CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	December 21, 2010
From	Mark S. Hirsch, MD
Subject	Cross-Discipline Team Leader Review
NDA #	21-463
Applicant	Endo Pharmaceuticals, Inc.
Date of Submission	June 30, 2010
PDUFA Goal Date	December 30, 2010
Proprietary Name / Established (USAN) names	FORTESTA™ testosterone gel
Dosage forms / Strength	Topical gel, 2%, supplied in 60 gm metered dose canisters
Proposed Indication(s)	Replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone
Recommended:	*Approval*

1. Introduction (Executive Summary)

This submission contains a Complete Response (CR) to the October 16, 2009, CR action letter issued to Endo Pharmaceuticals following the DRUP review of Endo's CR of April 17, 2009.

The information provided by Sponsor in the April 17, 2009, Complete Response consisted largely of the results from a new, Phase 3, efficacy and safety study (Study FOR01C). The data from that adequate and well-controlled study, along with supportive evidence from other Phase 2 and Phase 3 studies, was reviewed in great detail and appeared sufficient to support the efficacy and safety of FORTESTA for the testosterone replacement therapy in hypogonadal men.

However, shortly before the Approval action was to be taken, the Division of Scientific Investigations (DSI) identified several deficiencies in the analytical methods and quality control measures used to analyze specimens from Study FOR01C from their audit of the (b) (4) located in (b) (4) The deficiencies identified at (b) (4) were of such a magnitude as to raise doubt regarding the validity of the data from Study FOR01C. Since the data from Study FOR01C were the principal evidence in support of NDA approval, it was not possible to approve NDA 21-463 with unresolved questions about the reliability of the data itself.

Therefore, the Division issued a Complete Response letter with the following two deficiencies:

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

- ***CLINICAL PHARMACOLOGY:*** *Sufficient information to adequately assess the known risk of secondary transfer of testosterone to children and women from men using this product has not been provided. Therefore, safety data are needed to determine if secondary transfer could occur after washing of the application site.*

The Complete Response letter contained the following statements regarding information needed to address the two deficiencies:

- ***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.*

In addition to these specific requests, the October 16, 2009, action letter also required Sponsor to submit the following items:

- **LABELING:** At the time of the action, labeling remained unresolved. The Sponsor was informed to include updated labeling in the CR.

- **RISK EVALUATION AND MITIGATION STRATEGIES REQUIREMENTS**: Consistent with all approved topical testosterone gel products, a Risk Evaluation and Mitigation Strategy (REMS) was deemed necessary for FORTESTA to ensure that the benefits of the drug outweigh the risk of secondary exposure of children to testosterone from men using the product. Like all approved topical testosterone gel products, the REMS for this product was to consist of a Medication Guide and a timetable for submission of assessments.

- **SAFETY UPDATE:** A safety update was to be included in the CR. The CR letter stipulated that 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. The safety update was also to include a summary of worldwide experience on the safety of this drug, including an estimate of use of the drug marketed in other countries.

Subsequent to the October 16, 2009, CR action, the Division met with the Sponsor in a Type A meeting on December 1, 2009. The meeting included discussion of how to resolve the CR deficiencies, including 1) 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, and 2) a confirmation of the Division's October 1, 2009, agreement that the "wash-off" study could be performed as a post-marketing requirement (PMR).

The Division met again with the Sponsor on June 10, 2010, at a Type C Guidance meeting. At that time, Endo 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, Endo noted that their re-analysis of available samples provided strong support for the conclusions from the original analysis.

In this Complete Response, submitted on June 30, 2010, the Sponsor provided all the requested information needed to address the Clinical and Clinical Pharmacology deficiencies as well as the requested labeling, REMS, and safety update.

Regarding the Clinical deficiency: The Sponsor noted that they have worked closely with the (b) (4) to address the deficiencies identified by DSI in order to re-establish the adequacy and reliability of the data from Study FOR01C. They have conducted a re-analysis of all available back-up samples from that study, comprising most of all the original samples, to demonstrate the validity of the original data. The Sponsor believes that the re-analysis data are strongly concordant with the original data. They believe that the concordance correlation analysis result, together with the statistical analysis of the re-assay data, and the supportive analyses confirm the reliability of the original analysis. They believe that the conclusion regarding clinical efficacy and safety of FORTESTA as demonstrated by the original FOR1C data (and as confirmed by the Division's prior review and review of the re-analysis data) remains unchanged.

Upon submission of the CR, a DSI consult was obtained to assess the Sponsor's contentions that the deficiencies identified by DSI in its first visit to (b) (4) had been addressed. DSI conducted a follow-up, on-site audit of the (b) (4) on August 9-17, 2010. In short, DSI concluded that the deficiencies at (b) (4) had been satisfactorily addressed and that the re-analysis data were acceptable for use in support of safety and efficacy. The primary medical officer, statistician and clinical pharmacologist have conducted a thorough review of the concordance analysis, the re-analysis and the supportive analysis, and they concur with the Sponsor's contentions. The reader is referred to later sections of this memo for details.

Regarding the Clinical Pharmacology deficiency: The Sponsor notes that at the time of a October 1, 2009, teleconference they were informed by DRUP that the "hand wash" study would be requested as a post-marketing requirement (PMR). The Division requested that a draft protocol be submitted for review. At the time of the Type A meeting held on December 1, 2009, the Division confirmed that the protocol for the "wash-off" study should be submitted in the upcoming CR submission, and it would be treated as a PMR. On January 22, 2010, the Sponsor submitted a draft protocol for the "wash-off" study to IND #76,634. The protocol called for an assessment of residual testosterone from the application site and hands after washing in 12 males. A copy of this protocol was included in the CR.

During review of the CR, the Sponsor was asked to submit specific dates for submission of a final protocol, completion of the study, and submission of the final study report, respectively, for the PMR study. The Sponsor provided acceptable commitment dates. The reader is referred to later sections of this memo for details.

Regarding labeling: The Sponsor submitted final draft labeling with the CR.

During review of the CR, labeling discussions were held with the entire review team on November 15 and 18, 2010. Another review team meeting was held on November 23, 2010 to discuss just the Dosage & Administration section. The Division's edited label was conveyed to Sponsor on November 26, 2010. Following the Sponsor's response on November 30, 2010, a second set of Division edits were conveyed on December 7, 2010. The Sponsor accepted virtually all of the Division's edits, and returned the document on December 9, 2010.

On December 6, 2010, the Division received an edited version of the Medication Guide from the Division of Risk Management (DRISK), and 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.

Therefore, as of December 9, 2010, the Division had received acceptable Prescribing Information labeling and an acceptable Medication Guide from Sponsor. Further, as of December 3, 2010, the Division had received acceptable carton and container labeling from the perspectives of the Office of New Drug Quality Assessment (ONDQA) and Division of Medication Error Prevention and Analysis (DMEPA) in the Office of Surveillance and Epidemiology (OSE). The reader is referred to later sections of this memo for details.

Regarding the REMS: The Sponsor notes that the requested REMS document was submitted on August 19, 2009, at the Division's specific request, and then it was re-submitted on September 17, 2009, with the Agency's requested changes. Therefore, this REMS had undergone thorough review during the prior CR. The current CR contains this same REMS document as well as the requested Medication Guide.

During this CR review, the REMS was re-reviewed by the Agency and was determined to be acceptable on December 9, 2010. The Medication Guide was reviewed by DRISK, and with Sponsor's acceptance on December 9, 2010 to all recommended edits, the Sponsor has submitted an acceptable Medication Guide.

Regarding the safety update: The Sponsor notes that no nonclinical nor clinical studies have been started or completed since the NDA was re-submitted on April 17, 2009. No studies are ongoing. Therefore, there are no new data from nonclinical or clinical studies. However, FORTESTA is approved in 20 European Union (EU) member countries and 2 non-EU countries. The product is marketed in 19 countries. The Sponsor provided an estimate of exposure, as requested, and a periodic safety update report (PSUR) from the most recent year of worldwide experience. The PSUR contained a total of 56 adverse event reports.

