR (300 – 1140 ng/dL) on Day 42/56
2) proportion of patients with both C_{min} and C_{avg} within the PR (300 – 1140 ng/dL) on Day 182
3) proportion of patients with C_{avg} within the PR (300 – 1140 ng/dL) on Day 182

Efficacy analysis:

Three efficacy analysis populations were defined by the sponsor for the efficacy analysis on Day 42/56. The **ITT** population (N=201) included all patients who were enrolled and received study drug and the **EE** population (N=89) included patients who met key enrollment criteria and were compliant with study requirements. The EE population was defined as those patients who: 1) used at least one dose of study drug 2) met the criterion for hypogonadism based on serum testosterone levels at screening 3) had no more than one missing time point on Day 1 and full PK profiles for the other two 24-hr PK evaluations (Days 14 and 42/56) during the treatment period without loss of a sample 4) had an adjustment to study drug dose in accordance with the protocol-specified criteria 5) used at least 70% but no more than 130% of the prescribed amount of study drug between Day 1 and Day 42/56 and 6) did not use prohibited concomitant medications. The **EE population was defined by the sponsor as the primary analysis population.** Because of the strict definition of the EE, a large number of patients were excluded, many with only minor deficiencies (e.g. missing one sample from a 24- hr PK analysis). The sponsor believes that there is need for a population that would not include patients who discontinued prior to Day 42/56, yet would be less restrictive than

the EE population. Consequently, a **MITT** (modified ITT) population (N=163), which "was composed of all patients who participated in the study up to the Day 42/56 assessment, regardless of any other criteria." The MITT group is defined in the protocol as "all subjects who used at least one dose of study drug and had more than one PK sample obtained during the 24-hr PK profile on Day 42/56." The sponsor believes that this **MITT group provides a more accurate assessment of the success of the dose-adjustment scheme than allowed by the ITT population.**

Primary endpoint: The primary efficacy variable is the proportion of patients with both C_{min} and C_{avg} within the physiologic range (PR) (300 – 1140 ng/dL) on Day 42/56 (CI non-inferiority margin > 20% for all).

Table 10 C_{avg}, and C_{min} on PK profile Day 42/56: Day 42/56 EE, MITT, and ITT population

Day 42/56 Population / Criterion	N	%	95% Conf. Int.
Efficacy evaluable population (EE, N=89)			
Patients with C_{avg} in [300 ng/dL, 1140 ng/dL] and $C_{min} \geq$ 300 ng/dL	38	42.7	(32.4, 53.0)
MITT population (N=163)			
Patients with C_{avg} in [300 ng/dL, 1140 ng/dL] and $C_{min} \geq$ 300 ng/dL	68	41.7	(34.1, 49.3)
ITT population [a] (N=201)			
Patients with C_{avg} in [300 ng/dL, 1140 ng/dL] and $C_{min} \geq$ 300 ng/dL	68	33.8	(27.3, 40.4)

Primary efficacy endpoint: Of the 89 **EE** patients, 38 (42.7%) had C_{avg} and C_{min} within the PR (300-1140 ng/dL). Based on the **MITT** population (N=163), 68 (41.7%) met the primary endpoint. For the **ITT** population (N=201), 33.8% of patients met the primary endpoint which was a 1% lower than the historical point estimate (35%). The sponsor notes that "this rate was higher than the historical point estimate (35%) selected for this analysis. Additionally, the lower bound of the 95% CI were higher than the non-inferiority margin of 20% (for a historical point estimate of 35% with an allowable delta of 15%) for all three populations.

In summary, the lower bound of the 95% CI for the percentage of patients with both C_{avg} and C_{min} within the PR was above the non-inferiority margin of 20% in all 3 populations. Therefore, the primary endpoint of the study was met in all 3 populations on the primary efficacy day.

Reviewer's comments: The agreed upon primary endpoint was achieved.

Secondary endpoints:

1) proportion of patients with C_{avg} within the PR on Day 42/56 (CI non-inferiority margin > 65% for all)

Table 11 C_{avg} on PK profile Day 42/56: Day 42/56 EE, MITT, and ITT population

Day 42/56 Population / Criterion	N	%	95% Conf. Int.
Efficacy evaluable population (EE, N=89)			
Subjects with C_{avg} in [300 ng/dL, 1140 ng/dL]	82	92.1	(86.5, 97.7)
MITT population (N=163)			
Subjects with C_{avg} in [300 ng/dL, 1140 ng/dL]	150	92.0	(87.9, 96.2)
ITT population [a] (N=201)			
Subjects with C_{avg} in [300 ng/dL, 1140 ng/dL]	150	74.6	(68.6, 80.6)

(1) 92% of the Day 42/56 **EE** patients (n=89), 92% of the Day 42/56 MITT (n=163), and 75% of the ITT patients (n=201) had C_{avg} values within the PR on Day 42/56. (2) The lower bound of the

95% CI for this percentage was above the 65% non-inferiority margin selected for significance in all 3 populations.

2) proportion of patients with both C_{min} and C_{avg} within the PR on Day 182 (CI non-inferiority margin > 20%)

Table 12 C_{avg} and C_{min} on PK profile Day 182: Day 182 EE, MITT, and ITT population

Day 182 Population / Criterion	N	%	95% Conf. Int.
Efficacy evaluable population (EE, N=84)			
Subjects with C_{avg} in [300 ng/dL, 1140 ng/dL] and $C_{min \geq}$ 300 ng/dL	41	48.8	(38.1, 59.5)
MITT population (N=146)			
Subjects with C_{avg} in [300 ng/dL, 1140 ng/dL] and $C_{min \geq}$ 300 ng/dL	62	42.5	(34.4, 50.5)
ITT population [a] (N=201)			
Subjects with C_{avg} in [300 ng/dL, 1140 ng/dL] and $C_{min \geq}$ 300 ng/dL	62	30.8	(24.5, 37.2)

(1) 48.8% of the EE patients (41/84) had both C_{avg} and C_{min} in the PR on Day 182. Corresponding percentages for the MITT and ITT populations were 42.5% (62/146) and 30.8% (62/201) respectively. (2) The lower bound of the 95% CI for Day 182 EE, Day 182 MITT and ITT population were 38.1%, 34.4% and 24.5% respectively, above the 20% non-inferiority margin in all 3 populations studied

3) proportion of patients with C_{avg} within the PR on Day 182 (CI non-inferiority margin > 65% for ITT)

Table 13 C_{avg} on PK profile Day 182: Day 182 EE, MITT, and ITT population

Day 182 Population / Criterion	N	%	95% Conf. Int.
Efficacy evaluable population (EE, N=84)			
Subjects with C_{avg} in [300 ng/dL, 1140 ng/dL]	81	96.4	(92.5, 100.4)
MITT population (N=146)			
Subjects with C_{avg} in [300 ng/dL, 1140 ng/dL]	139	95.2	(91.7, 98.7)
ITT population [a] (N=201)			
Subjects with C_{avg} in [300 ng/dL, 1140 ng/dL]	139	69.2	(62.8, 75.5)

a subjects who did not have a PK profile on Day 42/56 were included as failure (i.e., included in the denominator) in the analysis of the ITT population.
b two-side 95% confidence interval (p+-z.05*se(p) computed on the percentage of subjects meeting the specific criteria, using the normal approximation to the binomial.

(1) 81/84 Day 182 EE patients (96.4%) and 139/146 Day 182 MITT patients (95.2%), and 69.2% of the ITT patients had C_{avg} within the PR on Day 182. (2) The lower bound of the 95% CI was 92.5% for the Day 182 EE, and 91.7% for the Day 182 MITT, both above the 65% non-inferiority margin selected for comparison in both the Day 182 EE and MITT populations. In the ITT population, the lower bound of the 95% CI was 62.8%, below the 65% non-inferiority margin.

In summary, the secondary endpoints of the study were thus met in all populations on both the primary and secondary efficacy days except the lower bound of the 95% CI in ITT population for C_{avg} within the PR on Day 182

Reviewer's comments: Most of secondary endpoints including C_{avg} were achieved.

The sponsor also conducted other efficacy analyses such as C_{avg} within the PR and concentrations ≥ 300 ng/dL for at least 80% of dosing interval, testosterone concentration within the PR for > 80% of the dosing interval, duration of testosterone concentrations outside the PR with the effect of dose

adjustment, other serum hormone concentrations and ratios, effect of 6-month CP601B treatment on bone mineral density (BMD). These analyses were carefully reviewed.

Other PK data:

At study entry

The average serum testosterone concentration (C_{avg}) (± SD) on entry into the study was 181.0 ±88.61 ng/dL for the EE population (202.3±121.73 ng/dL for the Day 42/56 MITT population and 204.01±118.68 ng/dL for the ITT population). The testosterone baseline values (by final dose group) are shown in Table 14 . The data are consistent with inclusion criteria.

Table 14 Testosterone concentrations at study entry (by final dose groups) (EE population)

		Final dose group			All
	Statistic	2g (40 mg T)	3g (60 mg T)	4g (80 mg T)	
Day 1 C_0 (ng/dL)	N	15	36	38	89
	Mean±SD	161.1±99.91	197.8±77.31	173.0±93.48	181.0±88.61
	Median	145.0	214.0	177.5	193.0
	Range	25.0-309.0	25.0-359.0	25.0-356.0	25.0-359.0

Mean testosterone profiles on Days 1, 14, 42/56, and 182 and relationship to final dose groups:

Table 15 Summary of C_{avg}, C_{min} and C_{max} by PK Days (1, 14, 42/56, 182): Day 42/56 EE population

Parameter	PK Day	Final dose group			All (N=89)
		2g gel (40 mg T) (N=15) [b]	3g gel (60 mg T) (N=36) [b]	4g gel (80 mg T) (N=38) [b]	
C_0	Day 1	161.1±99.91	197.8±77.31	173.0±93.48	181.0±88.61
C_{avg}	Day 1	543.7±230.09	380.0±137.86	289.6±100.86	369.0±168.03
	Day 14	907.1±275.51	577.9±108.87	366.2±83.94	543.0±237.40
	Day 42/56	614.0±205.15	625.9±216.91	640.4±231.32	630.2±219.09
	Day 182	548.2±156.93	592.5±194.13	596.0±211.40	586.0±194.54
C_{min}	Day 1	142.8±95.02	184.4±75.28	152.0±86.97	163.5±84.73
	Day 14	453.5±136.76	319.3±66.62	195.2±49.11	288.9±120.59
	Day 42/56	299.5±126.22	331.1±120.83	299.2±93.36	312.2±111.69
	Day 182	295.9±111.44	306.1±116.40	299.0±102.06	301.2±108.19
C_{max}	Day 1	1302.0±754.51	704.2±567.88	457.4±210.34	699.6±569.77
	Day 14	2667.1±1155.96	1420.9±676.96	768.1±368.43	1352.2±946.52
	Day 42/56	1592.4±666.52	1608.2±835.10	1847.6±1191.43	1707.7±979.62
	Day 182	1224.7±528.13	1352.5±698.59	1387.5±887.42	1344.6±756.11

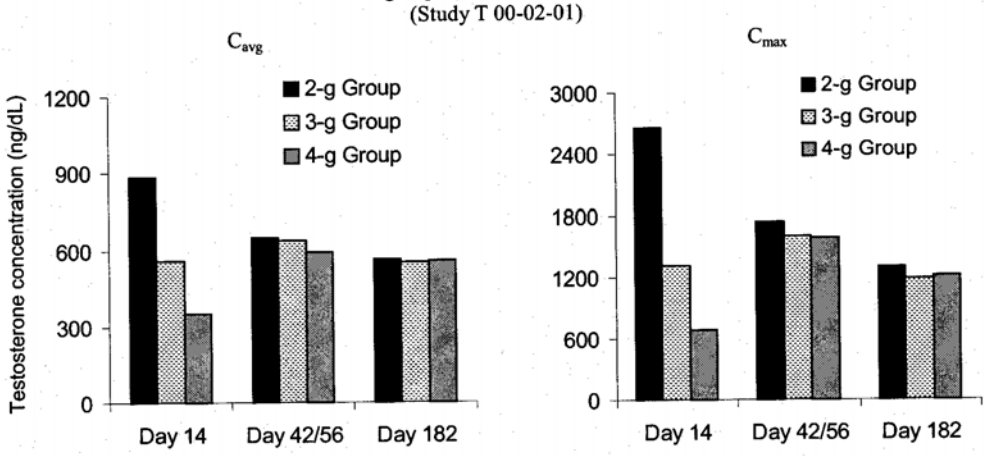
For the first 28 days of the study, all patients were to apply 3 g gel (60 mg testosterone) /day. Within 30 minutes of the application of 3 g, testosterone concentrations increased in 48% of the EE population (43 of 89 patients). By 4 hours after application, serum concentrations of testosterone were above 300 ng/dL in 67% of these patients.

On Day 14, the mean C_{max} for those patients who were changed from a 3 g dose to a 2 g dose was ≈ 2670 ng/dL. (see *Reviewer's comments* in safety section)

On Day 42/56, the mean C_{max} levels were ~ 1590 ng/dL for the group on 40 mg testosterone, 1600 ng/dL for the group on 60 mg, and 1850 ng/dL for the group on 80 mg testosterone. (see *Reviewer's comments* in safety section)

On Day 182, the mean C_{max} levels of the three dose groups are similar. The C_{max} for the 40 mg group is ~ 1225 ng/dL and ~ 1350 ng/dL for the 60 mg group and ~1390 ng/dL for the 80 mg group. (see the following figure)

Figure 7: Mean C_{avg} and C_{max} Before (Day 14) and After (Days 42/56 and 182) Dose Adjustment in the Three Dose Subgroups (N=163): MITT population (Study T 00-02-01)



Correlation of C_{avg} and C_{max} with BMI and weight: The sponsor also believes that "BMI can be a useful parameter in identifying the proper dose for a given patient indicating that BMI could be used in addition to Day 14 2-hour post-dose testosterone levels in selecting the proper dose in that group." There was a highly inversely significant correlation on Day 14 between BMI (and weight) and both C_{avg} and C_{max} in the EE and MITT populations. That correlation disappeared following dose adjustment in both the 2 g and 3 g groups (except C_{max} in 3g group), but remained in the 4 g group. Actually, the 4g subgroup had the most obese patients, suggesting that "a further increase in dose may be beneficial for morbidly obese hypogonadal men to achieve fully optimal testosterone replacement." The sponsor believes that "patients with a BMI of >45 kg/m^2, a 4 g dose of gel could be prescribed as early as Day 1."

Table 16 Correlation between the PK on Day 42/56 and BMI and weight in MITT population

Dose group	Variable	Statistics	C_{min}	C_{avg},	C_{max}
40 mg T		N	29	29	29
In 2g 2% gel	BMI	P value	0.3020	0.8809	0.9780
		R^2	0.0394	0.0008	0.0000
	Weight	P value	0.9502	0.5758	0.9956
		R^2	0.0001	0.0117	0.0000
60 mg T		N	71	71	71
In 3g 2% gel	BMI	P value	0.7488	0.2873	0.0001
		R^2	0.0015	0.0164	0.0920
	Weight	P value	0.4806	0.1232	0.0217
		R^2	0.0072	0.0341	0.0740
80 mg T		N	63	63	63
In 4g 2% gel	BMI	P value	0.0090	<0.0001	<0.0001
		R^2	0.1067	0.2575	0.2360
	Weight	P value	0.0417	0.0003	0.0002
		R^2	0.0662	0.1908	0.2051

Reviewer's comment: This reviewer agrees that the high dose could probably be imposed in obese patients but prospective proof of this conclusion is lacking.

The sponsor also believes that "BMI can be a useful parameter in identifying the proper dose for a given patient. There was a highly significant correlation on Day 14 between BMI (and weight) and all three key PK parameters (shown later). That correlation disappeared following dose adjustment in both the 2 g and 3 g groups, but remained in the 4 g group, indicating that BMI could be used in addition to Day 14 2-hour post-dose testosterone levels in selecting the proper dose in that group." The sponsor believes that "patients with a BMI of >45 kg/m^2, a 4 g dose of gel could be prescribed as early as Day 1."

Reviewer's comment: Prospective demonstration that weight can predict PK parameters is not submitted.

Other serum hormone concentrations and ratios:

DHT concentrations and serum DHT to testosterone ratio: In the MITT population, serum DHT concentrations increased from a mean of 18.5±10.83 ng/dL at baseline to a pre-dose level of 78.0±52.0 ng/dL on Day 14, 86.2±50.4 ng/dL on Day 42/56 and to 86.4±59.6 ng/dL on Day 182 in Day 42/56 MITT subjects. The serum DHT concentration increased after drug application on Days 14, 42/56, and 182 and returned to the pre-dose level by the end of 24 hour dosing interval. The DHT to T ratio increased from 0.12±0.15 at baseline to 0.21±0.09 on Day 14, 0.22±0.09 on Day 42/56 and 0.22±0.10 on Day 182 in the MITT group.

Table 17 Summary of ratio of DHT to T by PK hours and days (1, 14, 42/56, 182) in 3 populations:

Popu-lations	PK day	PK Hour				
		0	2	4	6	24
EE	Day 1 (N=88-89)	0.13±0.19	0.11±0.07	0.12±0.06	0.14±0.07	0.15±0.06
	Day 14 (N=89)	0.21±0.10	0.12±0.09	0.13±0.09	0.16±0.07	0.19±0.06
	Day 42/56 (N=87-88)	0.22±0.09	0.09±0.04	0.12±0.05	0.16±0.07	0.19±0.07
	Day 182 (N=79-83)	0.22±0.10	0.13±0.07	0.14±0.06	0.17±0.07	0.21±0.10
MITT	Day 1 (N=161-163)	0.12±0.15	0.12±0.08	0.13±0.08	0.15±0.08	0.16±0.06
	Day 14 (N=162-163)	0.21±0.09	0.12±0.08	0.13±0.08	0.17±0.08	0.19±0.07
	Day 42/56 (N=159-161)	0.22±0.09	0.10±0.06	0.12±0.05	0.16±0.07	0.20±0.07
	Day 182 (N=142-146)	0.22±0.10	0.13±0.07	0.14±0.07	0.17±0.07	0.21±0.10
ITT	Day 1 (N=197-200)	0.11±0.13	0.12±0.08	0.13±0.08	0.15±0.08	0.16±0.07
	Day 14 (N=184-186)	0.20±0.09	0.12±0.08	0.13±0.08	0.17±0.08	0.19±0.07
	Day 42/56 (N=159-161)	0.22±0.09	0.10±0.06	0.12±0.05	0.16±0.07	0.20±0.07
	Day 182 (N=142-146)	0.22±0.10	0.13±0.07	0.14±0.07	0.17±0.07	0.21±0.09

Reviewer's comments: The changes of serum DHT concentrations and DHT to T ratios during application of Fortigel gel are similar to those reported with other approved testosterone gel products.