During the course of the CR review, the safety update was assessed and no new safety signals were identified. The safety profile remains unchanged from that described in the April 17, 2009 CR submission. The reader is referred to later sections of this memo for details.

Overall, then, taking into consideration the information in the prior CR of April 17, 2009, and following the review team's thorough review of this CR, there remain no outstanding issues 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 a clear and colorless gel containing 2% testosterone USP (b) (4) for topical application. It is supplied in a 60 gm canister with a metered-dose pump that delivers 10 mg of testosterone (0.5 gm of gel) per actuation. The starting dose is 40 mg testosterone once daily, which translates into 4 actuations of the pump mechanism (or 2 gm of gel). The dose is applied to the anterior and medial thighs. Depending on the serum total testosterone concentration at 2 hours after dosing (C_2), after 14 days of use, the dose can be titrated up or down. The C_2 serum total testosterone concentration should be re-checked 14 days after each dose adjustment. The recommended dose adjustments are shown clearly in product labeling. The minimum and maximum doses are 10 mg and 70 mg once daily, respectively.

The active ingredient in FORTESTA is testosterone, an anabolic steroid and 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. Testosterone is known to maintain male secondary sex characteristics, such as masculine phenotype, libido, and sexual function. Lack of testosterone may also affect body composition, including bone mineral density, lean to fat tissue distribution, and muscle size and strength. In men with conditions associated with deficiency or absence of testosterone (hyogonadism), replacement of testosterone to the normal physiological range is appropriate.

All currently available testosterone formulations have limitations. Injectable depot solutions may be associated with pain at the injection site, transdermal patches may result in inflammation at the site of application, pellet implants can result in expulsion of the implant and infection, and methylated testosterone oral preparations may cause harm to the liver. There are two currently approved topical testosterone gels, AndroGel, Testim, and one topicl testosterone solution, Axiron. Endo Pharmaceuticals purports that FORTESTA provides a low-volume treatment option that is easily applied and may be adjusted to each individual's dosing requirements.

The principle support for safety and efficacy of FORTESTA is data from a single adequate and well controlled clinical trial (FOR01C) conducted in the US. This data were thoroughly reviewed by the Agency in the previous CR of April 17, 2009 and were found to support safety and efficacy, if not for the deficiencies identified by DSI at the (b) (4). In addition to Study FOR1C, the NDA contains supportive evidence from Phase 2 studies as well as a Phase 3 study (TSX/01/C) conducted in Europe.

2.2 REGULATORY HISTORY

On August 24, 1998, Cellegy Pharmaceuticals opened IND (b) (4) (2% testosterone gel for the treatment of male hypogonadism).

On June 3, 2002, NDA 21-463 for 2% testosterone gel (formerly FORTIGEL) was filed by Cellegy Pharmaceuticals. Support for safety and efficacy came largely from the results from a single Phase 3 trial (Study T 00-02-01). The original NDA also included the results from a showering study (T 00-02-03) and a transfer study (T 01-02-02).

On July 3, 2003, NDA 21-463 received a "Not approvable" action. The deficiencies noted were:

1. There is insufficient information to establish that the high supra-physiologic daily C_{max} 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 C_{max} values between 1500 and 1800 ng/dL, 14% had testosterone C_{max} values between 1800 and 2500 ng/dL, 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 a new clinical trial(s) using lower doses of FORTIGEL, or another testosterone gel formulation, and demonstrate that physiologic levels of testosterone can be attained while avoiding high supra-physiologic C_{max} levels of serum testosterone.

On July 30, 2003, a Type A meeting was held with Sponsor to discuss the deficiencies identified in the July 3, 2003, Not Approvable letter and to explore what other information was needed to address the deficiencies. At that meeting, the Sponsor showed new data from an additional study (CP601B 02-02-01) which they believe demonstrated a reduced C_{max} profile for FORTIGEL.

On January 12, 2004, the sponsor submitted an amendment to NDA 21-463 containing the results of 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. While the percentage of patients with supraphysiologic C_{max} was reduced compared to study T 00-02-01, the reduction was not substantive and safety concerns remained.

(b) (4) Cellegy Pharmaceuticals (b) (4) in February 2007, they transferred ownership of FORTIGEL to Strakkan Pharmaceuticals.

On April 6, 2007, Strakkan Pharmaceutical requested a Special Protocol Assessment (SPA) for a new phase 3 study entitled, **"***An Open Label Phase 3 Study of Fortesta Testosterone Gel*" (Study FOR01C). The protocol was submitted under a new IND (#76,634).

On May 24, 2007, a Type A meeting was held with Strakkan to discuss the study FOR1C protocol.

On August 23, 2007, the Division accepted the design and size of this new Phase 3 study FOR1C.

On March 20, 2008, a Type B, Pre-NDA meeting was granted to discuss the Sponsor's plan for a Complete Response submission to the July 3, 2003, Not Approvable letter. The basis of the CR would be the results of study FOR1C. In preliminary responses to Sponsor's meeting questions, DRUP acknowledged that the results of study FOR1C would be the basis of the CR and that such a submission was acceptable. The face-to-face meeting was subsequently cancelled.

On April 17, 2009, Strakkan submitted a Complete Response to NDA 21-463, based largely on the results of Study FOR01C. During the Division's review in 2009, it originally appeared that the efficacy and safety of Fortesta had been confirmed by results from the new study, FOR1C.

In study FOR1C, 149 patients applied Fortesta once daily to the thighs at a starting dose of 40 mg of testosterone per day, and the dose was adjusted to between 10 mg and 70 mg of testosterone 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 the percentage of subject with average serum total testosterone concentrations (C_{avg}) within the normal physiological range (≥ 300 and ≤ 1140 ng/dL) on Day 90. The bar for success was set at ≥ 75% of patients achieving C_{avg} within the normal range, with the lower bound of the 95% confidence interval set at 65%. Key secondary endpoints were the maximum serum total testosterone concentrations (C_{max}) < 1500 ng/dL in ≥ 85% of patients, C_{max} between ≥ 1800 and < 2500 ng/dL in < 5% of patients and C_{max} > 2500 ng/dL in no patients at Day 90. The primary and key secondary endpoints were achieved, and it appeared that the drug could be approved.

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, conveyed in the October 8, 2009 final DSI consult to DRUP, raised serious questions regarding the validity of the data that were 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.

On December 1, 2009, the Division held a Type A teleconference with the Sponsor to discuss 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.

On June 10, 2010, the Division met with the sponsor at a Type C Guidance meeting. At that time, the sponsor stated that they believed that the deficiencies identified in the DSI audit of the (b) (4) had been adequately addressed and that the original and re-analysis

data from Study FOR01C should be considered reliable. Further, the sponsor noted that their re-analysis of available samples achieved all primary and secondary study objectives and provide strong support for the conclusions from the original analysis.

On June 30, 2010, the sponsor submitted this second Complete Response.

3. Chemistry, Manufacturing and Controls (CMC)

The majority of the CMC information was reviewed during the initial NDA submission in 2002. Updated CMC information submitted in the Complete Response of April 17, 2009, included addition of a new manufacturing site, as well as updated methods and stability information.

In the final CMC review dated October 5, 2009, of the April 17, 2009, submission, Donna Christner concluded:

> "*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*."

Dr. Christner specifically noted a commitment by Sponsor to establish a specification for in vitro release within 12 months following product approval, and this commitment was acceptable.

In the final CMC review dated December 10, 2010 of the June 30, 2010 submission, Drs. Christner and Rhee concluded:

> "*The Review #3 made a recommendation of "Approval" from the CMC perspective based on the sufficient CMC information submitted to assure the identity, strength, purity, and quality of the drug product; adequate labels/labeling with required information; and 'Acceptable' cGMP compliance of the facilities.*
>
> *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 have been revised satisfactorily, making the previous 'Approval' recommendation from the CMC perspective still effective."*

Dr. Christner continued to find acceptable the Sponsor's commitment to establish a specification for in vitro release within 12 months following product approval.

4. Nonclinical Pharmacology/Toxicology

In their final Pharmacology/Toxicology review dated July 10, 2009 of the April 17, 2009 submission, Drs. Krishan Raheja and Lynnda Reid had the following conclusions and recommendations:

> ***"****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 noted that there were no Pharmacology/Toxicology 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.

In their final review dated November 19, 2010 of the June 30, 2010 submission, Drs. Raheja and Reid concluded:

> *"Recommendation on approvability: Although this NDA was issued a not approvable letter on 7-3-03 and a complete response on 10-16-09, Pharmacology had recommended approval of the NDA based on extensive preclinical 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. From the PT perspective, there were no safety concerns and P/T again recommends approval of the resubmitted NDA."*

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 15, 2010, Pharmacology provided a final memo concurring with final labeling.

5. Clinical Pharmacology/Biopharmaceutics

In their final review dated October 14, 2009 of the April 17, 2009 submission, the Clinical Pharmacology Review team, Hyunjin Kim and Myong-Jin Kim, made the following recommendation:

> *"The Division of Clinical Pharmacology 3/Office of Clinical Pharmacology finds the clinical pharmacology information submitted in NDA 21-463 not acceptable based on major deficiencies identified in the DSI report.*
>
> *T transfer potential after the washing of the primary user's application site has not been assessed in the current resubmission. Therefore, this needs to be addressed in the subsequent submission."*

CTDL Comment: As discussed in section 1 of this memo (Introduction), on October 1, 2009, DRUP informed the Sponsor that a hand and application site "wash-off" study would be requested as a post-marketing requirement (PMR). At the time of a Type A meeting held on December 1, 2009, the Division confirmed that the protocol for the "wash-off" study should be submitted in the upcoming CR submission, and it would be treated as a PMR.

While the Clinical Pharmacology review team did conduct a thorough review of the efficacy results and dose adjustment scheme from study FOR01C, they noted that their analyses could not be used to support approval as of October 14, 2009, due to concerns raised by the DSI audit re: reliability of the data. As discussed in section 1 of this memo (Introduction), a follow-up DSI audit of the (b) (4) was conducted and demonstrated that the identified deficiencies had been resolved such that the re-analysis data from FOR1C could be used to support approval. The concordance between the re-analysis data and the original data was very strong. Therefore, the Clinical Pharmacology team's original analysis of the FOR1C data review is considered relevant and is shown here.

As per the Clinical Pharmacology review team's original review, a starting dose of 40 mg of testosterone applied topically once daily to the thighs and adjusted between 10 mg and 70 mg of testosterone daily at Days 14, 35 and 60 (± 3days) based upon a single serum sample for total testosterone concentration at 2 hours post-dosing (C_2) achieved both primary and secondary endpoints (i.e. C_{avg} and C_{max}) as agreed upon previously with the Division.

For the primary endpoint, the percentage of patients who achieved C_{avg} within the normal physiologic range on Day 90 was 76.1% (105/138), with a 95% lower confidence bound of 69%. These results meet the pre-defined success criteria for the primary endpoint.

For the secondary endpoints, there were no patients with C_{max} above 2500 ng/dL (0%). A total of 6/138 patients (4.3%) had a Cmax between 1800 ng/dL and 2499 ng/dL. Finally, a total of 126/138 patients (91.3%) had a Cmax of ≤ 1500 ng/dL. Again, these results meet the pre-defined success criteria for the secondary endpoints.

Results for the primary and secondary endpoints are shown in Table 1 below.

In addition, 24-hour pharmacokinetic (PK) profiles for these parameters were obtained on Days 35 and 90 (± 3 days). Day 90 is the per-protocol primary timepoint for determining efficacy. The group average 24-hour serum total testosterone concentration-time profiles for Days 35 and 90 are shown in Figure 1 below.

Figure 1: **Mean (SD) Concentration-Time Profile of Total Testosterone**

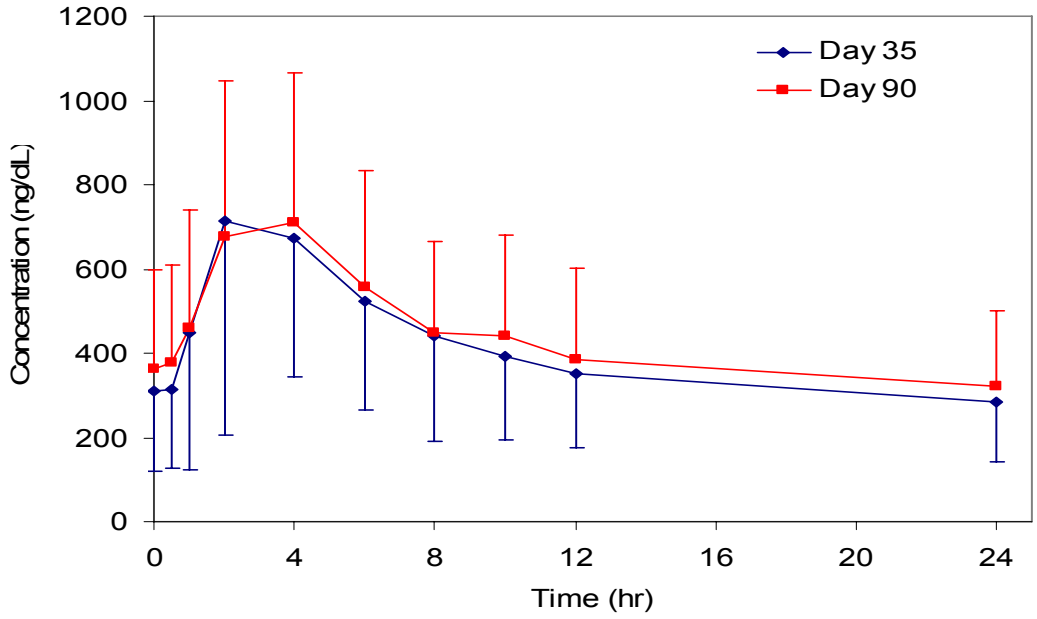

Table 1: **Efficacy Results (mITT Population)**

Primary Endpoint (C_{avg} of total T at Day 90)		***Targets for success***
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 (C_{max} 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%***

The Clinical Pharmacology review team concluded that in the mITT population, the mean (SD) $C_{avg-24hr}$ 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%.

The Clinical Pharmacology review team also commented that the dose adjustment for study FOR01C was properly instituted to achieve both primary and secondary endpoints. They analyzed the percentage of patients who achieved average serum total testosterone concentration with the normal physiologic range (≥300 and ≤1140 ng/dL) on Days 35 and 90 and those results were 73.2% and 76.1%, respectively. Thus, the number of patients who were out of normal physiologic range on Day 90 was modestly lower than the number out of physiologic range on Day 35 (19 failures versus 23 failures on Days 90 and 35, respectively). Finally, there were 2 patients and 0 patients, respectively who had maximum serum total T concentrations > 2500 ng/dL on days 35 and 90, demonstrating fewer patients with significantly out of range C_{max} values on Day 90. The Clinical Pharmacology team noted (on page 17 of 98 of their October 14, 2009, FORTESTA NDA review) that the increased number of successful C_{avg} responders on Day 90 compared to Day 35 suggested that one dose adjustment might not be sufficient for FORTESTA.

CDTL comment: The FORTESTA label will state that serum testosterone concentration should be measured on approximately Days 14 and 35 after initiating therapy, and approximately 14 and 35 days after any dose adjustment, and periodically thereafter.