Bioactive Testosterone (BAT) levels: Serum BAT concentrations increased from 96.8±69.3 ng/dL at baseline to pre-dose levels of 231.7±287.4 ng/dL on Day 14, 226.5±174.9 ng/dL on Day 42/56, and 220.8±157.2 ng/dL on Day 182 in Day 42/56 MITT subjects. The sponsor states that all values are within the normal range for adult males (120-430 ng/dL). The serum BAT concentrations

transiently increased after drug application on Days 14, 42/56, and 182 and returned to the pre-dose level by the end of 24 hour dosing interval.

Estradiol (E) concentrations: In the Day 42/56 population, serum estradiol concentrations increased from a mean of 1.6±0.8 ng/dL at baseline (time 0) to 3.2±1.8 ng/dL on Day 14, 3.6±1.9 ng/dL on Day 42/56, and 3.4±1.9 ng/dL on Day 182. The sponsor states that these values are within the mid-range for healthy young men. The increase in estradiol was highest in obese patients with a BMI >34 kg/m^2. The sponsor states that E/T ratios are within the PR of normal men and does not significantly change during treatment. The sponsor further states that this is consistent with the low frequency of gynecomastia observed. Three subjects developed gynecomastia (3/201, 1.5%) and one additional patient reported breast tenderness (1/201, < 1%). And three of these four men who developed gynecomastia or breast tenderness were obese with BMI of > 32 kg/m^2. The sponsor concludes that it is likely that increased aromatization of T to E in the adipose tissue in these individuals might have contributed to the development of breast enlargement.

FSH and LH levels: Serum levels of LH and FSH decreased in the EE, MITT and ITT populations.

Serum hormone binding globulin (SHBG) levels: SHBG levels did not change significantly from baseline at any of the PK evaluation days.

Effect of 6-month treatment on bone mineral density:

49 patients (including 39 Day 42/56 MITT patients) who had never used testosterone previously, "were considered" for BMD evaluation. The changes in BMD occurred in the Day 42/56 MITT patients who had data both at baseline and on Day 182 are shown in the following table.

Table 18 Bone Mineral density (BMD) changes & % changes from baseline to Day 182 for lumbar and hip, Patients naïve to previous testosterone supplements: Day 42/56 MITT population (Study T 00-02-01)

		Statistic	Final dose group			All doses
			40 mg T in 2g 2% gel	60 mg in 3g 2% gel	80 mg in 4g 2% gel	
Hip	Change (gHa/cm^2) From baseline	N	4	11	11	26
		Mean±SD	0.010±0.012	0.037±0.055	0.007±0.059	0.020±0.053
		p-value				0.0161
	Percent change from baseline	N	4	11	11	26
		Mean±SD	0.940±1.410	3.365±5.345	0.490±5.556	1.776±5.096
		p-value				0.0182
Spine	Change (gHa/cm^2) From baseline	N	4	12	11	27
		Mean±SD	0.036±0.041	0.031±0.052	0.020±0.029	0.027±0.041
		p-value				0.0004
	Percent change from baseline	N	4	12	11	27
		Mean±SD	4.017±4.285	3.038±4.314	1.689±2.666	2.634±3.671
		p-value				0.0006

The data represent approximate 2% increase in BMD. The effect on BMD was similar for the Day 42/56 EE (N=17) and for the ITT (N=28) populations

Reviewer's comment: The manner in which these patients were selected and the lack of a control group make interpretation of these data difficult. The bone mineral density data are considered exploratory.

Subgroup analyses:

Patients with no measurable testosterone at baseline (Day 1 C_0 < 50 ng/dL): The patients (N=15 for Day 1, Day 14, Day 42/56 and N=13 for Day 182) were evenly distributed across the three dose groups (4 in 2g, 5 in 4g, and 6 remained in 3 g group) after Day 28. The increase in C_{avg} over time

(C_{avg} = 274 ng/dL on Day 1, 536 ng/dL on Day 42/56 and 490 ng/dL on Day 182) was achieved. Additionally, with respect to the study primary and secondary endpoints, results in this population were comparable to results obtained with the main Day 42/56 EE and MITT populations. The sponsor believes, therefore, that pre-treatment testosterone levels are not a good predictor of the final dose required for replacement therapy. *Reviewer's comment: C_{avg} levels within the normal range were achieved in this patient subgroup.*

Patients with high BMI: The success rates for the primary and secondary endpoints in patients with a BMI ≥ 36 kg/m^2 (N=33 on Day 42/56) and in a subset of 9 subjects with BMI ≥ 45 kg/m^2 were similar to that observed for the main ITT population.

Effect of age: The correlation of C_{min}, C_{avg}, and C_{max} with age was studied on Day 14 and on Day 42/56; no correlation between age and any of the 3 PK parameters on either of the 2 days was found. With regard to the primary endpoint, 45% of the 71 Day 42/56 MITT patients who were ≥ age of 55 had both C_{avg} and C_{min} values within the PR on Day 42/56 compared with 39.1% of the 92 patients who were < 55 years of age. The percentage of patients with C_{avg} values alone within the PR was high for both population subgroups: 94.4% for patients ≥ 55 years of age and 90.2% for patients < 55 years of age.

Correlation between serum testosterone level 2 hours post-dosing on Day 14 with C_{min}, C_{max}, and C_{avg} on Day 14:

In the pivotal Phase 3 trial (T 00-02-01), dose adjustments were made based on a full 24-hr testosterone PK profile on Day 14. The sponsor recognizes that this is not a practical method to determine optimal dose. Furthermore, the sponsor believes that "a single testosterone concentration point (instead of a complete 24-hour PK profile) and other measures (e.g., BMI) can have clinical utility in making dose adjustment decisions." In the dosage section of the proposed label, the sponsor has proposed the following:

(b) (4)

The following are comments from the statistical reviewer:

The 'regression' analyses and correlation coefficients on page 99 are not that informative and do not give good statistical support for the proposed T2 rule.

The sponsor should present the numbers and percentages of patients cross-classified according to each of the three dose groups by D14C2 vs. D14 (trial). This is a simple 3x3 table. Note that Table 17 says that 30% of the patients are misclassified by rule T2, but the misclassification does not seem to extend beyond one level of dose change.

The rule given on page 100 needs to be supported by better analysis One way to do this is to show the rule minimizes the probabilities of misclassification, using the trial dose values as the reference. That is, the thresholds are 'optimum' discrimination boundaries. A key issue here is that these boundaries should be tested on a set of pts independent of the set upon which the rule was constructed. That is, one should

develop a rule from n patients and then test the rule in a separate group of m patients. Otherwise the rule is biased.

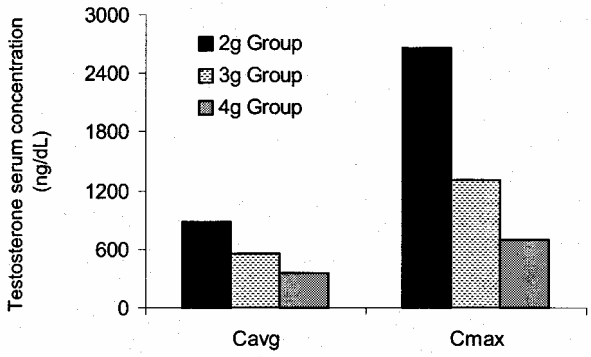


Figure 1 **Mean C_{avg} and C_{max} Day 14 (before dose adjustment) when all patients were under 3 g , by final dose group (N=163): Day 42/56 MITT population**

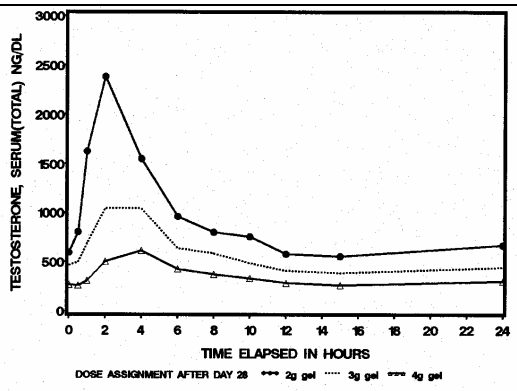


Figure 2 **Mean total serum testosterone concentrations on Day 14 by final dose group: Day 42/56 MITT population (N=163)**

The correlation of C_{avg} and C_2 ; C_{max} and C_2 ; C_{min} and C_2 on Day 14

The sponsor believes that "clear differences between the three final dose groups can be observed on Day 14, when all subjects are still on the same dose. These differences are particularly marked with C_{max} and C_{avg}. The sponsor further believes that "the time point providing the most spread between the three mean testosterone concentration time profiles on Day 14 is the 2-hour time point." The correlation between the testosterone concentration measured at 2-hour post-dose on Day 14 and all three PK parameters on Day 14 was evaluated. There was a significant correlation between the 2-hour post-dose sample (C_2) on Day 14 and the Day 14 C_{max} ($R^2 = 0.9042$). The correlation with C_{avg} was also strong (R^2=0.6608). The correlation with Day 14 C_{min} was only marginal ($R^2 = 0.1341$).

Because C_{avg} is directly related to testosterone treatment **efficacy**, and C_{max} is a key parameter to consider insuring patient's **safety** during therapy, the sponsor believes Day 14 C_2 is an optimal single time point to describe the full 24-hr PK profile on Day 14.

Dose adjustment methods used in the Phase 3 study and those proposed in Labeling are shown below:

Phase 3 pivotal study	Labeling
On Day 1 • Assign all patients to 3g of Fortigel (60 mg T applied to the skin) • 24 hr PK profile obtained after application of the 1st dose & on Day 14	(b) (4)
On Day 14 • If C_{min} < 300 ng/dL & C_{max} < 1000 ng/dl, increased dose to 4 g • If C_{min} > 400 ng/dL & C_{max} > 1000 ng/dl, decreased dose to 2 g • If C_{min} > 300 ng/dL & C_{max} < 1140 ng/dl, kept dose at 3 g	

Linear regression analysis of D14 PK (C_{max}, C_{avg}, and C_{min}) with 2 hour post dose serum testosterone level is shown in the following Figure.

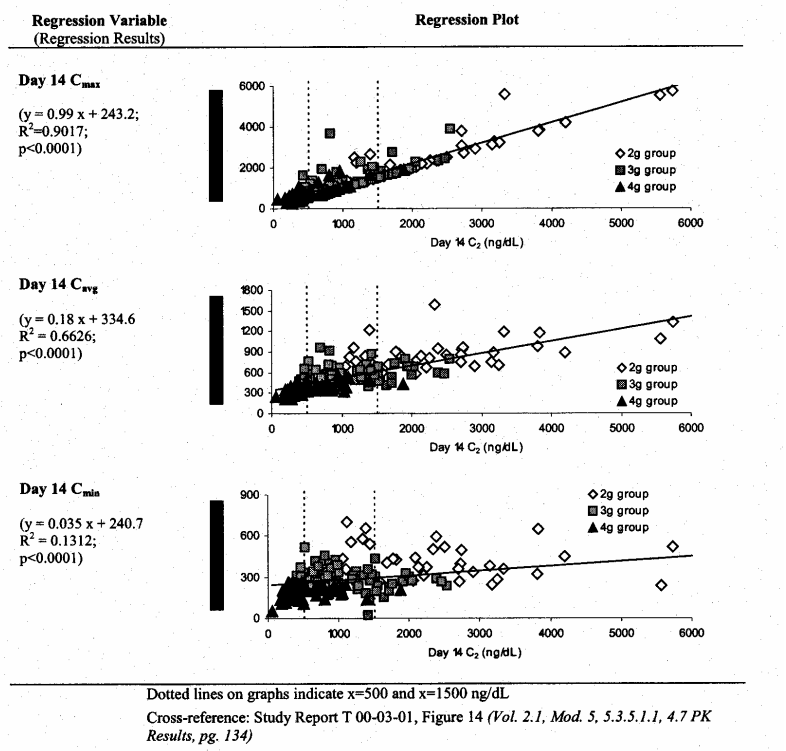


Figure 3 **Linear regression of Day 14 PK (C_{max}, C_{avg}, C_{min}) with Day 14 C2: ITT population**

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Table 19 Comparison of dose adjustment by various guidance (study T 00-02-01)

Rule	Criterion	Day 42/56 population	
		EE (N=89)	MITT (N=163)
Day 1 rule	% of subjects directly assigned to their final dose by starting all subjects on 3g CP601B gel on Day 1	40%	44%
C_2 rule on Day 14	% of subjects directly assigned to the same final dose in T 00-02-01 by using the Day 14 C_2 rule[a]	63%	69%
	% of subjects grossly misadjusted by using Day 14 C_2 rule[b]	0.0%	0.0%

[a] If C_2 < 500 ng/dL, increase dose to 4g gel; if C_2 1500 ng/dL, decrease dose to 2g gel; if C_2 500-1500 ng/dL, keep dose at 3g gel.

[b] % of subjects adjusted to 4g gel per Day 14 C_2 rule whose final dose should have been 2g gel based on Study T 00-02-01 adjustment guidance, or vice versa.

The sponsor acknowledged that by using Day 14 C_2 rule, the dose of 31 % patients of MITT or 39% patients of EE population would be misadjusted to too high or too low.

Actual Adjusted Dose in the trial	**Day14 C_2 rule predicted Dose**			**Total**
	40 mg	**60 mg**	**80 mg**	
40 mg	**22**	**7**	**0**	**29**
60 mg	**13**	**50**	**8**	**71**
80 mg	**0**	**22**	**41**	**63**
Total	**35**	**79**	**49**	**163**

The above table showed that the dose for 50 patients got misadjusted. Furthermore, C_{max} levels for about half patients in the whole population of the pivotal Phase 3 study were still too high even their dose got adjusted to either 40 mg or 80 mg. Using C_{max} > 1500 ng/dL as a cut point, the fail rate in dose adjustment is 50.5% for Day 182 and/or Day 42/56.

Table 20 Fail Rate in Dose Adjustment (C_{max} >1500 ng/dL)

Dose (mg gel)	C_{max}> 1500 ng/dL			Total
	D42/56 & D182	D 42/56 only	D 182 only	
40 (N=32)	8 (25%)	10 (31.3%)	1 (3.1%)	19 (59.4%)
80 (N=63)	11 (17.5%)	14 (22.2%)	4 (6.3%)	29 (46%)
Total (N=95)	19 (20%)	24 (25.3%)	5 (5.3%)	48 (50.5%)

At the meantime for those patients who remained at dose of 60 mg,, 56.3% of patients had their C_{max} >1500 ng/dL for Day 182 and/or Day 42/56.

Table 21 Fail Rate in Remaining Dose (C_{max} >1500 ng/dL)

Dose (mg gel)	C_{max}> 1500 ng/dL			Total
	D42/56 & D182	D 42/56 only	D 182 only	
60 (N=71)	11 (15.5%)	22 (31%)	7 (9.8%)	40 (56.3%)

(Please refer to the statistician's review)

Reviewer's Comment: Based on the above, it appears that adequate dose adjustment was not achieved regardless of the methodology proposed in the label.

Long-term effectiveness: Serum T levels were collected at the 6-month and 12-month visits during the extension phase.

Table 22 Summary of testosterone (T) levels during extension study

Dose group	Statistic	Day 1	Month 6 (mid-extension study)	Month 12 (end of study)
40 mg T in 2g gel	N	13	10	9
	Mean±SD	485.6±199.1	553.3±470.6	418.0±333.2
	Median	445.0	362.5	346.0
	Range	194-842	76-1504	67-1221
60 mg T in 3g gel	N	36	27	15
	Mean±SD	455.8±203.9	711.9±661.0	634.9±508.8
	Median	425.5	414.0	577.0
	Range	106-1226	100-2336	83-2157
80 mg T in 4 g gel	N	33	8	7
	Mean±SD	434.5±180.6	590.5±238.8	660.3±751.7
	Median	416.0	511.5	359.0
	Range	168-1166	395-1139	91-2224

Reviewer's comments: The limited number of subjects, different times of sampling following application, and the large inter-subject differences make interpretation of the mean testosterone levels difficult.. Ten patients with testosterone concentrations > 1140 ng/dL will be further reviewed in the safety section.

D. Efficacy conclusions

The primary endpoint was met in all 3 populations (EE, MITT and ITT). In the EE population, 42.7% [95% CI (32.4%, 53%)] of patients had Day 42/56 C_{avg} and C_{min} within the PR. The lower bound of the 95% CI was higher than the historical value of 20%. A secondary endpoint (C_{avg} within the PR) was also met in all 3 populations. In the MITT population (n=163), 92% of patients had C_{avg} within the PR. A secondary endpoint (C_{avg} within the PR) was also met in all three populations. In the MITT group (N=163), 92% of subjects had C_{avg} within the PR. Efficacy results in the EE and MITT populations were similar, thus confirming that results obtained in the smaller EE population could be generalized to a less restrictively defined study subgroup.

In the opinion of this reviewer, Fortigel is efficacious for testosterone replacement.