The Clinical Pharmacology review team also noted that there were 5 patients with a BMI > 35 kg/m^2, who were actually not supposed to have been enrolled by strict eligibility criteria. Therefore, Clinical Pharmacology conducted a review of the data with and without these 5 subjects. The results for the primary and secondary endpoints in the subpopulation of 133 patients (138 total minus these 5) were virtually identical to that in the total MITT population of 138.

Serum dihydrotestosterone (DHT) and free T concentrations were obtained at 2 hours after dosing on days 14 (± 3 days), 35 (± 3 days) and 60 (± 3 days). In addition, 24-hour pK profiles for these analytes were obtained at Days 35 (± 3 days) and 90 (± 3 days). Sex hormone-binding globulin (SHBG), luteinizing hormone (LH), follicle stimulating hormone (FSH), and estradiol (E2) concentrations were also obtained at two hours after study drug application on Days 35 and 90 (± 3 days). As expected, DHT and estradiol concentrations increased over time. SHBG concentrations remained constant, with a slight reduction at day 90. Both serum LH and FSH fell at Days 35 and 90, consistent with increased circulating T, with suppression of LH and FSH secretion from the pituitary.

Clinical Pharmacology also reiterated the Clinical Pharmacology findings from the original review of the male to female transfer study (T-01-02-02). The conclusion was that generally, a 1.5-2 fold increase in serum T concentration was observed in female partners at each time point (when 15 minutes of skin-to-skin rubbing contact was made); however, the potential for transfer "may be abolished by wearing occlusive clothing to cover the application site."

Clinical Pharmacology also reiterated the Clinical Pharmacology findings from the original review of the showering study (T-00-02-03). The conclusion was that no trend was detected to indicate that showering 2 hours post gel administration leads to a detectable difference in daily serum total T profiles.

In their final review dated December 15, 2010, of the June 30, 2010 submission, the Clinical Pharmacology recommendation for regulatory action was:

> *"The Division of Clinical Pharmacology 3/Office of Clinical Pharmacology finds the clinical pharmacology information submitted in NDA 21-463 acceptable provided that an agreement is reached between the sponsor and the Division regarding the language in the package insert."*

The Clinical Pharmacology review team noted that in the current submission, the sponsor submitted a new dataset to address the deficiencies in the bioanalytical assays after analyzing the back-up serum samples. In addition, the sponsor submitted a timeline to conduct the washing trial as a PMR. The following important findings from this review were stated:

- "…the DSI reviewer recommended that the dataset provided by the sponsor was valid, therefore, acceptable to review."
- When using the new dataset generated by the valid back-up samples (n=129), "Trial FOR1C met the primary and secondary endpoints…"

The Clinical Pharmacology review team provided the following table of efficacy results from the analysis of back-up samples (n=129). They acknowledged that in the current submission, 93.5% (129/138) of the patients' back-up serum samples were available for re-analysis compared to the original MITT analysis.

Table 2: **Efficacy Results (Back-up Sample Dataset)**

C_{avg} of total T on Day 90	
Mean (SD)	440.3 (163.4) ng/dL
% Patients with Values ≥300 and ≤1140 ng/dL, n/n[a]	77.5%, 100/129
95% CI* for % Patients with Values ≥300 and ≤1140 ng/dL	70.3 – 84.7%
% Patients with Values <300 ng/dL, n/n	22.5%, 29/129
% Patients with Values >1140 ng/dL, n/n	0%, 0/129
C_{max} of total T on Day 90	
Mean (SD)	827.6 (356.5) ng/dL
% Patients with Values ≤1500 ng/dL, n/n[b]	94.5%, 122/129
% Patients with Values ≥1800 and <2500 ng/dL, n/n[b]	1.5%, 2/129
% Patients with Values ≥2500 ng/dL, n/n[b]	0%, 0/129

a: primary endpoint; b: secondary endpoint
CI: confidence interval

For serum DHT, SHBG and LH, the Clinical Pharmacology team stated that the sponsor submitted a new dataset by analyzing back-up samples to address a deficiency in the stability of the original samples. For free T, FSH and estradiol, the sponsor submitted a new dataset by analyzing back-up samples to replace the original dataset due to deficiencies in accuracy or

precision of the analytical method. As expected, the DHT and estradiol concentrations increased over time, the FSH and LH concentrations decreased over time, and the SHBG concentrations remained constant (see tables 9 and 10 in the Clinical Pharmacologist's review). The DHT/T ratio did not change over time.

On December 17, 2010, the Clinical Pharmacology review team accepted the draft label with only deletion of two letters in the entire document.

6. Clinical Microbiology

On November 7, 2002, the microbiology reviewer, Bryan Riley recommended "Approval" of the original application from a microbiology perspective. The chemistry reviewer, Dr. Christner noted in her final review of the April 17, 2009 submission that there was no change in the microbiological information from what was submitted in the first review cycle. Microbiology information was reviewed during the first review cycle and was deemed adequate.

7. Clinical/Statistical- Efficacy

7.1 Clinical Program for Efficacy

The primary source of efficacy data for this NDA is Study FOR1C, a Phase 3, adequate and well controlled clinical trial of FORTESTA. While the NDA contains supportive evidence from Phase 2 studies as well as a Phase 3 study (TSX/01/C) conducted in Europe, the focus of this Clinical Efficacy section will be the original and re-analysis data from Study FOR1C.

The starting dose in Study FOR1C was 40 mg of testosterone applied once daily to the medial and anterior thighs, with a dose adjustment scheme ranging from a minimum of 10 mg of testosterone to a maximum of 70 mg of testosterone once daily, depending upon the serum testosterone level after 14 days of initial dosing or after a change in dose.

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 medial and anterior thighs, at a starting dose of 40 mg of testosterone per day. The dose of study drug was adjusted to between a minimum of 10 mg of testosterone per day to a maximum of 70 mg of testosterone 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 (as supported by the showering study results). 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 in Study FOR1C

Patients eligible for this study were hypogonadal men, aged 18-75 years, defined as males having a single morning serum total 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 in Study FOR1C

Dose adjustment was done on Days 14, 35 and 60 and was based on the results of the "C_2" draw; that is the sample drawn at 2 hours after dosing. This timepoint was selected because C_{max} was observed at 2 hours or at 4 hours after dosing in 77% of patients in previous studies results. Although, C_2 would not capture C_{max} in 100% of patients, the Division agreed to allow use of the single C_2 timepoint for dose titration in Study FOR1C because it would be feasible in clinical settings. The dose titration criteria; that is, the measured serum total testosterone concentration and the corresponding change in the amount of testosterone to use, is provided in Table 3.

Table 3: Dose Adjustment Criteria in Study FOR01C

Total serum Testosterone Concentration (C_2)	**Dose Titration**
C_2 ≥ 2500 ng/dL	**Decrease daily dose by 20 mg of testosterone**
1250 ≤ C_2 < 2500 ng/dL	**Decrease daily dose by 10 mg of testosterone**
500 ≤ C_2 < 1250 ng/dL	**No change - continue on current dose**
C_2 < 500 ng/dL	**Increase daily dose by 10 mg of testosterone**
If a patient had a C_2 total serum testosterone value > 2500 ng/dL at 2 successive visits, then the patient was withdrawn from the study.	

7.3 Efficacy Assessments and Endpoints in Study FOR1C

The primary endpoint in Study FOR1C was the percentage of patients with C_{avg} of total testosterone at Day 90 (± 3 days) in the normal physiologic range, defined as ≥300 ng/dL and ≤1140 ng/dL.

The bar for success for the primary endpoint was set at ≥ 75%, with lower bound of the 95% confidence interval not less than 65%.

The key secondary endpoints in Study FOR1C were the percentages of patients with certain pre-selected C_{max} values at Day 90, as follows:

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

Other endpoints in Study FOR1C included measurements of serum dihydrotestosterone (DHT), dihydrotestosterone to testosterone ratio (DHT:T), estradiol (E2), free testosterone (free T), luteinizing hormone (LH), and follicle stimulating hormone (FSH).

7.4 Populations and Data Analyzed in Study FOR1C

In the original dataset from the October 17, 2009, submission, the analysis populations were defined as:

- 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.

The data from the mITT population was used as the primary data to address primary and secondary endpoints in the original and the re-analysis, since the mITT population included all patients enrolled in the trial except for 11 patients who discontinued prematurely from the trial, and thus, those 11 patients did not have more than one PK sample for the 24-hour PK profile at Day 90.

Therefore, the disposition of the patients in FOR1C was as follows:

- Patients entering the trial: 149 (23 patients were ≥65 years old)
- Patients completing the trial: 138
- Patients discontinuing the trial: 11 – for the following primary reasons:
  - 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%)

The re-assay (re-analysis) population from the June 30, 2010, submission has a different number of total patients, because not all patients had back-up samples for re-analysis.

Of the 138 subjects in the original mITT population, 129 subjects' re-assayed total serum testosterone values were available for the re-analysis (the re-analysis population). The 9 subjects with no backup samples came from 5 different sites. The Sponsor provided two reasons why backup samples were unavailable for re-assay for these 9 subjects: 4 of the subjects had their backup samples used during the original assay, and 5 had their backup sample stored at the investigative site rather than shipped to the lab. This error was uncovered only 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 4 provides the original C_{avg} and C_{max} for all 9 subjects not included in the re-analysis:

Table 4. C_{avg} and C_{max} from the 9 subjects who did not have any Day 90 samples available for Re-assay

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

<u>CDTL comment</u>: The Sponsor's explanations for the missing backup samples from these 9 subjects are acceptable. Of these, 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).

Of the 129 subjects included in the re-analysis population, most had a complete set of ten serum samples for Day 90 (n=100), or nine samples (n=20), or eight samples (n=6). The other subjects had either seven or 6 samples available from Day 90.

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 in the mITT nonetheless; 4 of these obese men had samples available for re-assay and 1 did not.

Table 5: 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 any back-up samples, and some subjects had a few missing backup samples on Day 90, the Sponsor also provided a "supportive" statistical analysis, consisting of re-assayed values using imputation. Imputation means that when re-assayed values were not available, the original values were substituted for the missing re-assayed value. Therefore, the supportive analysis used all valid values: re-assayed valid values with imputation of original valid values where re-assayed values were not available, and this population consists of all 138 patients from the original mITT population.

7.5 Efficacy Results in Study FOR1C

Table 6 shows the results for the primary and key secondary efficacy endpoints from the original analysis (n=138), the re-analysis - referred to in the table as "re-assay" (n=129), and the "supportive analysis", consisting of the re-assayed values imputing valid original values where re-assay values were unavailable (n=138).

Table 6. 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	**138 (1368)**	**76.8 (69.8-83.9)**	**92.8**	**2.9**	**0**

The Sponsor concludes that the re-analysis data meet the pre-specified primary and key secondary efficacy endpoints. The Sponsor concludes that the reliability and accuracy of the original data are supported by the similarity of all three statistical analysis results. The analysis of the original data, the re-assayed data, and the data for the supportive analysis all meet the acceptance criteria for the primary and the secondary endpoints. Thus, the Sponsor believes that the conclusions of the original submission remain the same and support the original assessment of the efficacy associated with the use of FORTESTA.

CDTL Comment: The primary medical officer, Dr. Fang, concurs with the Sponsor that the conclusion of efficacy from the October 16, 2009, submission remains the same, and I concur with the medical officer.

As in the April 16, 2009, submission, the Sponsor conducted a subgroup analysis in the population of patients with BMI < 35 kg/m^2 ("non-obese'). Among 124 such subjects, 76.6% met the C_{avg} criterion for success on Day 90. The lower bound of the 95% CI was 69.2%. For the key C_{max} secondary efficacy endpoints, 94.4%, 1.6% and no patients had $C_{max} \leq 1500$ ng/dL, C_{max} of 1800 ng/dL to 2499 ng/dL, and $C_{max} \geq 2500$ ng/dL, respectively, on Day 90. Thus, the primary and key secondary endpoints were met in the "non-obese" subgroup.

Of note, the group mean C_{avg} on Day 90 in the 129 re-assay subjects was 440.3 ng/dL, with a standard deviation of 163.4 ng/dL. The group mean C_{max} on Day 90 in the 129 re-assay subjects was 827.6 ng/dL, with a standard deviation of 356.5 ng/dL.

Figure 2 describes the mean concentration-time profile of total T on Day 90.

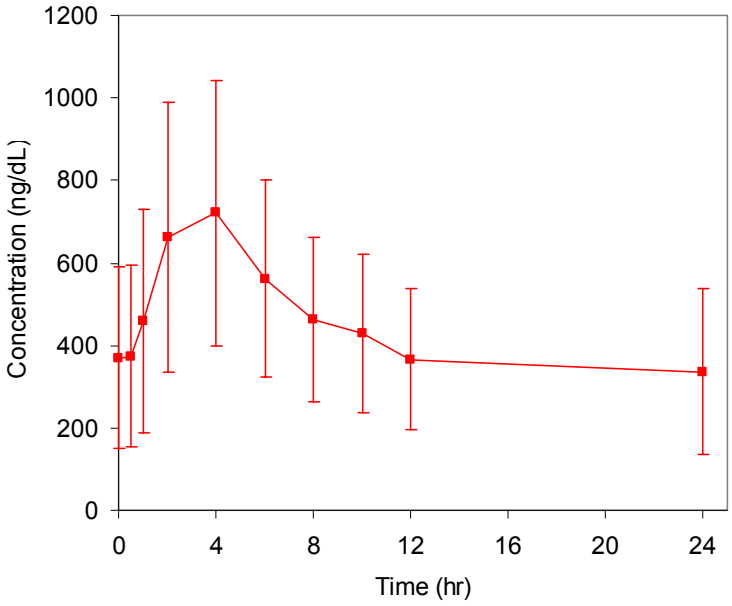

Figure 2. Mean (SD) Concentration-Time Profile of Total T on Day 90 (re-analysis population, n=129)

CTDL Comment: Based upon the starting dose of 40 mg of testosterone per day, and the individual (per-patient) dose adjustment parameters employed in Study FOR1C, the primary and key secondary endpoints were successfully achieved in the original and re-analysis populations.

"C_{max} Outliers"

In the original population (n=139), a total of 6 subjects (6/138; 4.3%) were considered "C_{max} outliers", defined as C_{max} >1800 ng/dL on Day 90. Less than 5% of all subjects were supposed

to reach this C_{max} in order for the study to achieve success, and thus the target was achieved. These subjects' data were shown by individual subject in Table 6 of Dr. Fang's original medical officer's review.

In the current submission, for the re-analysis population (n=128), only 2 subjects (2/129; 1.6%) were considered "C_{max} outliers", defined as C_{max} >1800 ng/dL on Day 90 (Subjects #018-002 and #016-003). For the other 4 subjects who previously had a C_{max} >1800 ng/dL on Day 90 in the original analysis, the re-assay values were modestly lower in two (Subjects #016-006 and #005-001), and re-assay values were unavailable in two (Subjects #018-001 and #032-042). Both subjects with missing back-up samples had valid original samples, therefore, the "supportive analysis", using imputed valid original samples, takes into account these two C_{max} outliers. The percentage of C_{max} outliers (defined as C_{max} > 1800 ng/dL), was 2.9% in the supportive analysis, again below the target for success of < 5%. Table 7 lists the subjects with C_{max} values >1800 ng/dL on Day 90 from the original analysis.