VII. Integrated Review of Safety

In the original ISS (November 2002) and the updated extension study safety report, AEs were analyzed by the following general categories:

1. Overall summary of tolerability and AE profile by treatment group
2. Treatment-emergent AEs reported in 2% or more subjects, regardless of causality
3. AEs (> 1%) possibly or probably related to Fortigel treatment
4. Application site reaction
5. Laboratory evaluations
6. SAEs and deaths
7. Discontinuations due to AEs

Reviewer's comments: The original ISS covers the pivotal Phase 3 study and other Phase 1 /2 studies. The pivotal study T 00-02-01 was designed as a titration study followed by continuous therapy following dose adjustment at Day 29 for up to 6 month. The subjects were evaluated on Day 14 with respect to serum testosterone PK profile. On day 29, the subjects on 60 mg (3g gel) could be increased to 80 mg (4g gel) or decreased to 40 mg (2g gel) or remain at 60 mg (3g gel) based on Day 14 serum testosterone PK profile. In the T 00-02-01 study report, safety summaries at Day 98 and Day 182 were presented by group after titration. In addition, summaries at Day 182 or summaries based on the entire study period were presented by combining the pivotal Phase 3 study with other Phase 1 /2 studies.

The updated extension study safety report covers just the one open label extension study (T-00-03E-01) with a cutoff date of July 02, 2002.

This review's analysis of safety will concentrate primarily on the original ISS. When data or tables from the extension study are used, it will be specifically noted. Likewise, when the reviewer believes there is a notable difference between the two reports, a specific comment will be made.

A. Conclusions (brief)

A large percentage of patients in the pivotal study experienced high testosterone C_{max} values (>1500 ng/dL). This high level of C_{max} statistically significantly correlated with increasing hematocrits and decrease of HDL-cholesterol values. The clinical risk(s) of daily high C_{max} levels of testosterone are not known

B. Extent of Exposure

Data presented in the Integrated Summary of Safety is drawn from a total of 325 patients enrolled in 6 completed studies (1 Multicenter Phase 3 pivotal study and 5 completed Phase 1 / 2 studies, all open-labeled) conducted in the United States. The 325 patients included 18 in a non-vehicle-controlled, randomized, 7 treatment regimen, 3-way, 3-period, matrix-type crossover study (T 98-02-01), 7 in a non-vehicle-controlled, randomized, 2-treatment, 2-period crossover study (T 00-02-03), 12 in a non-vehicle-controlled, randomized, 3-treatment with different area sizes, 3-period crossover study (T 00-02-07), 15 in a non-vehicle-controlled, randomized, 3-treament with different locations, 3-period, crossover study (T 00-02-08), 72 in a randomized, 3-treatment with vehicle only, parallel groups study (T 00-02-09), and 201 in the pivotal Phase 3 study (T 00-02-01). The patient population in the clinical trials reflects the probable marketing exposure.

Table 23 Extent of Exposure to CP601B by dose level for Phase 3 and Phase 1 / 2 studies: All enrolled patients

	Phase 3 study CP601B			Phase 1 / 2 study CP601B			
	40 mg T in 2g 2% gel	60 mg T in 3g 2% gel	80 mg T in 4g 2% gel	10 mg T in 1g 1% gel	20 mg T in 2g /1g 1%/2% gel	40 mg T in 2g 2% gel	60 mg T in 3g 2% gel
Days on therapy							
1-7 (WK 1)	0	8	0	13	7	9	9
8-14 (WK 2)	0	5	0	2	9	0	7
15-21 (WK 3)	0	5	0	0	0	0	0
22-28 (WK 4)	0	4	0	0	0	12	12
29-60 (Mon. 2)	1	13	6	0	0	0	0
61-90 (Mon. 3)	2	2	1	0	0	0	0
91-120 (Mon. 4)	1	2	1	0	0	0	0
121-150 (Mon. 5)	1	5	2				
151-186 (Mon. 6)	15	46	42	0	0	0	0
187-223 (Mon. 7+)	12	13	17	0	0	0	0
Total patients	32	201	69	15	16	21	28
Mean±SD	173.1±40.9	126.8±74.5	168.7±42.8	7.5±2.86	10.8±3.49	16.7±8.62	16.0±7.52
Median	184.5	180.5	183.6	7.0	12.5	24.0	14.0
Range	43.0±223.0	1.0-211.0	37.0-207.0	3.0-14.0	7.0-14.0	7.0-24.0	7.0-24.0
Missing	0	3	0	0	0	0	0
Amount of CTM (g of Gel)							
N	32	99	68	13	13	42	51
Mean±SD	340.1±99.8	317.±203.2	548.±173.7	6.1±1.28	8.6±3.32	14.1±3.05	20.9±7.83
Median	354.3	375.0	586.1	6.2	6.4	13.2	18.4
Range	92.6-495.0	2.8-764.6	86.6-994.2	2.2-7.2	5.7-13.4	11.0-25.4	7.2-43.0
Missing	0	4	1	0	0	0	0

The mean duration of exposure for the Phase 3 pivotal study was 173.1 days for the 2g group, 126.8 days for the 3g group and 168.7 days for the 4g group. The longest duration of exposure was in those patients using a final dose of 2g (223.0 days). The mean amount of gel used was 340 g for the 2g group, 317 g for the 3g group and 548 g for the 4g group.

C. Methods of Safety Review:

The Integrated Summary of Safety, the pivotal trial (T 00-02-01) and the 120 day safety update were reviewed for safety in detail. Trials T 98-02-01, T 00-02-03, T 00-02-7, T 00-02-08 and T 00-02-09 were reviewed individually.

Safety review is based on all data collected for treatment-emergent adverse events (AEs), and changes between the screening and exit visits in physical examination findings, vital signs measurements, and clinical laboratory results. An adverse event was defined as a treatment-emergent event that developed or increased in severity during the course of the study whether

thought to be related or unrelated to the condition under study. AEs, with the exception of application site reactions, were graded as mild, moderate or severe. The relationship between each adverse event and the study drug was also assessed.

D. Summary of Safety Findings: Pivotal Phase 3 study T 00-02-01

Study demographics

In the pivotal study T 00-02-01, 201 patients with a mean serum testosterone concentration 204.0±118.68 ng/dL were enrolled. Demographic characteristics of the patients are shown in Table 24.

Table 24 Demographic and baseline characteristics (Study T 00-02-01)

	Day 42/56 ITT (N=201)	Day 42/56 MITT (N=163)	Day 42/56 EE (N=89)
Age			
< 55	112 (55.7)	92 (56.4)	53 (59.6)
≥ 55	89 (44.3)	71 (43.6)	36 (40.4)
Mean±SD	53.2±11.47	53.2±11.22	51.8±11.52
Median	53.0	53.0	53.0
Range	19.0-74.0	19.0-74.0	19.0-74.0
Race			
Caucasian	169 (84.1)	135 (82.8)	77 (86.3)
Black	27 (13.4)	24 (14.7)	10 (11.2)
Asian	1 (0.5)	1 (0.6)	1 (1.1)
Hispanic	4 (2.0)	3 (1.8)	1 (1.1)
Other	0 (0.0)	0 (0.0)	0 (0.0)
Weight (kg)			
Mean±SD	102.2±21.56	102.5±22.42	101.2±22.11
Median	99.9	99.9	98.1
Range	56.8-202.9	56.8-202.9	64.1-202.9
Height (CM)			
Mean±SD	179.8±8.82	179.7±9.03	180.1±8.69
Median	180.3	179.1	180.3
Range	141.2-213.4	141.2-213.4	141.2-200.7
Body Mass Index (kg/m^2)			
Mean±SD	31.6±6.11	31.7±6.30	31.2±6.35
Median	30.4	30.4	29.9
Range	16.5-54.5	16.5-54.5	20.3-54.5
Prior testosterone supplement use			
Yes	152 (75.6)	124 (76.1)	68 (76.4)
No	49 (24.4)	39 (23.9)	21 (23.6)

The median age was 53 years, the race distribution was Caucasian 84% Black 13.5%, and others 2.5%, and the mean subject height, weight, and BMI were 180 cm, 101 kg and 31, respectively.

Frequency of All Adverse Events

A summary of adverse events in the pivotal Phase 3 study as well Phase 1 /2 studies is shown in Table 25.One hundred sixty of 201 patients in the pivotal Phase 3 study experienced a minimum of one treatment-emergent AE during the 6-month study duration and 26/52 (50%) patients experienced at least one treatment-emergent AE during the Phase 1 /2 studies. Reported significant adverse events (AEs) are primarily those related to application site reactions (ASRs). Almost half of (49.8%) the subjects overall experienced ASRs. Body as a whole was the second most frequent category of AEs (27.3% of subjects).

Table 25 Incidence of frequently reported (>2%) adverse events[c]

Body system / preferred term	Number of subjects					
	Phase 3 study (N=201)[a]		Phase 1 / 2 study (N=52)		Total subjects (N=253)[b]	
	n	(%)	n	(%)	n	(%)
Subjects with adverse events	160	(79.6)	26	(50.0)	186	(73.5)
Application site reaction	109	(54.2)	17	(32.7)	126	(49.8)
Erythema	67	(33.3)	16	(30.8)	83	(32.8)
Xerosis	49	(24.4)	6	(11.5)	55	(21.7)
Pruritus	34	(16.9)	6	(11.5)	40	(15.8)
Rash	21	(10.4)	1	(1.9)	23	(9.1)
Paresthesia	21	(10.4)	2	(3.8)	23	(9.1)
Body as a whole	63	(31.3)	6	(11.5)	69	(27.3)
Infection	16	(8.0)	0	(0.0)	16	(6.3)
Flu syndrome	13	(6.5)	0	(0.0)	13	(5.1)
Headache	10	(5.0)	2	(3.8)	12	(4.7)
Injury accidental	9	(4.5)	1	(1.9)	10	(4.0)
Pain back	8	(4.0)	2	(3.8)	10	(4.0)
Pain	7	(3.5)	2	(3.8)	9	(3.6)
Asthenia	5	(2.5)	1	(1.9)	6	(2.4)
Pain chest	5	(2.5)	0	(0.0)	5	(2.0)
Seasonal allergies	4	(2.0)	0	(0.0)	4	(1.6)
Respiratory system	40	(19.9)	2	(3.8)	42	(16.6)
Sinusitis	17	(8.5)	0	(0.0)	17	(6.7)
Pharyngitis	14	(7.0)	1	(1.9)	15	(5.9)
Rhinitis	6	(3.0)	1	(1.9)	7	(2.8)
Metabolic & nutritional disorders	32	(15.9)	5	(9.6)	37	(14.6)
Edema peripheral	11	(5.5)	2	(3.8)	13	(5.1)
Hypocholesterolemia	7	(3.5)	0	(0.0)	7	(2.8)
Hyperglycemia	6	(3.0)	0	(0.0)	6	(2.4)
Hyperlipemia	4	(2.0)	0	(0.0)	4	(1.6)
Hyperuricemia	4	(2.0)	0	(0.0)	4	(1.6)
Edema	2	(1.0)	3	(5.8)	5	(2.0)
Urogenital system	26	(12.9)	1	(1.9%)	27	(10.7)
Gynecomastia	5	(2.5)	0	(0.0)	5	(2.0)
Prostatitis	5	(2.5)	0	(0.0)	5	(2.0)
PSA ↑	4	(2.0)	0	(0.0)	4	(1.6)
Cardiovascular system	25	(12.40	4	(7.7)	29	(11.50
Hypertension	10	(5.0)	2	(3.8)	12	(4.70
Migraine	0	(0.0)	2	(3.8)	2	(0.8)
Nervous system	23	(11.4)	2	(3.8)	25	(9.9)
Depression	6	(3.0)	0	(0.0)	6	(2.4)
Dizziness	4	(2.0)	1	(1.9)	5	(2.0)
Insomnia	4	(2.0)	0	(0.0)	4	(1.6)
Skin and appendages	23	(11.4)	2	(3.8)	25	(9.9)
Xerosis	6	(3.0)	0	(0.0)	6	(2.4)
Erythema	4	(2.0)	0	(0.0)	4	(1.6)
Digestive system	19	(9.5)	2	(3.8)	21	(8.3)
Nausea	6	(3.0)	1	(1.9)	7	(2.8)
Diarrhea	5	(2.5)	0	(0.0)	5	(2.0)
Haemic & lymphatic system	10	(5.0)	2	(3.8)	12	(4.7)
Erythrocytosis	5	(2.5)	0	(0.0)	5	(2.0)
Eosinophilia	3	(1.5)	2	(3.8)	5	(2.0)
Musculoskeletal system	10	(5.0)	0	(0.0)	10	(4.0)
Special senses	9	(4.5)	0	(0.0)	9	(3.6)

[a] 3 subjects in study T 00-02-01 were enrolled twice, adverse events were consolidated for these subjects; therefore, the incidence of adverse events is based on the total number of unique subjects (N=201).
[b] Since subjects may be counted under more than one column, the sum of columns counts may exceed the total.
[C] Summarized by body system and preferred terms: Safety population in Phase 3 and Phase 1 / 2 studies

Adverse events which occurred in between 2.5% and 5% of patients were: infection, flu syndrome, asthenia, headache, accidental injury, pain, back pain, chest pain, sinusitis, pharyngitis, rhinitis, peripheral edema, hypocholesterolemia, hypoglycemia, gynecomastia, prostatitis, hypertension, diarrhea, nausea, depression, xerosis, and erythrocytosis. One patient developed deep vein thrombophlebitis and one patient reported urinary frequency.

Besides application site reactions, those events considered by the investigator as being related to study drug in > 2% of patients were: nervous system (4%), skin and appendage (3.5%), hypertension (3%), erythrocytosis (2.5%), headache (2%), gynecomastia (2 %), hypocholesterolemia (2%), and PSA increased (2 %).

Treatment Related Adverse Events

Table 26 Incidence of frequently reported (> 2%) AEs by maximum relationship to CP601B for T 00-02-01

Body system/preferred term	None	Possibly	Related	Unknown	Total related	% (N=201)
Subjects with adverse events	32	24	104	0	128	63.7%
Application site reaction	0	8	101	0	109	54.2
Erythema	0	3	64	0	67	33.3
Xerosis	1	2	1	0	20	10.0
Pruritus	0	3	31	0	34	16.9
Rash	0	2	20	0	22	10.9
Paresthesia	0	1	48	0	49	24.4
Body as a whole	58	2	3	0	5	2.5
Headache	6	1	3	0	4	2.0
Cardiovascular system	18	5	2	0	7	3.5
Hypertension	4	4	2	0	6	3.0
Hemato & lymphatic system	2	6	2	0	8	4.0
Eosinophilis	0	3	0	0	3	1.5
Erythrocytosis	0	3	2	0	5	2.5
Metabolic & nutritional disorders	21	11	0	0	11	5.5
Edema	2	0	0	0	0	0.0
Hypocholestorolemia	3	4	0	0	4	2.0
Nervous system	15	5	3	0	8	4.0
Skin & appendages	16	3	4	0	7	3.5
Urogenital system	12	12	2	0	14	7.0
Gynecomastia	1	3	1	0	4	2.0
PSA ↑	0	4	0	0	4	2.0

The majority of the application site reactions reported was assessed as related to the study drug. In contrast, the majority of treatment-emergent AEs for the other body systems were assessed as being unrelated to study drug application. Among them, the most common non-ASRs assessed as treatment-related were hypertension (6 patients, 3%) and erythrocytosis (5 patients, 2.5%). Both of these are recognized potential consequences of testosterone replacement therapy.

The high withdrawal rate in the ITT population due to adverse events is a major review concern. Thirty four of the 253 subjects (13.4%) in the safety population discontinued study drug due to a treatment-emergent adverse event. Thirty three patients (33/201, 16.4%) from the pivotal Phase 3 study and 1 in the Phase 1 / 2 studies withdrew from the trials. Application site reactions (ASRs), including erythema, pruritis, xerosis, rash, and paresthesia, accounted for 20 (20/33, 61%) of the

discontinuations. Patients most commonly discontinued therapy due to ASRs manifested as "non-immunologic contact urticaria (NICU)" symptoms in combination with xerosis (7 patients) and "multiple NICU symptoms" (5 patients). Four patients discontinued due to rash and 2 due to erythma. One patient each was due to xerosis and pruritus. None of the ASRs were assessed as serious. The non-application site reactions most commonly leading to discontinuation were cardiac-related (4 patients). Three patients discontinued due to erythrocytosis.

Table27 Relationship between serum testosterone C_{max} / C_{avg} and discontinuation due to treatment emergent non-application site reaction (Non-ASR) (N=13) (Study T 00-02-01)

Dose at AE	Subject ID	Age	Adverse events (preferred term)	Day 14		Day 42.56		Day onset	Days in therapy	Relation to Fortigel
				C_{max}	C_{avg}	C_{max}	C_{avg}			
60 mg	002-106	65	Dyspnea + chest pain	370	306	Discontinued		23	27	None
60 mg	002-115	54	Erythrocytosis	915	562	Discontinued		36	28	Possibly
60 mg	002-116	62	Prostate cancer	1250	586	2484	683	150	149	Possibly
60 mg	006-110	38	Headache	Discontinued		Discontinued		1	15	Related
60 mg	010-103	64	Heart failure right [a]	880	472	2453	1064	48	84	Possibly
60 mg	014-114	54	Coronary occlusion [a]	1885	657	2270	760	137	139	None
60 mg	014-141	41	Dyspnea [a]	491	358	Discontinued		27	59	None
60 mg	017-117	63	Anxiety	674	357	Discontinued		24	24	None
60 mg	018-101	61	Arthritis	587	347	Discontinued		26	52	None
60 mg	018-115	41	Erythrocytosis	2461	580	2259	613	99	120	Related
60 mg	018-117	62	Prostatitis	3143	755	Discontinued		4	30	Related
80 mg	014-137	54	Erythrocytosis	629	285	483	387	96	102	Possibly
80 mg	018-102	51	SGOT↑, SGPT↑	538	333	Discontinued		45	52	Possibly

Most of the patients withdrawn for application site reactions were discontinued during the first month of therapy. Most of the discontinuations for other types of events occurred later in the study. In the extension study (T 00-02E-01), 2.4% (2/82) of patients were withdrawn from the study due to adverse events unrelated to ASRs (one with deep vein thrombosis, the other with erythrocytosis).

Reviewer's comments: The 16.4% (33/201) withdrawal rate is high and is primarily secondary to the high withdrawal rate from skin reactions.

Deaths: No deaths occurred during the study.