Table 7. Subjects with C_{max} Values >1800 ng/dL on Day 90 from the Original Analysis

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

There were no new subjects with C_{max} values >1800 ng/dL based on the re-assay of backup samples.

It is of interest that the clinical data from these 6 patients was analyzed by Dr. Fang in his original medical officer's review and he found no clinically significant increases from baseline in serum PSA in this group, two with modest decreases from baseline in serum high density lipoprotein (HDL) concentrations, and two with increases from baseline in hematocrit (+1.5% and +6.7%).

CTDL Comment: The percentage of C_{max} outliers is not excessive, and even within this small group, there is no clear evidence of clinical harm.

Additional Endpoints

Other endpoints in Study FOR1C included measurements of serum dihydrotestosterone (DHT), dihydrotestosterone to testosterone ratio (DHT:T), estradiol (E2), free testosterone (free T), luteinizing hormone (LH), and follicle stimulating hormone (FSH).

In the analysis from the original population, the SHBG level remained about the same over time. Both serum gonadotropins were lower at Day 35 and 90 compared to baseline, consistent with increased circulating testosterone which suppresses LH and FSH secretion from the pituitary gland. Estradiol concentrations increased over time, consistent with

aromatization of the exogenous testosterone to its metabolite estradiol. Free testosterone levels increased over time as expected. Finally, the ratio of DHT/total testosterone was essentially unchanged from baseline over time, indicating that the testosterone levels were rising without an excessive amount of metabolism to DHT via skin 5α-reductase.

Changes from baseline to Days 35 and 90 in SHBG, LH, FSH and estradiol concentrations from the original analysis are shown in Table 8. Also shown in Table 8 are the mean free and total testosterone concentrations, as well as the mean DHT:T ratios on Days 35 and 90 in Study FOR01C.

Table 8: Other Endpoints of Interest – Change from Baseline in Study FOR01C (original mITT Population)

	Baseline Mean (SD)	Mean change from baseline (SD) Visit 4 (Day 35)	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)	136.1 (178.6)	127.9 (116.1)
Total testosterone (ng/dL)	190.2 (64.4)	527.0 (519.0)	485.2 (377.6)
Ratio DHT/Total testosterone	0.13 (0.07)	0.04 (0.08)	0.04 (0.09)

Source: Module 5.3.5.1 FOR01C: Main Report.

For the re-analysis of these additional analytes in the current submission, it is important for the reader to be aware that in addition to total testosterone concentrations, the Form 483 issued to (b) (4) by DSI raised concerns in regard to dihydrotestosterone (DHT), estradiol, and free testosterone (free T) concentrations.

DSI's subsequent audit and Sponsor's additional responses to the recent DSI audit have clarified that the original data for DHT, estradiol, free T and SHBG are acceptable for analysis (*the reader is referred to Section 11 of this memo, under the heading, Division of Scientific Investigation [DSI]*) except for the data from invalid original runs. Data from original invalid runs still are still not usable, but backup samples from those runs have been re-assayed. Data have been assessed by original values, original values with values from failed runs removed, and values for re-analyzed backup samples alone.

A summary of the change from baseline of the 24 hour C_{avg} of DHT/Total T ratio is shown in Table 9. The medical officer's analyses of concentrations of DHT, DHT:T ratio, estradiol, FSH and free T are shown in Table 10.

Table 9. DHT/T ratio and changes from baseline to Days 35 and 90 in Study FOR01C

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

Table 10. Mean (SD) concentrations of DHT, DHT/T ratio, estradiol, FSH and free T at baseline and 2 hours after FORTESTA application (H2) on Days 35 and 90 in Study FOR01C

		Baseline		Day 35 H2		Day 90 H2	
		N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
DHT (ng/dL)	Original	137	22 (7.6)	134	74.2 (42.3)	137	76.5 (41.8)
	Original w/o FR*	121	21.7 (7.7)	122	73.4 (42.2)	110	77.0 (43.9)
DHT/T Ratio	Original	137	.13 (.07)	134	.13 (.07)	136	.13 (.06)
	Original w/o FR*	120	.13 (.08)	116	.12 (.06)	99	.13 (.06)
Estradiol (ng/dL)	Original	133	1.69 (0.79)	132	2.79 (1.47)	131	2.99 (1.70)
	Original w/o FR*	87	1.72 (0.79)	85	2.75 (1.37)	103	2.99 (1.67)
	Re-assay of failed runs	27	1.56 (0.64)	22	2.66 (1.25)	14	2.78 (0.97)
FSH (IU/L)	Original	137	10.51 (15.94)	132	5.40 (11.43)	133	4.06 (11.48)
	Original w/o FR*	80	11.51 (17.69)	62	5.42 (11.43)	48	3.54 (8.14)
	Re-assay of failed runs	45	7.87 (12.5)	43	4.23 (8.48)	57	3.06 (9.67)
Free T (pg/mL)	Original	136	33.1 (16)	134	168.4 (176.4)	137	160.8 (118.3)
	Original w/o FR*	119	33.7 (15.8)	116	172.1 (185.5)	119	161 (118.9)
	Re-assay of failed runs	13	32.5 (18.4)	10	159.3 (142.3)	9	159.2 (107.7)

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

CDTL comment: As demonstrated in these tables and according to the Clinical Pharmacologist's final review of the June 30, 2010, submission, the Sponsor has provided convincing evidence that the DHT and estradiol concentrations increase over time, the FSH and LH concentrations decrease over time, the SHBG concentrations remain constant, and the DHT/T ratio does not change over time.

7.6 Statistical Review

In their final review dated October 8, 2009, of the April 16, 2009, submission, the Statistical reviewers Kate Dwyer and Mahboob Sobhan, stated:

> *"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".*

In their final review dated November 19, 2010, of the June 30, 2010, submission, Drs. Dwyer and Sobhan, stated the following conclusion:

> "*Results from phase 3 study FOR01C with original and re-assayed values support the efficacy of Fortesta for testosterone in male hyogonadism. 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 supra-physiologic concentrations of testosterone levels".*

The Statistical reviewers note that the re-analysis data were used as the primary basis for assessing efficacy and the re-analysis results are shown in the label. The Statistical reviewer notes that the Sponsor provided a detailed accounting of any missing backup samples, as well as a "concordance analysis" of the re-analysis data and the original data, so as to support the validity of the original results.

Missing backup samples

Of a total of 3696 samples from Study FOR1C, a total of 290 of these samples came from "invalid runs". These runs were considered "invalid" by DSI for the reasons stipulated in Section 11 of this memo, under the heading, Division of Scientific Investigation (DSI). Of the 290 samples from invalid runs, most of these (n= 250) came from Day 35 (n= 97 samples) and Day 90 (n=153 samples), respectively. These were the days on which a 24-hour pK profile was generated from 10 samples per patient. Single samples were also drawn on Days 14 and 60 for titration purposes.

Day 90 is the day for assessment of primary efficacy. A total of 1374 samples were obtained on this day and a total of 1247 (or >90%) of these had back-up samples available. For the 127 original samples with no back-up samples available, 121 had original valid results. Only 6 samples out of 1374 total Day 90 samples had neither a valid original result nor an available back-up sample.

Concordance analysis

The Statistical reviewers note that the concordance analysis was used by Sponsor to study the similarity of the original and re-assayed values. The concordance correlation coeffients for

original and re-assayed samples for all days and Day 90 only were 0.947 and 0.941, respectively. In summary, the Statistical reviewers conclude that a high percentage of the original samples were re-assayed and strong concordance was shown between the original and re-assayed samples.

7.7 Overall Assessment of Efficacy

In the medical officer's final review dated December 15, 2010, Dr. Guodog Fang's efficacy conclusion is stated as follows:

> "*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.*"

I concur with the medical officer. The results of the re-analyses are considered valid on their own as an accurate assessment of efficacy of FORTESTA, and just as importantly, are concordant with the original analysis. My impression is that efficacy was demonstrated on Day 90 in Study FOR1C, when a starting dose of 40 mg of testosterone was used, coupled with assessment of the serum total testosterone concentration at 2 hours after dosing on Days 14 (± 3 days), 35 (± 3 days), and 60 (± 3 days) of the study, and adjustment of the FORTESTA dose in 10 mg and 20 mg gradations as pre-defined in the study.

The percentage of successful C_{avg} responders increased modestly from Day 35 (73%) to Day 90 (76%), and the number of C_{max} outliers (>2500 ng/dL), decreased from n=2 to n=0. As noted by the Clinical Pharmacology team, this data suggests that a single dose adjustment might not be sufficient for FORTESTA. While a third dose adjustment was incorporated in Study FOR1C, it does not appear that a third titration step significantly increases the overall efficacy or safety of FORTESTA. Only a small number of subjects (n=12) with normal range testosterone concentrations on both Days 14 and 35 in Study FORIC required dose adjustment on Day 60. In almost all of these patients (n=11), the dose adjustment on Day 60 was small (10mg). Only one of these patients required a dose reduction of 20mg. However, it is clear that the intra-subject variability is high for all topical testosterone gels and solutions, including FORTESTA, which may explain this single outlier value on Day 60. Further, the label will advise prescribers to assess serum testosterone concentration not just on approximately Days 14 and 35 after initiation of therapy or after dose adjustment, but also periodically thereafter, which should serve as an additional safety precaution.

Therefore, the proposed product label will:

1. Instruct prescribers to check the serum testosterone concentrations at approximately 14 and 35 days after starting therapy (using the serum T concentration at 2 hours after dosing – "C_2").
2. Adjust the dose by a specific amount based upon the Days 14 and 35 serum testosterone concentrations (at C_2).

3. Instruct prescribers to re-check the serum total testosterone concentrations after 14 and 35 days following any dose adjustment.
4. Instruct prescribers on the dose adjustments that are needed based upon the follow-up serum total T concentration measurements.
5. Instruct prescribers to check serum testosterone concentrations periodically thereafter

This dosage and administration paradigm was discussed with the Clinical Pharmacology review team (Drs. Hyunjin Kim and Myong-Jin Kim) and the Clinical reviewer (Dr. Gudong Fang), who all found it to be acceptable.

In my opinion, therefore, the results from Study FOR1C and the monitoring stipulated in labeling provide adequate support for the efficacy of FORTESTA as testosterone replacement therapy in hypogonadal men.

8. Safety

In their review of the April 16, 2009, submission, the Clinical review team (Drs. Fang and Kaul) conducted a thorough review of the safety data from the phase 3 study FOR01C, and in addition, reviewed safety data from an integration of the Phase 1/2 and supporting Phase 3 studies from the original submission. The FOR01C safety information is summarized in this section of the memo.

This section also includes a description of the results from the male to female transfer study (with and without shorts), as this is an important potential safety issue for all testosterone gel products.

Finally, this section also contains a brief summary of the post-marketing use experience for FORTESTA in the 19 countries where it is currently marketed. This information is derived from a PSUR submitted in the current (June 30, 2010) submission and constitutes the only new safety data since the October 16, 2009, regulatory action.

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 1/2 and 3 studies as shown in the Table 11.

Table 11: Fortesta Safety Database

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

Dr. Fang's Clinical safety review primarily focused on the phase 3 pivotal study FOR01C and a supporting European study TSX/01/C, along with a general overview of safety from other phase 3 studies. The duration of exposure in study FOR1C is shown in Table 12.

Table 12: Duration of Exposure to Study Drug in Study 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 – l77
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.

8.2 Demographics (in Study FOR1C)

Table 13: 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

CDTL Comment: The overall demographics in Study FOR1C are appropriate for the target population.

8.3 Discontinuations due to Adverse Events (in Study FOR1C)

There were five subjects in study FORO1C in whom an adverse event leading to study discontinuation was reported. One of the five patients presented with moderate contact dermatitis and the second patient presented with moderate skin reaction. The adverse events in these two patients were considered to be probably related to study medication by the study investigator. The third patient who discontinued due to an AE had "gastrointestinal hypo-motility", considered as possibly related to study medication, and the remaining two patients had dyspnea and contusion, respectively, that were both considered unrelated to the study medication.

8.4 Deaths

No deaths were reported in Fortesta-treated subjects during any of the Phase 1/2 or Phase 3 United States clinical studies, including study FOR01C. One death due to myocardial infarction was reported in Study TSX/01/C, which was a supporting study conducted entirely in Europe. This event occurred in a placebo-treated subject, who had other pre-existing co-morbid medical conditions.

8.5 Serious Adverse Events (SAEs)

According to the primary medical officer's review, there were 5 subjects in study FOR1C in whom a serious adverse event was reported. Intestinal obstruction was reported in 2 subjects and rectal hemorrhage related to colon cancer in a third. Dyspnea was reported in 1 subject. Cellulitis was reported in 1 subject. According to the medical officer, his review of the case narratives failed to reveal a relationship to study drug for any of these 5 events.

The medical officer's review of the April 17, 2009, submission contains a list of all SAEs reported in all clinical trials supporting this application. His detailed review of all narratives from Study FOR1C and TSX/01/C reveals no SAE with a relationship to study drug.

However, among SAEs from other studies, the medical officer's Table 7.9 in his October 14, 2009 review reveals 3 cases of polycythemia and 1 case of deep venous thrombosis (DVT) which were considered by the investigator to be related to study drug. The reason for these two specific SAEs (polycythemia and DVT) may have been the supraphysiologic serum testosterone concentrations observed in these studies, when a higher starting dose of FORTESTA was used compared to the starting dose in Study FOR1C, and when dose adjustment was not carried out using small gradations, as in Study FOR1C. There was also one case of cardiac congestive failure, considered related to study drug. Congestive heart failure (CHF) is a known potential risk of testosterone replacement therapy in subjects with pre-existing CHF, related to peripheral edema.

8.5 Common Adverse Events (in Study FOR1C)

The most common treatment-emergent adverse events reported in study FOR1C, reported on an all-causality basis, and in greater than 2% of subjects were: application site reaction (16.8%), upper respiratory infection (6.7%), sinusitis (4%), and hypertension (2.7%). The following adverse events were reported in 2% of subjects: diarrhea, vomiting, and cough.

Table 14: Treatment Emergent AEs Sorted by System Organ Class and Preferred Term (in 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.

All adverse events in study FOR1C were mild or moderate in severity. There were no skin-related AE that were judged to be severe. In 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. The results, shown in Table 15, provide no evidence of significant irritation.

Table 15. Study FOR01C: Results of Dermato1ogic Exam of Thigh Application Sites by Visit

	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.

Finally, in the integrated Phase 3 database, a total of 42 subjects (8%) experienced at least one severe AE. The most commonly reported severe AE by preferred term was application site reaction (4 subjects).

8.6 Safety Issues of Particular Interest

8.6.1 Changes in Clinical Laboratories

Testosterone replacement can be associated with increases in hematocrit (or even polycythemia), decreases in serum concentration of high-density lipoprotein cholesterol (HDL-cholesterol) and increases in serum prostate specific antigen (PSA). These lab results are sometimes used as surrogate biomarkers for longer-term risk (e.g. serum PSA is used by some as a marker for prostate cancer, etc).

Therefore, a comprehensive review was conducted to examine the relationship between changes in 1) hematocrit, 2) serum concentration of HDL-cholesterol, and 3) serum concentration of PSA with pharmacokinetics of Fortesta in Study FOR1C.