Serious Adverse Events: (Table 28) A total of 11 patients had events meeting the definition of serious during the 6-month study. However, two of these patients had SAE's that began either before administration of Fortigel (#104-128) or more than 14 days after completion of the study (#015-100). Four of the patients (#010-103, #014-114, #014-137, #014-141) withdrew from the study due to the event. During the 12-month extension phase of the pivotal study, 9 serious AEs (SAE's) occurred in 8 patients. Three patients had SAE's which began before administration of study drug in the extension phase and thus were not deemed treatment emergent (#014106, #014133, and #022103). Two patients (#002105 and #014118) were withdrawn from the extension study because of SAE's (DVT, erythrocytosis, respectively).

Five (#014118, #014137 #022103 in original Phase 3 study, #014118 and #022103 in the extension study) of the six SAE's deemed probably related or related to treatment with Fortigel were erythrocytosis. The other SAE assess as probably related to study medication was a second episode of deep vein thrombosis (DVT) in #002105.

In the Phase 3 pivotal study, 6 SAE's (dehydration, kidney tubular disease, right heart failure, abdominal pain/colitis, dyspnea, and polycythemia) were classified as severe. In the Phase 3 extension study, 7 SAE's (bowel obstruction, DVT, diverticulitis, difficulty walking, back pain.

foot infection with Staph. bacteria and polycythemia) were classified as severe. Severe SAE's (right heart failure, dyspnea) led to study discontinuation in 2 patients, with congestive heart failure deemed possibly related to the study drug.

Table 28 Serious Adverse Events During 6-month (T 00-02-01) and Extension Study (T 00-02E-01)

Subject	Age	Do[a] -se	Preferred Term	Adverse events (preferred term)	Day[b] Onset	Duration	Severity	Relationship to Fortigel[c]	Outcome
T 00-02-01									
010103	64	60	Dyspnea	Orthopnea	45	4	Moderate	None	Resolved
		60	Pain chest	Chest pain	47	1	Mild	None	Resolved
		60	Heart fail R	Congest heart failure[d]	48	3	Severe	Possibly	Resolved
		60	Arrhythmia	Arrhythmia	50	1	Moderate	None	Resolved
011109	63	60	Apnea	Obstruct Sleep Apnea	1	105	Moderate	None	Resolved
		40	Dehydrat	Dehydration	109	4	Severe	None	Resolved
		40	Pain	Poor pain control	109	4	Moderate	None	Resolved
014106	46	60	Pain/abdo	Pain abdominal/	183	29	Severe	None	Resolved
			Colitis	diverticulitis[d]				None	Resolved
014114	54	60	Occlus coronary	Coronary artery blockage	137	3	Moderate	Possibly	Resolved
014118	63	60	Erythrocyto	Elevated hematocrit	186	On-going	Moderate	**Probably**	Unchanged
014128	52		Occlus	Arterial blockage[f]	-22	5	Moderate	None	Resolved
014137	54	80	Erythrocyto	Elevated hematocrit[d]	96	On-going	Moderate	**Probably**	Lost to Follow-up
014141	41	60	Dyspnea	Increase of shortness of breath[d]	27	33	Severe	None	Resolved
015100	44		Obesity	Worsen morbid obesity[g]	165 (30 PT)	5	Moderate	None	Resolved
020110	66	40	Kidney Tubil dis	Renal artery stenosis	135	50	Severe	None	Resolved
022103	60	80	Erythrocoto	Polycythemia	109	100	Severe	**Related**	Resolved
T 00-02E-01									
001131	74	60	Obstruct intest	Bowel obstruction	270	2	Severe	None	Resolved
002105	74	40	Thrombo-Phleb deep	Deep vein thrombosis	165		Severe	**Probably**	Improved
006116	51	60	Infarct myo	Myocardial infarction	10	4	Mild	None	Resolved
014106	46	60	Pain/abdo/	Pain abdomen[a, f]	-3	29	Severe	None	Resolved
			Colitis	Diverticulitis[a, f]				None	Resolved
014118	63	60	Erythrocyto	Elevated hematocrit[f]	1	64	Moderate	**Probably**	Resolved
014133	53	60	Gait abnor	Difficulty walking	1±[e]		Severe	None	Resolved
		60	Pain back	Back pain	1±[e]		Severe	None	Resolved
021105	69	60	Infect	Staph infect . to Wound right foot	221	14	Severe	None	Resolved
022103	60	80	Erythrocoto	Polycythemia[f]	-85	100	Severe	**Related**	Resolved

[a] Dose at onset of SAE

[b] Relative to start of therapy or extension study (Day 1). PT refers to the number of days posttherapy relative to the last day of study drug administration

[c] Based on investigator's and the reviewer's assessment.

[d] Subject discontinued therapy due to the SAE.

[e] ±Missing onset date on AE CRF record as Day 1 of CTM subject #014-106 had 2 terms representing the same event.

[f] Not considered a treatment-emergent event because the day of onset proceeded first day of drug administration or first day of extension study and the severity did not increase.

[g] Not considered a treatment-emergent event because the day of onset was 14 days after the date of last application of CTM.

Narratives for these SAE's (in original trial) are as follows (N=9):

Patient 010-103 (dyspnea, chest pain, right heart failure, and arrhythmia) This 64-year-old man had a history of rheumatic fever followed by CHF, depression, hypertension, erectile dysfunction and seasonal allergies. He began 3 g testosterone/day on 09/18/2000. On (b) (6), he experienced shortness of breath. A CXR was consistent with CHF. He was admitted to the hospital. The event resolved. The investigator believed the event to be possibly related to study medication. Concomitant medications included naproxen, lisinopril, paroxetine, and aspirin.

Reviewer's comments: The reviewer agrees that relationship to study drug is possible.

Patient 011-109 (apnea, dehydration, pain) This 63-year-old man had a history of mild obstructive sleep apnea. He had been administering study medication (40 mg/day) since 08/20/2000. On (b) (6), he experienced dehydration and pain and was hospitalized following planned outpatient surgery for sleep apnea. The events resolved and he continued on study medication. The investigator believed that the events were not related to study medication.

Reviewer's comments: The reviewer agrees that relationship to study drug is unlikely. Sleep apnea is associated with testosterone administration.

Patient 014-106 (abdominal pain, colitis) This 46-year-old man had no significant past medical history. He had been receiving study drug since 08/24/2000. On (b) (6), he was hospitalized with a 4-day history of abdominal pain and diarrhea. A diagnosis of diverticulitis was made on CT scan. The event resolved and the investigator believed that it was not related to study medication.

Reviewer's comments: The reviewer agrees the relationship to study drug is unlikely.

Patient 014-114 (chest pain) This 54-year-old man had a history of hyperlipoproteinemia, myocardial infarction (MI), and quadruple bypass surgery. He had been on 60 mg study drug since 09/01/2000. On (b) (6), he was hospitalized with chest and left shoulder pain. Cardiac catheterization with stent placement was performed on (b) (6). The event resolved and the patient was withdrawn from the study. The investigator believed that the event was not related to study medication.

Reviewer's comments: The reviewer considers the relationship to study drug unlikely.

Patient 014-118 (erythrocytosis) This 63-year-old man had no significant past medical history. He began 60 mg study drug on 09/16/2000. On 03/20/2001, at the Week 26 visit, elevations in hemoglobin (18.4 g/dL) and hematocrit (56.9%) were detected. Study medication was withheld from the extension phase and he was placed on aspirin. Subsequent laboratory tests showed H/H to be 18.3 g/dL / 53.5% on 03/30/2001 and 17. g/dL / 53.5% on 04/23/2001, respectively. The investigator believed that the event was "possibly" related to study drug.

*Reviewer's comments: The reviewer considers this event **probably** related to study drug.*

Patient 014-137 (erythrocytosis) This 54-year-old man had no significant past medical history. He had been administering 80 mg of study drug since 01/13/2001. On 04/18/2001 (Week 14), elevations in hemoglobin (18.2 g/dL) and hematocrit (54.0%) were detected. Study medication was withdrawn as of 04/24/2001 and he was placed on aspirin. He was withdrawn from the study and the outcome of the event is unknown. The investigator considered the event as "possibly" related to study medication. These was no concomitant medications at the time of the event.

*Reviewer's comments: The reviewer considers this event **probably** related to study drug.*

Patient 014-141 (dyspnea) This 41-year-old man had a history of hypertension, CHF, MI, and double bypass cardiac surgery. He had been administering 60 mg study drug since 01/05/2001. On (b) (6), he was hospitalized with shortness of breath and was diagnosed with CHF. He underwent cardiac catheterization and improved, but was discontinued from the study. The investigator rated the event as "not related" to study drug. Concomitant medications included digoxin, citalopram, furosemide, quinapril, omeprazole, spironolactone, atorvastatin, quinine, glyburide/metformin and glimepiride.

Reviewer's comments: The reviewer considers the relationship to study drug unlikely.

Patient 020-110 (kidney tubule disorder) This 66-year-old man had a history of hypertension. He had been administering study drug (3 g) for 4 weeks and then 4 g beginning 12/11/2000. On (b) (6) he experienced a lacerated artery with peritoneal bleeding during outpatient stent placement to correct renal artery stenosis. Emergency surgery to repair the renal artery was performed and successful. The event resolved. Study drug was withheld from 05/03/2001 and restarted on 05/11/2001. The investigator considered the event to not be related to study drug.

Reviewer's comments: The reviewer agrees the relationship to study drug is unlikely.

Patient 022-103 (erythrocytosis) This 60-year-old man had a medical and surgical history of vertigo, tinnitus, back pain, seasonal allergies, impotence and decreased libido, obesity, cholecystitis, nocturnal enuresis, headache and numerous surgeries. He had been administering study drug (4g) since 10/15/2001. Concomitant medications included acetaminophen and diphenhydramine. Serial hemoglobin (14.0-18.0 g/dL normal range) and hematocrit (42-52%) values were as follows:

Assessment	Hemoglobin (g/dL)	Hematocrit (%)
Baseline (09/14/2001)	15.7	48.0
Week 14 (01/31/2002)	18.9	56.7
Week 14 repeat (02/05/2002)	19.1	58.4
Week 26 (04/24/2002)	18.2	53.7
Follow-up (/5/10/2002)	15.4	Not reported

The patient completed the 6-month study and entered the extension phase on 04/26/2002. Polycythemia was diagnosed on 04/30/2002. Study drug was discontinued on 05/02/2002 and phlebotomy was performed on 04/30/2002 and again on 05/03/2002. Hemoglobin and hematocrit returned to normal on 05/10/2002 at follow-up. The investigator considered the event to be "possibly" related to study drug.

*Reviewer's comments: The reviewer considers this event **probably** related to study drug.*

<u>The following are 5 additional subjects with treat-emergent SAE"s from the extension study</u>

Patient 001-131 (Bowel obstruction) This 74-year-old Caucasian man had a medical and surgical history of colitis, colon polyps, hives, gout, erectile dysfunction and appendectomy. He began treatment with study medication in the extension phase on (b) (6) The dose at onset of the SAE was 3 g. Concomitant medications included probenecid, colchicine, and sildenafil. About 9 months after starting study medication in the extension phase (b) (6)), the patient experienced

sudden onset of severe, left lower abdominal pain accompanied by nausea and vomiting. He was admitted to the hospital and CT scan was consistent for small bowel obstruction. The plain film next day showed no obstruction. He was treated with intravenous medication and discharged on the same day. The event was considered resolved. Study drug was withheld during the 2-day hospitalization and restarted at the previous dose. The investigator considered the event to not be related to study drug.

Reviewer's comments: The reviewer agrees there is no relationship to study drug.

Patient 002-105 (Deep vein thrombosis) This 74-year-old Caucasian male had a history that included hypertension, panhypopituitarism, and scoliosis. He began treatment with study medication in the extension phase on 08/08/2000 with a dose of 2 g gel. Concomitant medications included potassium, hydrochlorothiazide, and lisinopril. The patient developed a DVT in the left leg in Dec. 2000 (~ 5 months after entering the extension phase), which did not require hospitalization. On (b) (6) the patient experienced pain and warmth in his right leg and was diagnosed with DVT, and hospitalized. The hematocrit was 52.4% in the ER compared with 48.7% 7 months earlier (02/10/2001). The DVT improved by subcutaneous enoxaparin and oral warfarin and he was discharged. Study medication was discontinued due to the event on 09/20/2001. The investigator considered the DVT to be severe in intensity and possibly related to the study medication.

Reviewer's comments: The reviewer believes this event is probably related to study drug.

Patient 006-116 (Myocardial infarction, MI) This 51-year-old Caucasian male had a medical and surgical history of type 2 diabetes mellitus, hypertension, hyperlipidemia, seasonal allergies, depression, alcoholism, subdural hematoma, herniated testicular surgery and appendectomy. He had been administering study drug with a dose of 3 g in the extension study since 09/24/2001. Concomitant medications included pioglitazone, rosiglitazone, loratadine, metformin, and paroxetine. (b) (6) days after starting study drug (b) (6), he experienced chest pain and the ECG confirmed a myocardial infarction (MI). He was hospitalized and underwent stent placement. He was discharged (b) (6). Study medication was withheld during hospitalization and then resumed. The investigator considered the MI to be mild and unrelated to study medication.

Reviewer's comments: The reviewer agrees the relationship to study drug is unlikely.

Patient 014-133 (Back pain, difficulty walking) This 53-year-old Caucasian male had a medical and surgical history including spinal fusion back surgery, renal transplantation, hypertension, coronary artery bypass graft, diabetic dermopathy, stasis dermatitis, hypercholesterolemia, hypertriglyceridemia, diabetes, obesity, gastroesophageal reflux, nephropathy, right great toe amputation, below the knee amputation (left leg), carpal tunnel syndrome, gout, peripheral neuropathy, glaucoma, and retinopathy. The patient has been administering study drug (3 g) in the extension phase since 12/02/2000. Concomitant medications included aspirin, atorvastatin, azathioprine, cyclosporin, dorzolamide/timolol ophthalmic solution, furosemide, gemfibrozil, insulin, latanoprost, losartan, prednisone, ranitidine and TMP/SMZ. At an unspecified time during the study period, the patient had complaints of back pain and difficulty walking. An MRI indicated the presence of a herniated disc. He was admitted to the hospital for a lumbar fusion and discharged 5 days later with improvement. He continued on study medication. The investigator believed that the events were severe but not related to study medication.

Reviewer's comments: The reviewer considers the SAE to be not related to study drug.

Patient 021-105 (*Staph* infection to wound of right foot) This 49-year-old Caucasian male had a history of type 2 diabetes mellitus, diabetic nephropathy, diabetic neuropathy, diabetic retinopathy, hypertension, hyperlipidemia, coronary artery disease, coronary artery bypass graft, systolic murmur, impotence, bilateral Dupuytren's contractures, trace edema, generalized muscle aches, uvulopalatopharyngoplasty, and sleep apnea corrected by surgery. He had been administering study drug (3 g) since 12/15/2000. Concomitant medications included quinapril, aspirin, hydrochlorothiazide, gemfibrozil, simvastatin, glimepiride, and ibuprofen. More than 7 months after starting the extension phase (b) (6), a blister formed on the patient's right foot (between 4th an 5th toes) and ruptured 01/24/2002 with drainage from the site. The patient's right lower leg, ankle, and foot were red and swollen the next day and further deteriorated over the next 2 days. He was hospitalized (b) (6) and treated and the event was resolved. The culture from the wound grew Staphylococcus. Study drug was withheld starting 01/30/2002 and then resumed 02/13/2002. The investigator believed the event to be severe but not related to study drug.

Reviewer's comments: The reviewer considers the SAE to be not related to study drug.

Application site reactions (ASRs)

Patients enrolled in trial T 00-02-01 were given a template and instructed to apply study drug to the same site on the inner thigh once daily in the morning after showering or bathing. One hundred nine of 201 subjects (54.2%) reported one or more ASRs that were either possibly related or related to Fortigel. Seventy seven percent (84/109) of ASRs occurred during the first 28 days. The percentage of subjects who developed ASRs did not appear to be related to the amount of testosterone or gel applied. There were no reports of skin reactions beyond the border marked by the template used to define the application area.

Table 29 Treatment emergent adverse events of application site reactions: safety population

	ITT (N=201)	
	N	(%)
Subjects reporting treatment-related ASRs	109	(54.2)
Subjects treated with concomitant medications for ASRs	13	(6.5)
Subjects discontinued due to ASRs	20	(10.0)

Thirteen patients used concomitant medications on the site of Fortigel gel application to treat the ASR. 19/20 subjects who discontinued from the study had mild to moderate ASRs. Based on medical history, 2/20 subjects who withdrew due to ASRs had previously developed dermatitis while using a topical testosterone product (#002-109 and #006-112) and the onset of both ASRs was within the first month of the study. In the 20 subjects who discontinued treatment due to the ASRs, the ASR resolved in 14 subjects and improved in other subjects. In addition, 13 of the 20 had their ASR resolved without using concomitant medications on the application site.

Any ASR observed or reported by the subject was evaluated using a 5-point scale:

Grade	Description
0	Normal skin, no erythema
1	Questionable erythema not covering entire site
2	Definite erythema covering entire site
3	Swelling or induration and definite erythema
4	Blister formation and/or necrosis

Five types of ASRs were frequently reported during the use of Fortigel gel: erythema, paresthesia, pruritus, rash and xerosis. Since Fortigel contains a large concentration of alcohol, alcohol-induced vasodilation may contribute to development of erythema and rash.

Outcome of the ASRs:

Table 30 : Number (%) of subjects with ASRs and their outcomes as a function of dose

	Dose level of Fortigel			Any dose
	2 g (N=32)	3 g (N=201)	4 g (N=69)	(N=201)
Total subjects with ASRs	3 (9.4%)	91 (45.3%)	22 (31.9%)	109 (54.2%)
Resolved	1 (33.3%)	40 (44.0%)	8 (36.4%)	44 (40.4%)
Improved	1 (33.3%)	2 (2.2%)	0 (0%)	3 (2.8%)
Unchanged	1 (33.3%)	45 (49.5%)	12 (54.5%)	56 (51.4%)
Worsened	0(0%)	4 (4.4%)	2 (9.1%)	6 (5.5%)

The ASR completely resolved in 44 subjects and improved in 3 subjects by the end of the 6-month study while continuing daily Fortigel application.

In attempt to reduce the incidence of ASRs developed during application of the study drug, the sponsor allowed subjects to rotate the application site to a different area of the inner thigh, although considerable overlap was inevitable (Protocol T 00-02-01 Amendment1). The results from showed that a smaller percentage of subjects, although not significantly different, developed an ASR or dropped out when allowed to move the site of application on the thighs.

Adverse events known to be related to testosterone administration

Erythrocytosis: The sponsor regarded that 5 patients had adverse events of erythrocytosis that were reported as increased hematocrit levels (#014-118 and #014-137), increased hemoglobin levels (#002-115) or both (#018-115 and #022-103). Three of these 5 patients were assessed as serious and are summarized in table 31. The remaining 2 patients developed erythrocytosis of moderate severity while on the 3 g dose and both were withdrawn from the study. The outcome of the 5 patients were resolution in 2, unchanged in 2 and the last was lost to follow-up. The onset of erythrocytosis occurred anytime from Day 36 to Day 186 during the use of 3g (3 patients) or 4g (2 patients) gel. The highest recorded hematocrit in these 5 patients was 58.6 % (#018-115). None of the participants reported neuro-occlusive symptoms in association with the increased hematocrit. The sponsor further reported that 12 other patients had increased hematocrit or increased hemoglobin level above ULN at the end of treatment but these were not considered to be adverse events.

Testosterone replacement is associated with increase in red cell mass presumably through its effects on erythropoietin and stem cell proliferation.
Hemoglobin (Hb) levels in the patients treated with Fortigel for 6 months increased by 0.5±1.3 g/dL (3.3%). Two patients (2/190, 1.1%) with Hb concentrations within the normal range at baseline developed treatment-related Hb concentrations above the upper limit of normal (ULN). Of these 2 patients, 1 had a C_{max} > the mid- physiologic range (1140 ng/dL), but the other did not. The sponsor concluded that this limited data suggest that elevation of peak testosterone concentrations are not related to elevations of serum Hb.
The mean hematocrit in the patients from the pivotal Phase 3 study (T 00-02-01) increased from 44.0±4.2% at baseline to 46.0±4.5% at Day 182. This level was achieved on Day 98 and appeared relative stable thereafter. The 6.5% (9/139) of patients who developed hematocrit levels above the ULN was more than the percentage of patients that developed Hb levels above the ULN.

According to the study report, 9/139 patients developed hematocrit level above ULN. This reviewer identified **fifteen** patients who had hematocrit values >52% in the electronically submitted data file (see below Table 31):

Table 31 Erythrocytosis (15 subjects had markedly ↑ hematocrit values ranging from 52.9% to 58.6%) (#002-115, hemoglobin ↑ alone, not listed)

I.D.	Dose	Hematocrit (%)			Day 14		Day 42/56		Day 182		Day 1	
		Base	Day 98	Day 182	C_{max}	C_{avg}	C_{max}	C_{avg}	C_{max}	C_{avg}	C_{max}	C_{avg}
001-126	60 mg	42.4	50.0	53.5	2770	533	3713	863	3098	978	1201	580
002-104	60 mg	49.3	50.7	54.0	1255	679	1326	732	1843	856	285	235
006-100	60 mg	48.3	53.7	ND	804	413	1366	556	1378	577	248	202
006-117	60 mg	49.7	56.7	51.6	3684	920	3917	1251	1964	700	2440	824
007-106	60 mg	46.0	49.8	52.3	1655	511	1361	617	2259	778	414	327
014-106	60 mg	40.3	54.3	49.0	1965	720	1670	664	1042	587	530	365
014-118	60 mg	49.0	50.7	56.9	963	475	1092	434	729	477	156	121
014-137	80 mg	51.2	54.0	54.3	629	285	483	387	Lost to follow-up		329	264
014-154	40 mg	49.3	49.4	52.9	2184	836	1123	482	1610	608	1996	781
017-129	80 mg	48.0	53.4	48.2	758	400	1375	570	1475	672	410	331
018-115	60 mg	47.8	54.8	58.6	2461	580	2259	613	Withdrawn?		3162	691
020-102	80 mg	50.3	50.5	54.2	470	361	1679	566	721	565	231	196
020-123	80 mg	44.7	48.7	53.2	1026	412	1466	631	1230	567	840	462
022-103	60 mg	48.0	58.4	53.7	398	298	2913	719	884	360	374	274
023-110	80 mg	48.6	53.0	52.9	814	360	816	448	723	468	352	260

The sponsor listed 5 AE's of erythrocytosis:

- Severe: #014-118, #014-137, #022-103
- Moderate or mild: 002-115 (hemoglobin ↑ alone), #018-115

The outcome of these 5 subjects with erythrocytosis was:

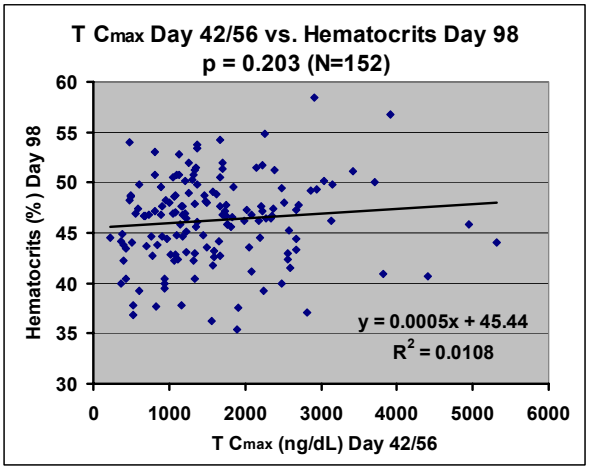
- Resolved: #002-115, #022-103
- Unchanged: #014-118, #018-115
- Lost to follow-up: #014-137

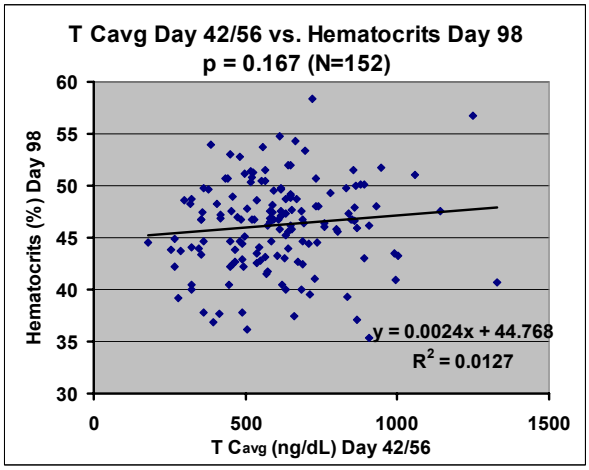
In the above Table 31, 11/15 (73%) had Day 42/56 C_{max} > 1140 ng/dL and 8/13 (62%) had Day 182 C_{max} > 1140 ng/dL (#018-115 discontinued and #014-137 lost to follow-up)

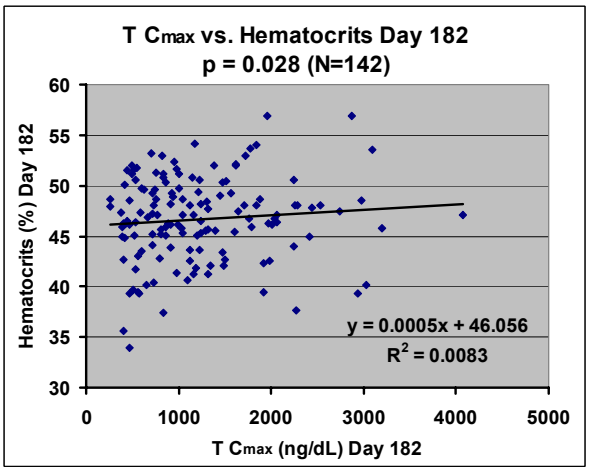
Except for subject #018-115 with the highest recorded hematocrit (58.6%), the sponsor claims that "12 other subjects had elevated hematocrit or hemoglobin levels above ULN at the end of treatment that were not considered to be adverse events."

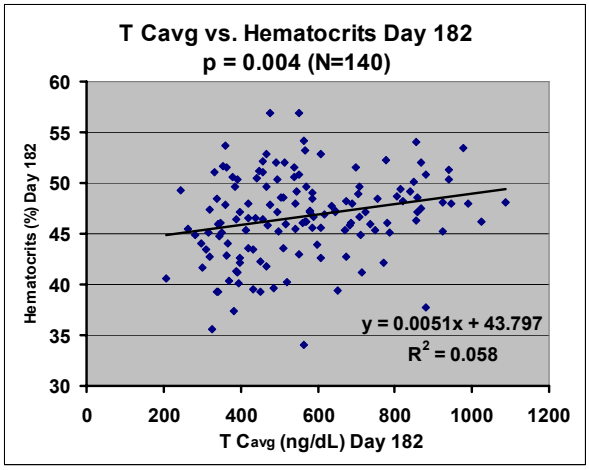
However, in the extension study, 5/15 (33.3%) patients with C_{max} >1800 ng/dL on Day 182 had their hematocrits increased from normal to high, while a similar change in hematocrits occurred in only 6/46 (13%) patients with $C_{max} \leq 1800$ on Day 182.

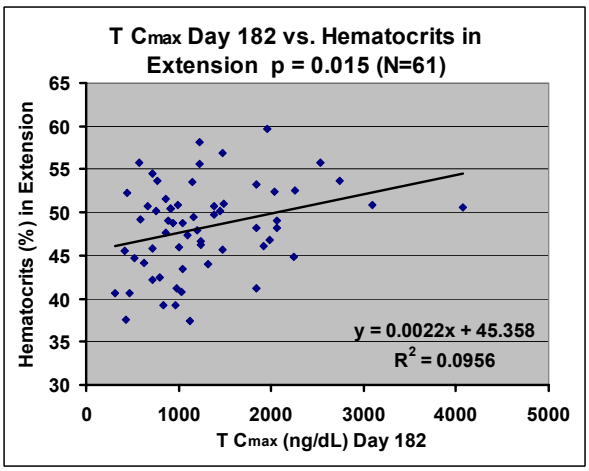
Additional hematocrit Analysis: Regression analysis showed that hematocrits on Day 182 and in the extension study were statistically significantly correlated with C_{max} as well as C_{avg} on Day 182. (see figures below)

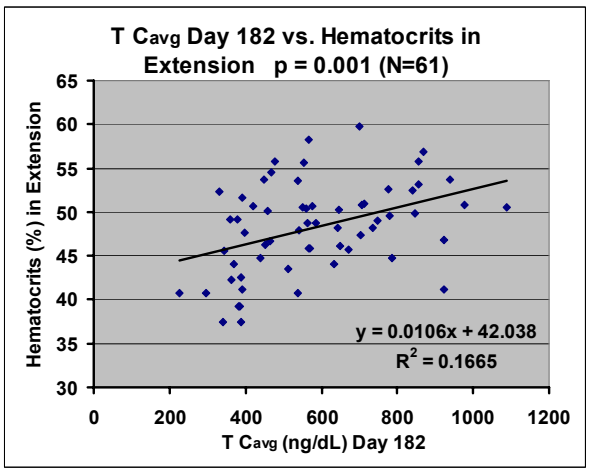

T Cmax Day 42/56 vs. Hematocrits Day 98
p = 0.203 (N=152)
Hematocrits (%) Day 98
T Cmax (ng/dL) Day 42/56
y = 0.0005x + 45.44
R2 = 0.0108

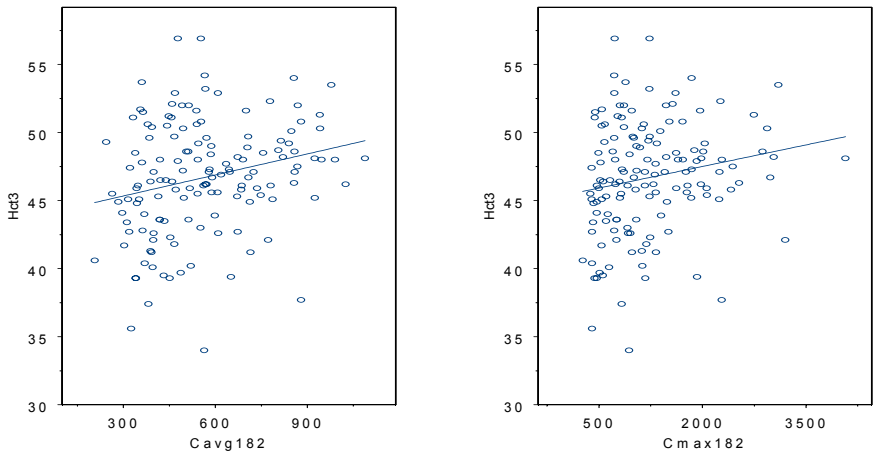

T Cavg Day 42/56 vs. Hematocrits Day 98
p = 0.167 (N=152)
Hematocrits (%) Day 98
T Cavg (ng/dL) Day 42/56
y = 0.0024x + 44.768
R2 = 0.0127


T Cmax vs. Hematocrits Day 182
p = 0.028 (N=142)
Hematocrits (%) Day 182
T Cmax (ng/dL) Day 182
y = 0.0005x + 46.056
R2 = 0.0083


T Cavg vs. Hematocrits Day 182
p = 0.004 (N=140)
Hematocrits (%) Day 182
T Cavg (ng/dL) Day 182
y = 0.0051x + 43.797
R2 = 0.058


T Cmax Day 182 vs. Hematocrits in Extension p = 0.015 (N=61)
Hematocrits (%) in Extension
T Cmax (ng/dL) Day 182
y = 0.0022x + 45.358
R2 = 0.0956


T Cavg Day 182 vs. Hematocrits in Extension p = 0.001 (N=61)
Hematocrits (%) in Extension
T Cavg (ng/dL) Day 182
y = 0.0106x + 42.038
R2 = 0.1665



***Reviewer's comments: Increasing hematocrits appear to correlate with increasing testosterone C_{max} levels.* Other researchers have reported that about 20% of the subjects in the higher dose testosterone gel group had a Hct that was elevated to above normal range on day 180 of treatment (Wang C, Swerdloff RS, et al.: J Clin Endocrinol Metab. 85:2839-2853, 2000).**

Gynecomastia: 4 patients (#003-100, 006-111, 010-103, and #014-143 reported as #014-130) developed signs or symptoms of gynecomastia or breast tenderness. Two patients developed gynecomastia (1 taking 60 mg and 1 taking 40 mg T) and 1 patient experienced worsening previous gynecomastia (40 mg T). One patient taking 60 mg T developed left breast tenderness. None of these patients had persistently high estrogen levels, but 3 of the patients were obese. One patient reported a history of gynecomastia. All 4 cases of gynecomastia were assessed as mild. Gynecomastia is a well-recognized adverse event of testosterone replacement therapy. The frequency (2%) of gynecomastia in this Phase 3 study appears to be consistent with results from other androgen replacement data.

Reviewer's comments: The dosage of testosterone replacement therapy in obese patients was routinely higher than in patients with normal weight. It is not surprising that the 3 men who developed gynecomastia were obese with BMI > 30 kg/m^2 and had the peak level of serum estradiol > ULN. It's likely that increasing aromatization of testosterone to estradiol in the adipose tissue in these individuals might have contributed to the development of breast enlargement.

Prostate disease and elevations of PSA: Nine patients had an adverse event associated with the prostate gland with 5 prostatitis among them. Two of these 5 patients with prostatitis also had increased PSA. Increased PSA in these 2 may have been due to the prostatitis. Increases in PSA were reported in another 2 patients. One of them had an enlarged prostate, and the other had an indurated prostate noted on his exit PE. The latter was diagnosed with prostate carcinoma even though he had normal PSA levels. Two of these 9 patients withdrew from the study due to their events including one patient with prostate carcinoma but a normal PSA. The other patient had a PSA of 20 ng/mL after 1 month of 3g CP601B and the event resolved (PSA returned to 0.9 ng/ml 3 months after discontinuing treatment). The prostate –related events were classified as mild to moderate in the remaining 7 patients. In 3 patients, the events (prostatitis, enlarged prostate with increased PSA, and indurated prostate) occurred at the end of the study, and the patients were under follow-up at the time the study report was submitted.. The other 4 cases were reported as mild and resolved with continued CP601B; prostatitis was treated with antibiotics in 3 of these patients. All

patients who had elevated PSA had their levels return to normal by the end of the study. For the prostate carcinoma case, the investigator assessed the event as severe in intensity and possibly related to CP601B gel administration. The patient had received intramuscular testosterone for hypogonadism before participating in the study.

Additional analysis of changes in PSA (Delta PSA) vs. serum testosterone C_{max} and C_{avg} on Day 182 did not reveal a statistically significant relationship between changes of PSA and either C_{max} or C_{avg} on Day 182

Reviewer's comments: There was no placebo group in this pivotal study.

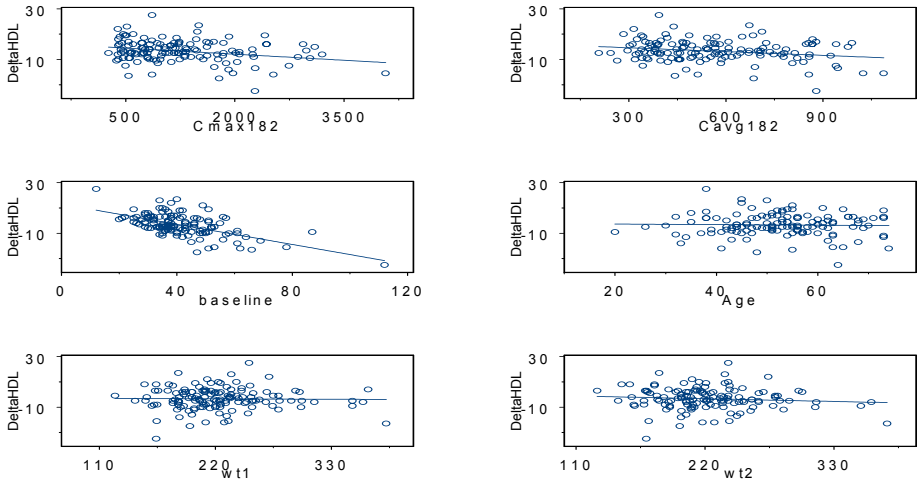
HDL reduction (Δ HDL)

	Age	Wt. 1	Wt. 2	Baseline HDL	C_{max} 42/56	C_{avg} 42/56	HDL Day98	C_{max} 182	C_{avg} 182	HDL 182	Δ HDL 182
Mean	52.9	223	223	41.03	1562	826	36.51	1218	715	37.99	-3.04
SD	10.8	44.7	42.5	12.89	927	348	10.30	722	319	10.61	9.03

Δ HDL 182 = HDL Day 182 – HDL baseline

In study T 00-02-01, the mean HDL-C concentrations were decreased by 8% (from 41.0±12.9 of baseline to 38.0±10.6 mg/dL at Day 182). The decrease (ΔHDL) was more commonly seen in those patients whose C_{max} > 1140 ng/dL (22.8%) than those below (15.8%), and it further increased to 40% of patients with C_{max} > 1140 ng/dL in 12-month extension study. Analysis of the HDL-C data showed:

- A negative slope was found in the relationship between HDL and testosterone concentrations indicating a decrease in HDL (ΔHDL) corresponding to an increase in T concentrations (C_{avg} and C_{max}).
- ΔHDL appears to be greater in patients with higher baseline HDL values, lower baseline body weight, and sustained exposure to T. It should be noted that the correlation with low baseline body weight might be confounded with higher T concentrations (C_{avg} and C_{max}).
- The results from a mixed effect modeling analysis (to analyze all the factors together, including the effect of baseline HDL, baseline body weight and T concentration at day 42/56 on the ΔHDL on Day 182) suggest that baseline HDL, baseline body weight and sustained T exposure are statistically significantly covariates for ΔHDL at a given T concentration on Day 182.

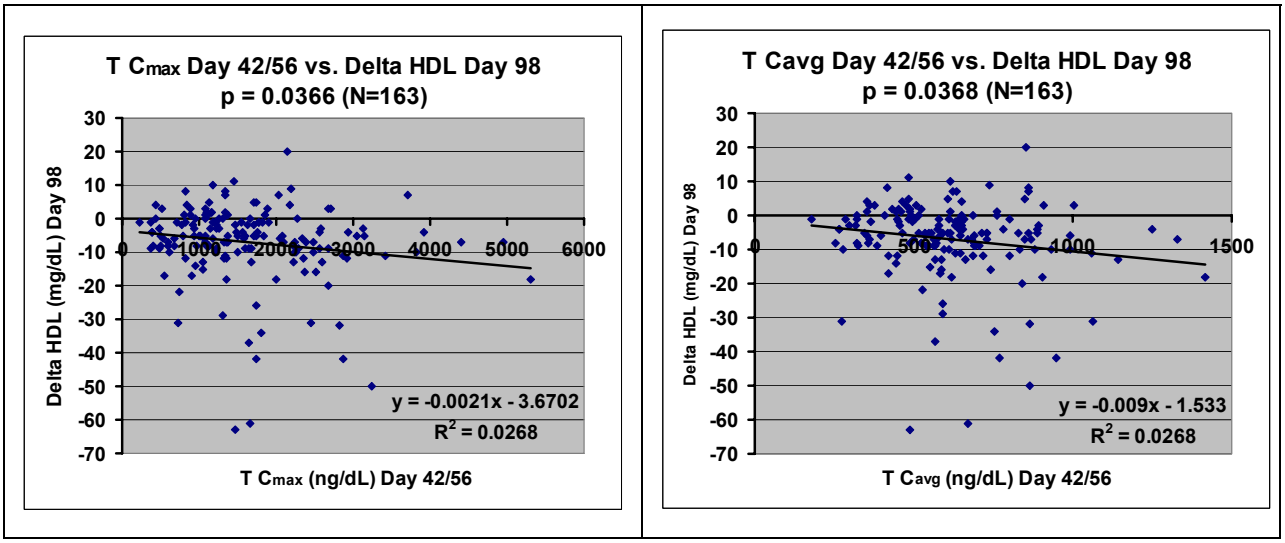


There is a potential risk for testosterone replacement therapy to adversely affect plasma lipoprotein profile and increase the risk of atherosclerotic heart disease. The decrease in HDL-C in response to testosterone administration is the result of the testosterone increasing hepatic lipase activity. The long-term consequences of testosterone administration and the effect of high C_{max} testosterone levels on heart disease, however, remain unknown.

In the pivotal Phase 3 study T 00-02-01 mean HDL concentrations were decreased by 8%.

The regression analysis showed that

- ΔHDL on Day 98 was significantly correlated with C_{max} or C_{avg} on Day42/56.
- ΔHDL on Day 182 was statistically significantly correlated with C_{max}, or C_{avg} on Day 182
- ΔHDL in extension study was still significantly correlated with C_{max} on Day 182.



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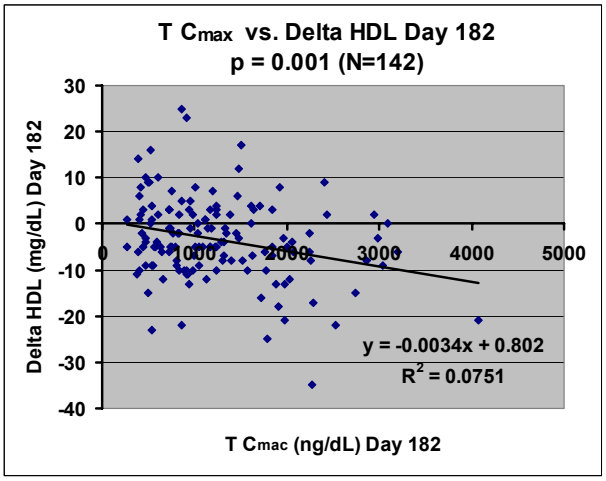
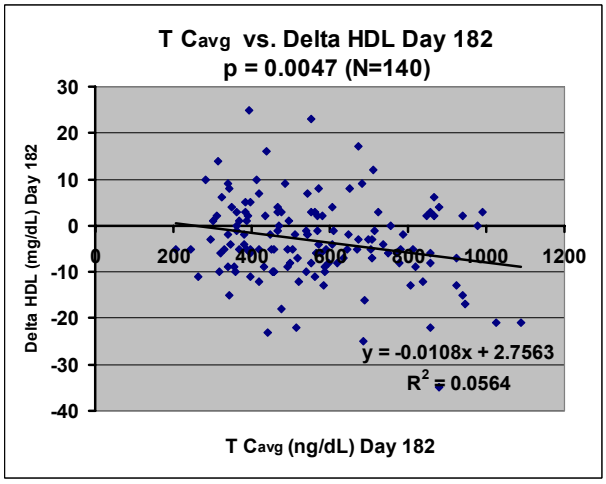
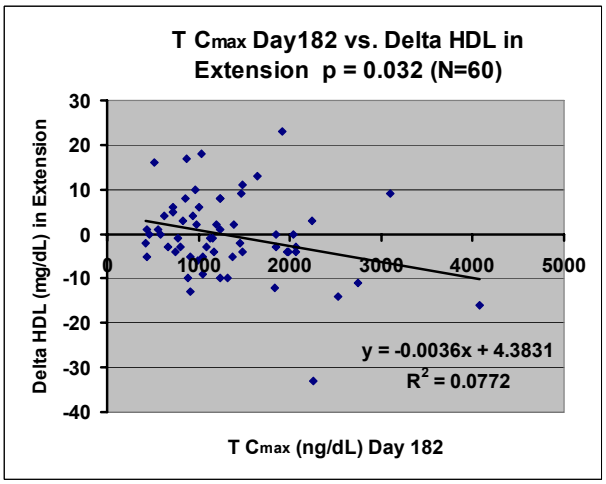
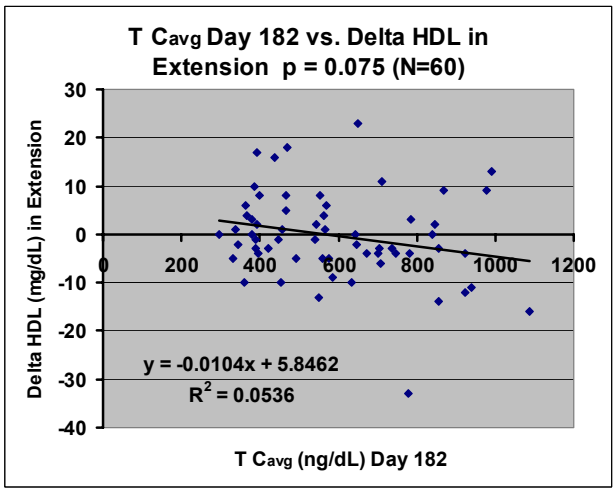








Supraphysiologic Exposure

One of major concerns regarding potential risks in patients using Fortigel 2% gels is **high level of C_{max}**. Based on results of the pivotal Phase 3 study, this product was found to result in supraphysiologic serum T levels in a significant proportion of the study population (physiologic serum total T level is 300 - 1140 ng/dL):

- On Day 42/56 (1 month at final dosing regimen), 5/165 (3%) patients had **C_{avg}** values > 1140 ng/dL and 1 had C_{avg} value > 1700 ng/dL
- On Day 42/56, 23/165 (14%) patients had C_{max} values between 1500 - 1800 ng/dL; 28/165 (17%) had C_{max} values between 1800 - 2500 ng/dL and 26 (16%) had C_{max} values between 2500 - 5311 ng/dL (3 values were > 4000).
- On Day 182, 13/147 (8.8%) patients had C_{max} values between 1500 - 1800 ng/dL; 20 (14%) had C_{max} values between 1800 - 2500 ng/dL, and 9(6%) had C_{max} >2500 ng/dL with 1 value > 4000.

List of patients with C_{max} > 1800 ng/dL on Day 42/56 or/and Day 182

Day 42/56 (N=54)			Day 182 (N=29)		
Patient #	**Dose (mg)**	**C_{max} (ng/dL)**	**Patient #**	**Dose (mg)**	**C_{max} (ng/dL)**
001-104	80	2478			
001-108	40	2820	001-108	40	2276
001-115	80	2519			
001-126	60	3713	001-126	60	3098
001-131	60	2189	001-131	60	1921
			002-104	60	1843
002-105	40	3416	002-105	40	1882
002-116	60	2484			
			003-105	80	1976
003-109	60	2245			
			004-110	60	2281
005-103	60	1895			
006-107	40	1907			
006-111	40	2371	006-111	40	1914
006-117	60	3917	006-117	60	1964
006-121	80	3247			
006-123	40	2028			
006-125	80	3041	006-125	80	3032
			007-103	60	1981
			007-106	60	2259
007-117	80	5311	007-117	80	4071
010-101	60	2675	010-101	60	2247
010-103	60	2453			
010-105	60	2339			
010-108	60	1817			
010-118	80	2153			
010-127	80	2049	010-127	80	2060
011-102	60	2578			
011-103	80	1852	011-103	80	2982
011-106	80	2868			
011-110	60	2218			
011-112	40	2598	011-112	40	3198
012-100	40	4401	012-100	40	2411
012-102	40	2672			
			012-110	60	2032
			012-111	80	2009
012-117	80	2089			
012-130	80	2388			
014-105	80	2174			
014-113	80	4945	014-113	80	2868
014-114	60	2270			
014-139	60	2707			
014-145	60	2585			
			015-111	60	2064
017-100	60	2937			
017-108	60	2079			
017-110	60	2863			
017-112	60	2286			
017-113	60	2229	017-113	60	2743

018-113	80	3133	018-113	80	2436
018-115	60	2259			
018-118	80	2235	018-118	80	2937
019-105	60	1806			
019-107	40	2562			
			020-101	60	2241
020-106	40	1834	020-106	40	1843
020-111	60	2561			
021-108	80	3821			
022-103	80	2913			
022-112	60	1992	022-112	60	2529
023-105	60	2680			
023-108	80	3147			
023-116	80	2352	023-116	80	1835

Twenty patients had C_{max} > 1800 ng/dL on both Day 42/56 and Day 182. This reviewer assumes that these 20 patients (10% of the ITT population) were exposed to C_{max} > 1800 ng/dL on a daily basis for 6 months.

The sponsor's analysis included 54 patients with C_{max} > 1800 ng/dL defined as "subjects with C_{max} > 1800 ng/dL on Day 42/56 or Day 182 or on both days are counted in C_{max} > 1800 ng/dL group". According to this definition, this reviewer believes that the number of patients should be 63 instead of 54. The sponsor believes that hypogonadal men with these transient (for < 4.8 hrs of a 24-hr dosing interval) supraphysiologic concentrations (> 1800 ng/dL) do not appear to have significantly greater risk of developing an adverse events than do patients with C_{max} values below that concentration (40/52, 76.9% vs. 70/110, 64.5%. From this reviewer, the relationship of AE's to testosterone C_{max} levels > and ≤ 1800 ng/dL is shown in table 32.

Table 32 Summary of changes related to AEs from baseline to Day 182 for ITT population

Value at Day 182 vs. baseline	Testosterone C_{max} (ng/dL)	
	≤ 1800 (N=85)	> 1800 (N=54)
Hemoglobin (from normal to ↑)	1 (1.2%)	1 (1.9%)
Hematocrit (from normal to ↑)	5 (5.9%)	4 (7.4%)
(from high to further)	1 (1.2%)	1 (1.9%)
HDL-C (from normal to ↓)	17 (20.0%)	12 (22.2%)
(from low to normal)	6 (7.1%)	2 (3.7%)
LDL-C (from normal to abnormal)	5 (5.9)	7 (13.0%)
PSA (develop to 4.0 ng/dL)		1 (1.9%)
Cancer of prostate, PSA normal		1

Reviewer's comments: This reviewer believes that the AE's show a trend, in general, to be more common in the > 1800 ng/dL C_{max} group.

In the extension study T 00-02E-01, 7 of 45 (15.6%) patients had at least one serum testosterone concentration >1140 ng/dL at 6 months (1775±364 ng/dL, MEAN ±SD) and furthermore, 3 of 31 (9.7%) patients have at least one serum testosterone concentration >1140 ng/dL at 12 months (1867±561 ng/dL).

Patients who had at least one serum testosterone (T) concentration > 1140 ng/dL during extension study

6 months (N=7)			12 months (N=3)		
Patient #	**Dose (mg)**	**T (ng/dL)**	**Patient #**	**Dose (mg)**	**T (ng/dL)**
			002-104	60	2157
005-101	40	1504			
			006-107	40	1221
006-117	60	1696			
007-106	60	2027			
			010-113	80	2224
017-113	60	1919			
020-125	60	1731			
021-102	60	2336			
021-103		1215			

For these 10 patients with at least one serum testosterone concentration >1140 ng/dL either at 6 months or at 12 months, 9 patients (90%) developed adverse events including 4 with hypertension (40%), 2 with ASRs (pruritus, erythema), 1 with prostate enlargement, 1 with lower HDL and 1 with increase of blood and urinary glucose level. The incidence of AEs was higher than in those with testosterone levels within the normal range.

Reviewer's overall assessment of safety:

Safety data for Fortigel 2% gel were derived from a single pivotal Phase 3 study (T 00-02-01) and several Phase 1 /2 studies, as well as an open-label extension study (T 00-03E-01).

Overall, a significant percentage of the patients studied were exposed to high serum C_{max} concentrations of testosterone. In the pivotal Phase 3 clinical trial, the high C_{max} as well as high C_{avg} were correlated with increasing hematocrits and decrease in HDL.

In the long-term, extension study comprised of 82 patients with exposure for up to 12 months, the high C_{max} continued to be correlated with increasing hematocrits and decrease of HDL-C.

Overall, the skin reaction rate of Fortigel was high compared with the other two marketed testosterone gel products. Two findings in the Phase 3 pivotal trial deserve emphasis:

(1) High C_{max} levels:

One of major concerns regarding potential risks in patients using Fortigel 2% gels is **high C_{max} levels**. Based on results of the pivotal Phase 3 study, this product was found to result in supraphysiologic serum T levels in a significant proportion of study population (physiologic serum total T level is 300 - 1140 ng/dL):

- On Day 42/56 (1 month at final dosing regimen), 5/165 (3%) patients had **C_{avg}** values > 1140 ng/dL and 1 among them had C_{avg} values > 1700 ng/dL
- On Day 42/56, 23/165 (14%) patients had C_{max} values between 1500 - 1800 ng/dL; 28/165 (17%) had C_{max} values between 1800 - 2500 ng/dL and 26/165 (16%) had C_{max} values between 2500 - 5311 ng/dL (3 values were > 4000).
- On Day 182, 13/147 (8.8%) patients had C_{max} values between 1500 - 1800 ng/dL; 20 (14%) had C_{max} values between 1800 - 2500 ng/dL, and 9(6%) had C_{max} >2500 ng/dL with 1 value > 4000.

(2) Exposure – Response:

The hematocrits (Hct.) and the changes of HDL-C (ΔHDL) were statistically significantly correlated with serum T C_{max}, and C_{avg} concentrations on Day 182.

Hematocrits: There was a statistically significant trend of increasing Hct values with either an increase in serum T C_{avg} (p = 0.0042) or C_{max} (p = 0.0303).

HDL-C (ΔHDL): A negative correlation between ΔHDL and T concentrations (C_{avg} or C_{max}) was apparent, which indicated a general decrease in HDL values corresponding to an increase in T concentrations.

Overall, the Cmax values are high and there were not enough patients enrolled to provide reassuring safety data to support the safety of Fortigel.

Compared to other commercially available products for the same indication, the C_{max} values of T of Fortigel are significantly higher (Tables 33 and 34).

Table 33 Steady-State serum testosterone concentrations during therapy (Mean±SD, ng/dL)

Trade Name	Testim (Day 30)		Androgel (Day 180)			Fortigel 2% gel (Day 182)*		
Dose/day	50 mg	100 mg	5 g	7.5 g	10 g	2 g	3 g	4 g
C_{avg}	365±187	612±286	555±225	601±309	713±209	548±157	593±194	596±211
C_{max}	538±371	897±565	830±347	901±471	1083±434	1225±528	1353±699	1388±887
C_{min}	223±126	394±189	371±165	406±220	485±156	295±111	306±116	299±102

* based on EE population

Table 34 Comparison of PK Outliers in T- Gels at Steady State*

Products	C_{max} (ng/dL)				C_{avg} (ng/dL)	N
	1200-1500	1501-1800	1801-2500	>2500	>1100	
Fortigel	***14 (9%)***	***11 (7%)***	***20 (14%)***	***9 (6%)***	***0 (0%)***	***147***
Androgel	**4 (2%)**	**4 (2%)**	**7 (5%)**	**0 (0%)**	**5 (3%)**	**151**
Testim	**20 (14%)**	**13 (9%)**	**4(2%)**	**0 (0%)**	**2 (1%)**	**162**

* 6 month post treatment for Fortigel & Androgel, 3 months for Testim.

VIII. Dosing, Regimen and Administration Issues

The initial [redacted] (b) (4) of Fortigel 2% gel and dosage adjustment on [redacted] (b) (4) was selected based on results from pilot Phase 1 /2 studies. The recommended starting dose in the labeling is the same as in the pivotal Phase 3 study, but the basis of dose modification is changed to serum T concentration 2-hour post dosing (C_2) instead of the [redacted] (b) (4).

Application site of Fortigel should be allowed to dry prior to dressing. Hands should be washed thoroughly with soap and water immediately after Fortigel has been applied. The transfer study has shown that once the hands are washed and the application site is covered with clothing, there is little risk of transferring Fortigel to another person due to bodily contact. However, to assure adequate absorption of the testosterone, the application site should not be washed for at least two hours after gel administration.

IX. Use in Special Populations

Gender differences: Fortigel testosterone gel is indicated for replacement therapy in men for conditions associated with deficiency or absence of endogenous testosterone. The drug is contraindicated in women.

Racial differences: The effect of race of pharmacokinetics has not been studied. The number of non-Caucasian patients in the clinical trials is too small (13.1%, including 10.7% for Black, 2.0% for Hispanic, and 0.4% for Asian) to draw meaningful conclusions.

Issues with the elderly: The pharmacokinetics and pharmacodynamics were evaluated in pivotal Phase 3 study T 00-02-01 in 201 patients including 89 patients of age ≥ 55 (44.3%). Exposure to testosterone, represented by AUC and C_{max}, was not statistically different between age groups. The incidence of major adverse events appeared to be no different between age groups.

Fortigel did not significantly affect PSA levels during the 6-month Phase 3 study, as only one patient developed an increased PSA level at the end of the study. Increased PSA levels were also observed in 6 patients on Day 98 or other times. These increases were associated with prostatitis in 2 patients and returned to pretreatment levels following resolution of the infection without stopping CP601B administration. Two others returned to normal upon repeat examination and the remaining 2 are being evaluated.

Many older men have microscopic foci of cancer in their prostate. At this moment there is no data to clarify whether testosterone administration will make these subclinical foci of cancer grow and become clinical overt.

Renal/Hepatic impairment: The effect of renal or hepatic impairment on Fortigel pharmacokinetics has not been studied in this submission.

Pediatric issues: Fortigel has not been clinically evaluated in males less than 18 years of age. The sponsor requested deferral of pediatric trials until appropriate studies can be planned and completed in the pediatric population.

Pregnancy use information: Fortigel is contraindicated in women. Since testosterone may cause fetal harm, pregnant women are contraindicated to have skin contact with Fortigel application sites in men.

X. Conclusions and Recommendations

Final Safety Conclusions

Exogenous testosterone has been available for decades and has been widely used and studied. In last several years, there has been renewed interest in testosterone replacement therapy with emphasis on the potential to benefit normal older men.

Two testosterone gel products have already been approved by the FDA for use in hypogonadal men. Cellegy Pharmaceuticals Inc. evaluated the safety of its topical gel testosterone formulation (CP601 and CP601B) in one Phase 3 as well as several Phase 1 / 2 trials. The majority of the safety information is derived from the single multicenter, pivotal Phase 3 study (T-00-02-01) conducted in adult males with baseline testosterone levels < 300 ng/dL. The three dosages of the treatment were Fortigel 40mg, 60 mg, and 80 mg.

A significant percentage of patients in the pivotal study experienced high testosterone C_{max} values (>1500 ng/dL). This high level of C_{max} statistically significantly correlated with increasing hematocrits and decrease of HDL-cholesterol values. The clinical risk(s) of daily high C_{max} levels of testosterone are not known.

In conclusion, from the submitted Fortigel Phase 3 trial, the C_{max} values of testosterone are high and there were not enough patients enrolled to provide reassuring safety data to support the safety of Fortigel.

Recommendations on Approvability (Regulatory Action):

This reviewer recommends non-approval of Fortigel™ 2% (testosterone gel).

Guodong Fang, M.D.
Medical Officer, HFD-580
Division of Reproductive and Urologic Drug and Products

Appendix A

Study T 98-02-01: Phase 2 determination of dose, dosing interval, and site of application

Design:

This was an open-label, randomized, 6 treatment regimen, 3-way, 3-period crossover matrix type, Phase 1 / 2 study conducted in two sites in the US. A 7th open-label treatment regimen was added by protocol amendment. 18 subjects enrolled in the study (6 subjects were to participate in 3 treatment regimens). Each subject was randomized to 3 treatment phases (I, II, III) of testosterone gel administration. During each treatment phase, the subject was to follow one of 6 treatment regimens (A to F). In all treatment regimens, testosterone gel was applied as 1 gram per 100 cm^2 surface area of skin. During treatment phase IV, treatment regimen G was added as a 7th regimen to the original design.

Table 35 Treatment description in Study T 98-02-01

Treatment	Description
Regimen A	1 g of 2% testosterone gel (20 mg testosterone) was applied q.d. to the same site on the upper arm
Regimen B	1 g of 1% testosterone gel (10 mg testosterone) was applied q.d. to the same site on the upper arm
Regimen C	1 g of 2% testosterone gel (20 mg testosterone) was applied q.d. to the same site on the upper arm on Study Days 1, 3, 5, and 7 and to the outer thigh on Study Days 2, 4, and 6
Regimen D	1 g of 1% testosterone gel (10 mg testosterone) was applied q.d. to the same site on the upper arm on Study Days 1, 3, 5, and 7 and to the outer thigh on Study Days 2, 4, and 6
Regimen E	1 g of 2% testosterone gel (20 mg testosterone) was applied b.i.d. to the same site on the outer thigh in the morning, and 7 and to the same site on the upper arm in the evening (total daily dose 40 mg testosterone)
Regimen F	1 g of 2% testosterone gel (20 mg testosterone) was applied b.i.d. to the same site on the outer thigh in the morning, and 7 and to the same site on the upper arm in the evening (total daily dose 40 mg testosterone)
Regimen G	1.5 g of 2% testosterone gel (30 mg testosterone) was applied q.d. to a 150 cm^2 area of skin at the same site on each outer thigh (total daily dose 60 mg testosterone)

The order of treatment regimens was to be randomized with a minimum 3-day drug washout period between treatment phases. Venous blood samples were obtained before and at specified times following the morning gel administration to assay serum concentrations of testosterone on Study Days 1 and 7 of treatment phase I, II, and III. On Days 3 and 5, blood samples were obtained before (and 1.5 hrs after, in treatment regimen G) gel administration.

Enrollment: Males between 18 and 75 years of age with primary or secondary hypogonadism, defined as a serum testosterone concentration < 300 ng/dL at the screening period (< 300 ng/dL in 2 consecutive blood samples obtained at least 7 days apart, or ≤ 250 ng/dL in a single sample).

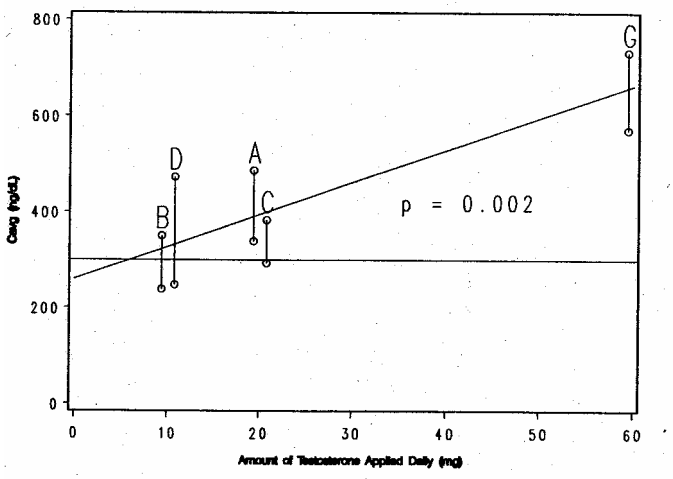
Test articles included testosterone gel CP601B 2% (20 mg) or 1% (10 mg).

Results

Table 36 Summary statistics for C_{avg} on study Days 1 and 7 (Study T 98-02-01)

		Treatment regimen						
		A	B	C	D	E	F	G
Day 1	N	8	7	8	8	9	8	nd
	Mean (ng/dL)	360	219	385	300	352	246	nd
	SD	165	114	153	159	104	101	nd
	Median (ng/dL)	329	272	374	285	342	220	nd
	Range (ng/dL)	208-746	36-311	195-644	135-583	196-545	120-405	nd
Day 7	N	8	7	8	8	9	8	6
	Mean (ng/dL)	413	294	338	360	448	401	652
	SD	208	148	127	317	135	182	198
	Median (ng/dL)	377	264	325	264	436	351	596
	Range (ng/dL)	192-766	43-506	206-601	91-1098	272-680	210-787	434-918

Figure: Random coefficient analysis of C_{avg} for single dose regimens A, B, C, D, and G



The results of examination of linearity of C_{avg} and C_{min} with the total amount of testosterone applied daily showed that the effect of dose was highly significant and regimen G (3 g of 2% gel applied once daily split between both thighs) best maintained the serum testosterone concentration within the physiological range of 300-1140 ng/dL:

- The mean C_{avg} (652 ng/dL)was significantly higher than the 300 ng/dL lower limit of the PR and all subjects had C_{avg} > 300 ng/dL, and the percentage of patients predicted to show C_{avg} > 300 ng/dL was calculated to be 96.3%.
- The mean C_{min} (383 ng/dL) was significantly higher than the 300 ng/dL lower limit of the PR, 50.0% of the subjects had $C_{min} \geq$ 300 ng/dL, and the predicted percentage of patients above 300 ng/dL was calculated to be 69.5%
- The majority of subjects (≥ 67%) had their serum testosterone concentrations between 300 and 1140 ng/dL throughout the day.

Safety: No safety issues were evident during the study.
Conclusions:

- Based on the results obtained with regimen G, it's anticipated that a regimen consisting of once daily application of 3 g CP601 per 300 cm2 should provide an adequate dose of testosterone to maintain the serum testosterone concentration in the PR for the large majority of hypogonadal men.
- The correlation between the testosterone dose applied to the skin and C_{avg} and C_{min} demonstrated that, for those hypogonadal men whose serum testosterone concentrations would not be adequately raised by the 3 g dose, adjustment to a lower (e.g., 2 g) or higher (e.g., 4 g) amount of gel would shift their testosterone levels in the desired direction.

Appendix B

Study T 00-02-03: Effect of showering on testosterone pharmacokinetics

Design: This was an open-label, non-vehicle-controlled, randomized, 2-treatment, 2-period crossover pharmacokinetic (PK) study conducted in one site in the US. 7 subjects were enrolled in the study. Each was to participate in 2 seven-day treatment periods. During both study periods, the subject applied 3 g of CP601B 2% gel (60 mg testosterone) daily as 1.5 g applied to a 150 cm2 area of skin on each anteromedial thigh from Day 1 to Day 6. On Day 7, subjects reported to the study site for testosterone gel administration and blood collection for a 24-hr PK profile at prior to (Time 0), 0.5, 1, 2, 4, 6, 8, 10, 12, 15, 20 and 24 hrs following application of CP601B. At time of entry, subjects were assigned to a

sequence of treatment (AB or BA), In treatment A, the subjects were to shower 2 hrs after application of the gel and after the 2-hr postdose blood samples were obtained. In treatment B, the subjects were not to shower during the 24-hr PK profile period, but could shower at the study unit before gel application, if desired. Subjects continued to apply study medication for at least 6 additional days. On Day 7 of second period, the subject was admitted to the study unit for the second 24-hr PK profile under the alternate showering condition.

Enrollment: Males between 18 and 75 years of age with primary or secondary hypogonadism, defined as a serum testosterone concentration < 300 ng/dL at the screening period (< 300 ng/dL in 2 consecutive blood samples obtained at least 7 days apart, or ≤ 250 ng/dL in a single sample). Subjects were otherwise in satisfactory health based on results of medical history, physical examination, ECG and clinical laboratory test results at a screening
Test articles included testosterone gel CP601B 2% (20 mg)(Lot # 0D067A).
Results:

Table 37 Mean±SD pharmacokinetic parameter estimates on Day 7 (Study T 00-02-03)

Pharmacokinetic parameter (Mean±SD)	Treatment A (shower, N=7)	Treatment B (No shower, N=7)
AUC 0-24 (ng-h/dL)	8939±2107	9199±3216
C_{max} (ng/dL)	893.6±357	790.6±459
C_{avg} (ng/dL)	372.3±87.6	383.3±134.0
C_{min} (ng/dL)	201.7±73.6	246.4±65.1
T_{max} (h)	4.60±1.50	4.29±2.43

Table 38 Ratios of geometric means and 95% confidence intervals for Day 7 Pharmacokinetic parameter estimation

Pharmacokinetic parameter	N	Ratio of geometric means[a] (B/A)	95% confidence limits for Ratio[b]
C_{max} (ng/dL)	7	0.83	(0.47 – 1.44)
C_{avg} (ng/dL)	7	1.03	(0.79 – 1.34)
C_{min} (ng/dL)	7	1029	(0.91 – 1.85)

[a] Exponential of difference of least square means (LSM) from the analysis of variance
[b] Exponential of difference of LSM from the analysis of variance ± t (0.025, DF) x SE of difference, where LSM is the adjusted mean and SE is its standard error, where the error degrees of freedom (DF) =5.

Safety results: No SAE recorded and the CP601B 2% gel was well tolerated. One single treatment-emergent adverse event occurred (hematuria) which was not deemed related to the study drug.

Conclusion: Based on the analysis of all 3 key PK parameters ($C_{avg,}$ C_{min} , and C_{max}), it was concluded that showing 2 hrs after application of CP601B 2% gel had no statistically significant nor clinically relevant effect on the pharmacokinetics of topically applied testosterone.

Reviewer's comments: The conclusion regarding the effect of showering 2 hrs post application of the gel is appropriate.

Appendix C

Study T 00-02-07: Effect of different surface areas of application on the pharmacokinetics of testosterone following application of a fixed dose of CP601B

Design: This was a multi-center, open-label, randomized, 3-treatment, 3-period crossover pharmacokinetic (PK) study conducted at two sites in the US. Twelve subjects were enrolled in the study.

During each of the 3 treatment periods, subjects applied 2g of the gel over a 200 cm^2 (Treatment A), 400 cm^2 (Treatment B), or 800 cm^2 (Treatment C)area of skin on the anteromedial thigh (total daily dose: 40 mg testosterone applied to the skin) each morning for 8 consecutive days (Day 1 to 8). There was a washout interval of at least 3 days between treatment periods. During each study period, venous blood samples were obtained for PK evaluation prior to application (Time 0) on Days 7 and 8, and at specified times (0.5, 1, 2, 4, 6, 8, 10, 12, 16, 20 and 24 hrs) following application on Day 8.

Safety evaluations: Treatment-emergent adverse events, protocol-specified assessment of inflammation at the application site, clinical laboratory results, vital sign measurements, physical examination (PE) findings, and ECG results.

Enrollment: Males between 18 and 75 years of age with primary or secondary hypogonadism, defined as a serum testosterone concentration < 300 ng/dL at the screening period (< 300 ng/dL in 2 consecutive blood samples obtained at least 7 days apart, or ≤ 250 ng/dL in a single sample). Subjects must have been willing to discontinue any current testosterone medication until serum concentration was < 300 ng/dL, and were otherwise in satisfactory health based on results of medical history, physical examination, ECG and clinical laboratory test results at a screening.

Results:
Following 8 days of daily application of 2g of 2% CP601B to the thigh treatment A: 200 cm^2, B: 400 cm^2, and C: 800 cm^2), the mean testosterone concentration-time profiles were nearly superimposable.

Table 39 Ratio of geometric means and 95% CI for PK parameter estimates on Day 8: Subjects with PK data for at least 2 periods (study T 00-02-07)

Surface area ratios	N	Ratio of geometric means for PK (95% confidence limits for ratio)		
		C_{max} (ng/dL)	C_{avg} (ng/dL)	C_{min} (ng/dL)
400 cm^2 (Y) vs. 200 cm^2 (X)	12	1.32 (1.09, 1.60)	1.13 (1.02, 1.26)	1.10 (0.89, 1.35)
800 cm^2 (Y) vs. 200 cm^2 (X)	12	1.04 (0.86, 1.26)	1.12 (1/.01, 1.26)	1.21 (0.99, 1.49)
800 cm^2 (Y) vs. 400 cm^2 (X)	12	0.79 (0.65, 0.95)	0.99 (0.89, 1.09)	1.10 (0.90. 1.36)

The differences in C_{avg} between treatment groups were small and not statistically significant and C_{avg} values for all 3 treatments were or nearly were bioequivalent to each other. The C_{max} for treatment B was significantly higher compared to either A or C, but only by 32% and 21% respectively. The 95% confidence intervals associated with the geometric mean of the ratios were also wider than other 2 treatments.

Safety results: No SAE reported. A total of 5 application site reactions were reported and were judged by the investigator to be mild and related to the study drug.

Conclusion: The application of 2g CP601B 2% testosterone gel over a 4-fold range of application areas did not result in clinically significant or relevant differences in serum testosterone concentrations.

Appendix D

Study T 00-02-08: Effect of different site of application on the pharmacokinetics of testosterone following application of a fixed dose of CP601B
Design: This was a multi-center, open-label, randomized, 3-treatment, 3-period crossover Phase 1 pharmacokinetic (PK) study conducted at two sites in the US. Fifteen subjects were enrolled in the study, with each subject randomly assigned to one of 6 treatment sequences that specified the order in which the 3 treatments were administered (i.e., ABC, ACB, BAC, BCA, CAB, CBA). A washout interval of at least 3 days separated each treatment sequence. During each of the 3 treatment periods, the subject applied 3 g of CP601B 2% gel to the thigh (Treatment A), upper arm (Treatment B), or abdomen (Treatment C) for 8

consecutive days. Venous blood samples were obtained for PK evaluation prior to application (Time 0) on Days 7 and 8, and at specified times (0.5, 1, 2, 4, 6, 8, 10, 12, 16, 20 and 24 hrs) following application on Day 8.

Safety evaluations: Treatment-emergent adverse events, protocol-specified assessment of inflammation at the application site, clinical laboratory results, vital sign measurements, physical examination (PE) findings, and ECG results.

Enrollment: Males between 18 and 75 years of age with primary or secondary hypogonadism, defined as a serum testosterone concentration < 300 ng/dL at the screening period (< 300 ng/dL in 2 consecutive blood samples obtained at least 7 days apart, or ≤ 250 ng/dL in a single sample). Subjects must have been willing to discontinue any current testosterone medication until serum concentration was < 300 ng/dL, and were otherwise in satisfactory health based on results of medical history, physical examination, ECG and clinical laboratory test results at a screening.

Results:
Mean serum testosterone concentrations for Treatment A (to the thighs) and Treatment C (to the abdomen) were comparable throughout the dosing interval; in contrast, mean serum concentrations were higher with Treatment B (to the upper arms) compared with both other treatments.

Table 40 Ratio of geometric means and 95% CI for PK parameter estimates on Day 8: Subjects with PK data for at least 2 periods (study T 00-02-08)

Surface area ratios	N	Ratio of geometric means (95% confidence limits for ratio)		
		C_{max} (ng/dL)	C_{avg} (ng/dL)	C_{min} (ng/dL)
Abdomen (Y) vs. thigh (X)	12	1.58 (1.10, 2.26)	1.16 (10.89, 1.52)	0.99 (0.84, 1.17)
Upper arm (Y) vs. thigh (X)	12	2.96 (2.06, 4.25)	1.84 (1.40, 2.40)	1.41 (1.20, 1.67)

For Treatment A (thighs) and Treatment C (abdomen), the ratio analysis showed differences in C_{min} and C_{avg} which did not reach statistical significance. However, C_{max} was significantly higher after applied to the abdomen. Application to the upper arms resulted in testosterone concentrations that were significantly higher than when the same dose was applied to the thighs or abdomen.

Safety results: No SAEs were reported. ASRs were reported and all were assessed as mild and related to study drug.

Conclusion: Application of 3g CP601B 2% testosterone gel to the abdomen resulted in mean testosterone concentration-time profiles that were similar to those observed following application of the same dose of gel to the thighs. In addition, there were no significant differences in C_{avg} and C_{min} between these 2 sites. Application to the upper arms resulted in significantly higher testosterone levels. Both the abdomen and the upper arms resulted in significantly higher C_{max}; however, the extent of the increase for the abdomen was much less than for the upper arms. These results show that the abdomen and thighs are interchangeable as sites for application of testosterone gel, based on the 2 critical PK parameters for efficacy, C_{avg} and C_{min}.

Appendix E

Study T 01-02-02 : Phase I – Potential of T Transfer into partners
Design: This was an open-label, vehicle-controlled, pharmacokinetic study conducted in healthy couples at two sites in the US. The objectives of this study were to determine 1) whether transference of CP601B testosterone gel 2% from a male to female would significantly raise the serum testosterone and bioactive

testosterone levels in the female as assessed by a 24-hr serum testosterone PK profile, and 2) if transference occurs, whether covering the application site with clothing would prevent it.
The study consisted of 3 phases: one non-transfer profile phase (Treatment A: Phase I - vehicle only) and two potential transfer profile phases (Treatment B for Phase II - uncovered CP601B testosterone gel 2% exposure and Treatment C for Phase III - covered CP601B testosterone gel 2% exposure). The order of the 3 phases was randomized in a 3-period crossover design. Each phase was conducted on Day 25±2 of 3 consecutive menstrual cycles of the female partner of each couple. Day 1 of the cycle was defined as the first day of menses. In Treatment A (non-transfer control Phase I), the male partner applied the vehicle to a 150 cm² area of the anteromedial thigh. In Treatment B (uncovered Phase II), the male applied 1.5 g of CP601B testosterone gel 2% to a 150 cm² area of the thigh, and in Treatment C (covered Phase III), the male applied 1.5 g of CP601B testosterone gel 2% and wore boxer shorts that covered the site of application. During each phase, the female partner rubbed the application site with the volar surface of her forearm for 15 consecutive minutes, beginning 2 hrs after the clinical trial material (CTM) was applied. Blood samples were obtained from the female partner at Time 0 (just before rubbing), 0.5, 1, 2, 4, 6, 8, 10, 12, 15, and 24 hours. Blood samples were analyzed for determination of testosterone, bioactive testosterone and sex hormone binding globulin (SHBG) concentrations.

Safety evaluations: Treatment-emergent adverse events, protocol-specified assessment of inflammation at the application site, clinical laboratory results, vital sign measurements, physical examination (PE) findings, ECG results, and voluntary reports. Female subjects were to contact the investigator immediately if any signs of virilization (acne, hirsutism, coarsening of voice, etc.) occurred.
Enrollment: A total of 8 couples were enrolled and randomized at the 2 investigator sites.

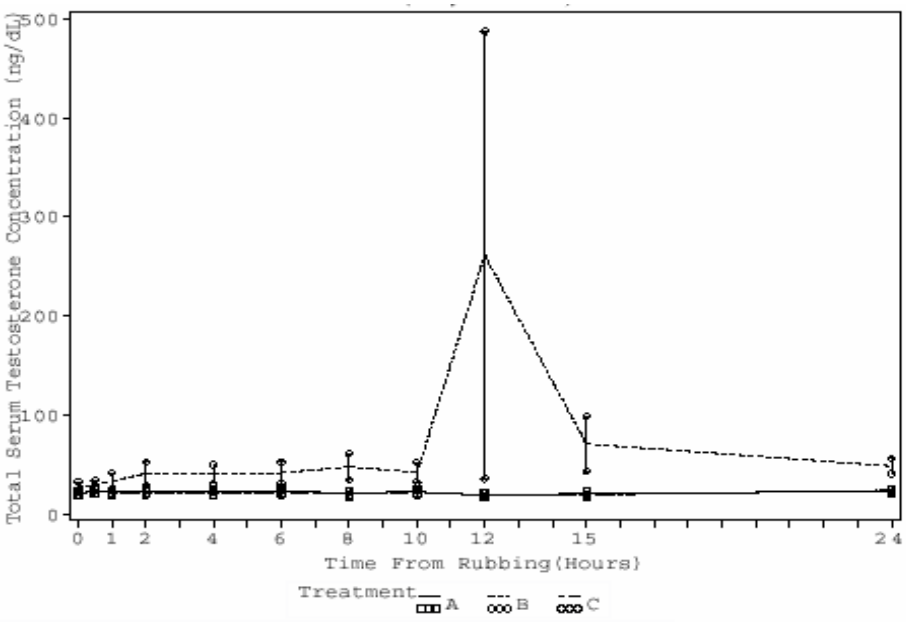
Table 41 Number of couples by study center and treatment sequence (Study T 01-02-02)

Center (site #)	A/B/C	B/C/A	C/A/B	B/A/C	C/B/A	A/C/B	Total
Fosbineder (123)	2 (1)	0	2 (1)	4 (2)	0	4 (2)	12 (6)
Harris (103)	0	2(1)	0	0	2(1)	0	4 (2)

Results:

Figure : Mean (±SE) Total serum testosterone concentration profile in female subjects after transference including all values (Study T 01- 02- 02)

(Figure includes the Hour 2, 4, 12, and 15 outlier concentration values for subject 123-102, Treatment B)



A = Phase I: Male applied 1.5g vehicle/ 150 cm² to one anteromedial thigh; female rubbed
B = Phase II: Male applied 1.5g CP601B/ 150 cm² to one anteromedial thigh; female rubbed
C = Phase III: Male applied 1. 5g CP601B/ 150 cm² to one anteromedial thigh, application site is covered; female rubbed

Table 42 Summary statistics for PK parameter estimates: PK evaluable population including all outlier values (Study T 01- 02- 02)

PK parameter	Statistic	A (N=6)	B (N=6)	C (N=6)
AUC_{0-24} (ng•h/dL)	Mean±SD	525.0±118.90	1083.2±571.64	508.7±101.68
	Median	531.2	933.9	487.5
	Range	383.7-665.5	520.8-1887	402.1-670.0
	Geometric mean	513.4	961.6	500.6
	Approximate CV (%)	62.3	70.1	61.8
C_{max} (ng/dL)	Mean±SD	26.0±4.86	58.0±30.11	26.5±6.80
	Median	26.5	46	24.5
	Range	20.0-32.0	25.0-102.0	21.0-39.0
	Geometric mean	25.6	51.8	25.9
	Approximate CV (%)	61.8	69.6	62.3
C_{avg} (ng/dL)	Mean±SD	21.6±4.90	44.7±23.52	21.0±4.23
	Median	21.9	38.5	20.1
	Range	15.8-27.4	21.7-77.8	16.6-27.6
	Geometric mean	21.2	39.7	20.7
	Approximate CV (%)	62.3	70	61.8
C_{min} (ng/dL)	Mean±SD	17.3±5016	26.7±9.79	15.8±3.97
	Median	17	27	17.5
	Range	11.0-24.0	14.0-37.0	10.0-19.0
	Geometric mean	16.7	25	15.4
	Approximate CV (%)	63.6	65.7	63
T_{max} (hr)	Mean±SD	9.4±8.16	18.1±7.16	13.1±12.27
	Median	8.3	19.8	14.2
	Range	0.8-24.3	8.3-24.3	0.7-24.3

Table 43 Ratios of geometric means and 95% CI for total serum testosterone PK parameter estimates: PK evaluable population including all outlier values (T 01- 02- 02)

PK parameter	Treatment Group ratio	Ratio of Geometric means	95% confidence Limits for ratio	p-value
C_{avg} (ng/dL) (N=6)	B/A	1.81	(1.37, 2.40)	0.0012
	C/A	0.91	(0.68, 1.22)	0.4768
C_{max} (ng/dL) (N=6)	B/A	1.93	(1.39, 2.68)	0.0017
	C/A	0.92	(0.65, 1.30)	0.5868

Safety results: No SAEs were reported. Eight treatment-emergent AEs were reported in 5 female subjects. These mild systemic events were determined not to be related to the CTM. None of the events were suggestive of pharmacologic activity of testosterone. Nine treatment-emergent AEs were reported for 5 male subjects with severity range of mild to moderate.

Conclusion: After male subjects applied 1.5g testosterone gel 2% to the thigh, female subjects who rubbed the uncovered site 2 hrs later for 15 consecutive minutes were observed to have mean total testosterone and bioactive testosterone C_{avg} and C_{max} that were significantly higher (20 times) than the mean C_{avg} and C_{max} after rubbing of the covered site of CP601B testosterone gel 2% application, or after rubbing the site of vehicle application. These mean increases, however, remained within the physiologic range for reproductive age female. Total and bioactive testosterone concentrations in the female partners after rubbing the covered application site provide evidence that transference and absorption is prevented by covering the site.

Reviewer's Comments

- Generally a 1.5-2 fold increase in serum T levels were observed in female subjects at each time point due to the transfer of the gel from their male partners (Treatment C vs. Treatment B).
- One of the females had an exceptionally high T value at 12 hrs in the Treatment B arm (C_{max} approximately 1400 ng/dL). This definite outlier is quite possibly an analytical error.
- Comparison of the PK profiles and parameters between Treatment A (vehicle) and C (active gel with area of application covered) is essentially the same, indicating that the potential for transfer may be abolished by wearing occlusive clothing to cover the application site.

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/s/

Guodong Fang
7/3/03 11:50:47 AM
MEDICAL OFFICER

George Benson
7/3/03 12:07:33 PM
MEDICAL OFFICER

NDA – 21463

Medical Officer Memorandum

Date: December 17, 2002
Drug: Tostrex
Sponsor: Cellegy Pharmaceuticals, Inc.
Re: Proposed Trade Name "Tostrex"

Background: NDA-21463 was submitted on May 31, 2002. A consultation concerning the tradename Tostrex was obtained from the Division of Medication Errors (Office of Drug Safety).

Medical Officer Review: The following comments from DMETS were excerpted from their consultation and should be forwarded to the sponsor.

Recommendation: *DMETS does not recommend the use of the name "Tostrex". DMETS*

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/s/

Marcea Whitaker
12/17/02 01:46:54 PM
MEDICAL OFFICER

George Benson
12/17/02 04:43:31 PM
MEDICAL OFFICER

Filing Meeting (Clinical)

NDA 21463 - Tostrex (2% Testosterone gel) - Cellegy Pharmaceuticals

Pre-NDA meeting held on October 29, 2001

Testosterone gel for transdermal delivery. The gel is supplied in a metered dose canister (2% testosterone) and is applied as [redacted] (b) (4). Each depression of the piston delivers 0.5 g gel (10 mg testosterone).

Completed or ongoing studies:

	Status
1) T-98-02-01. Phase 1 dose finding study. (n=18)	Completed
2) T-00-02-01. Single phase 3 pivotal study.	**Efficacy 1/15/02 Safety 6/1/02 (to be submitted with safety update)**
3) T-00-02-03. Effect of showering on PK (n=6-8)	Completion 12/15/01
4) T-00-02-07. Effect or increasing surface area of fixed dose	Completion 12/15/01
5) T-00-02-08. Different body sites (n=12)	Completion 12/15/01
6) T-00-02-09. Site and dose and skin irritation (n=72)	Completed
7) T-01-02-02. Male to partner transfer study	Ongoing (to be submitted with safety Update)

Indication: Tostrex testosterone gel is indicated for replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone.

1) Primary hypogonadism (congenital or acquired) – testicular failure due to cryptorchidism, bilateral torsion, orchitis, vanishing testis syndrome, orchiectomy, Kleinfelter's syndrome, chemotherapy, or toxic damage from alcohol or heavy metals. These men usually have low serum testosterone concentrations and gonadotropins (FSH and LH) above the normal range.
2) Hypogonadotropic or secondary hypogonadism (congenital or acquired) – idiopathic gonadotropin or LHRH deficiency or pituitary –hypothalamic injury from tumors, trauma, or radiation. These men have low serum testosterone concentrations but have gonadotropins in the normal or low range.

In clinical study section portion of label, mean testosterone levels rather than primary endpoint (% of patients with C_{avg} and C_{min})are presented).

Dosage: [redacted] (b) (4)

Efficacy: One Phase 3 Trial: 200 patients used at least one dose of drug. 163 completed PK at Day 42/56. Approximately 40% of patients hit C_{avg} and C_{min} (primary endpoint Day 42/56). This is better than 35% point estimate agreed upon. Approximately 50% hit endpoint at Day 182. The primary endpoint was reached in all three study populations.

The submission contains results for the primary efficacy endpoint for all subjects (Day 42/56) but is ongoing at the time of data cutoff. Results at Day 182 and remainder of safety data and ongoing transference study will be submitted with the 120 day safety update. Results of extension study (up to an additional 12 months of therapy) will also be submitted with safety update. 200 patients in ITT group. Modified ITT group is 163 patients who completed PK at Day 42/56. Efficacy evaluable (EE) group included 89 MITT patients who also met "strict" entry and compliance criteria. On Day 182, ITT = 167, MITT=116, and EE=62 patients.

Bone mineral density also measured in subset of patients.

Pediatric plan: Sponsor requests deferral of pediatric data until appropriate studies can be planned and completed in the pediatric population.

Safety: 30 patients discontinued because of adverse events (19 of these were skin problems). Overall, skin site reactions were reported in 103 (52%) of patients. Gynecomastia in 1.5%. PSA above the normal range in 2.5% of patients at end of study. 3 SAE's considered drug related (1 "heart failure" and 2 "blood dyscrasias")

Negotiating this combined electronic and paper submission is not straight-forward. The "clinstat" and "pharmtox" sections of the electronic submission contain only references. Case report forms are included electronically under the individual study reports, but data for the primary efficacy and safety study are included under 2 numbers (T-00-02-01 and T-00-03-01). I think one of these numbers designates the protocol and one the study report).

On superficial review, a summary and analysis of the number and description of patients with high (very high) testosterone levels is not included in the clinical section. These values are present in the data line listings. This reviewer recommends that a letter be sent to the sponsor requesting the following information:

"Please provide the dosage strength, serum total testosterone (T) concentration, day of study, and action taken for each patient who had a serum total T >1800 ng/dL in Study T-00-02-01. Please provide these listings by individual patient identification number. If a given patient had more than one serum T >1800 ng/dL during the course of this study, please list each separately under the patient's identification number. In addition, please provide an executive summary discussing the safety implications for these supraphysiologic testosterone levels."

Recommendation: From a clinical standpoint, this NDA submission can be filed. The previous underlined paragraph should be sent to the sponsor in a regulatory letter.

DSI:

Site 014 – Jorge Pino (29 patients)
Site 020 – Richard McDavid (18 patients)
Site 006 – Wayne Meikle (17 patients)

George S. Benson, MD
Medical Officer
Division of Reproductive and Urologic Drugs

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/s/

George Benson
8/1/02 03:42:10 PM
MEDICAL OFFICER

Mark S. Hirsch
8/1/02 05:52:41 PM
MEDICAL OFFICER