Table 16 shows the correlation coefficients between changes on hematocrit, HDL and PSA with C_{avg} and C_{max} in Study FOR1C. The medical officer and statistical reviewer showed no statistically significant correlations between changes from baseline to Day 90 for hematocrit, HDL and PSA and Day 90 serum total testosterone C_{avg} or C_{max}.

Table 16: Correlation of D90 serum testosterone C_{max}, C_{avg} with Day 90 changes from baseline for hematocrit, serum HDL, and serum 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.

Hemoglobin and Hematocrit

Table 17 shows shifts from baseline to Day 90 in hemoglobin and hematocrit in study FOR01C.

Table 17: Shifts from Baseline to Day 90 in Hemoglobin and Hematocrit in Study FOR1C

Parameter	n	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

In this study, a total of five subjects (3.6%) had hematocrit changes from normal baseline to "high" at Day 90. However, none of these five patients had any clinically significant symptoms associated with the lab abnormality. None required treatment, nor were any prematurely discontinued for this lab abnormality. Of note, in these 5 patients, the increase from baseline in hematocrit did not correlate with elevated C_{max} values for serum testosterone on Day 90.

Among 131 patients with available data, hematocrit increased from baseline to Day 90 by a mean of 0.01%, with 95% CI -0.53%, 0.56%. Finally, it is notable that of the 3 subjects who had "high" hematocrit levels at baseline, in two cases, the hematocrit levels decreased to "normal" on Day 90.

High-density Lipoprotein-Cholesterol (HDL-cholesterol)

Table 18 shows shifts from baseline to Day 90 in serum HDL-cholesterol in study FOR01C.

Table 18: Shifts from Baseline to Day 90 in HDL-cholesterol in Study FOR1C

Parameter	n	Visit 6 Value	Baseline Value		
			Number (%) of Patients		
			Low	Normal	High
HDL Cholesterol (mmol/L)	145	Low	52 (35.9)	13 (9.0)	0
		Normal	9 (6.2)	48(33.1)	3 (2.1)
		High	1 (0.7)	4 (2.8)	15 (10.3)

Although there are 13 subjects who were found to have slightly lower serum HDL-cholesterol after the drug therapy compared to baseline, the decrease in the serum HDL-cholesterol level was not clinically significant and did not correlate with the serum total testosterone C_{max} on Day 90.

Among 137 patients with available data, serum HDL-cholesterol concentration changed from baseline to Day 90 by a mean of -0.55 mg/dL, with 95% CI -1.82 mg/dL, 0.71 mg/dL.

Serum PSA
There were only 2 patients (2/149, 1.3%) in study FOR01C that showed a non-significant increase in PSA.

Among 135 patients with available data, serum PSA concentration increased from baseline to Day 90 by a mean of 0.24 ng/mL, with 95% CI 0.14 ng/mL, 0.35 ng/mL.

8.6.2 Potential for Testosterone Transfer from Patients to Partners

Study T 01-02-02 was an open-label, vehicle-controlled, pharmacokinetic study in healthy couples which evaluated serum testosterone level in females who were required to engage in 15 minutes of skin-to-skin contact with the application sites of FORTESTA users, and also evaluated whether covering the application site with clothing would prevent transfer of testosterone. Two hours after FORTESTA 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. There were no significant changes from baseline in total testosterone concentration in any female partner when the application site was covered with clothing. This demonstrates that transference and absorption is prevented by covering the application site with clothing. The Clinical Pharmacology review team stated that the potential for transfer "may be abolished by wearing occlusive clothing to cover the application site."

8.6.3 Effect of Showering on Testosterone Pharmacokinetics

While not a safety issue, it is important to know when a patient may shower or swim after they have applied FORTESTA without the risk of losing efficacy. Study T-00-02-03 was an open-label, non-vehicle-controlled, randomized, two-treatment, two-period crossover study, in which the effects of showering on the pharmacokinetics of total testosterone following topical application of FORTESTA 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.

8.6.4 Removal of Testosterone from the Skin By Washing

The Sponsor has not yet conducted a "wash off" study to provide evidence that that FORTESTA may be removed from the application site and hands by simply washing the site with soap and water. While it is considered likely that FORTESTA can be removed from the skin by soap and water, the Sponsor has nonetheless been asked to conduct such a study in human subjects as a post- marketing requirement (PMR). The Sponsor has agreed to conduct this study as a PMR and has provided acceptable commitment dates.

8.7 Postmarketing Experience

FORTESTA has marketing authorizations in 20 member states of European Union (EU) and 2 other countries. It is marketed in 19 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. The Sponsor submitted Periodic Safety Update Report (PSUR) covering the 12 month period April 1, 2009, to March 31, 2010. For that time period, the 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. Overall, the adverse reactions reported are consistent with the expected safety profile for topical testosterone preparations. There are no new safety concerns from these data.

8.8 Overall Safety

FORTESTA (testosterone gel 2%) was well-tolerated in the Phase 3 study FOR01C with a starting dose of 40 mg of testosterone, and dose adjustment on days 14, 35 and 60, and doses ranging from 10 mg of testosterone to 70 mg of testosterone. The dose adjustment was in gradations of 10 mg or 20 mg of testosterone. The product labeling reinforces that the serum total testosterone concentration at 2 hours after application should be checked after approximately 14 and 35 days of initial use, after approximately 14 and 35 days after any change in dose, and periodically thereafter. The product clearly denotes that amount of testosterone to administer based upon the serum total T concentration. The Clinical Pharmacology review team and medical officer recommend this dosage and administration strategy in labeling.

The incidence of treatment emergent adverse events (TEAE's) in Study FOR1C was low and was consistent with the adverse event profile for already approved topical testosterone products. The incidence of skin reactions is in line with already approved products in this class. The majority of these reactions were mild and none were severe. Several patients showed increases from baseline in hematocrit, decreases in serum HDL-cholesterol, and increases in serum PSA, and these too are known adverse reactions to testosterone. These abnormalities were not excessive in study FOR1C and the label clearly advises prescribers to monitor for these clinical labs. The overall incidences of serious adverse events and adverse events that led to premature study discontinuation were low.

The Sponsor has shown that covering the application sites with clothing is an effective barrier to transfer. Finally, the Sponsor has agreed to conduct a "wash-Off" study as a post-marketing requirement.

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

In the April 17, 2009 submission, the Sponsor 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 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 (PMHS) 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)

In their final review dated October 8, 2009, of the April 17, 2009 submission, Drs. Rivera-Lopez, Kassim and Yau of DSI reported on the results of their audit of the clinical and analytical portions of study FOR01C. The DSI team audited two clinical sites (sites in Mariana, Florida and in Tucson, Arizona), and one laboratory ((b) (4)).

In regard to the clinical site inspections, there were no significant observations at the Tucson site. There were several observations at the Florida clinical site, but of most significance to DSI were three patients who were enrolled despite not meeting the inclusion and exclusion criteria. In two of these cases (#032-050 and #032-051), the patients did not meet the restricted BMI criterion (BMI < 35 kg/m^2) and in one case the patient did not comply with a full 8-week washout period prior to enrollment (#032-014). The DSI recommended that the data from these three patients be excluded from evaluation. Additionally, there was one patient in whom an SAE was not promptly reported to Sponsor.

CDTL Comment: I do not agree that the data from patients #032-050 and #032-051 should be excluded from evaluation. It is of significant value to have data from patients with differing BMI's. The study data have been analyzed by BMI by the Clinical Pharmacology team and there were no significant differences demonstrated in C_{avg} or C_{max} for the following BMI categories: 22 to 25, 25 to 30, and 30 to 35 kg/m^2. There is actually an increased C_{avg} and C_{max} in patients with BMI > 35 kg/m^2, but this group still has C_{avg} and C_{max} averages within the normal physiologic range. In addition, I would not summarily dismiss the data from patient #032-014 just because he did not have a full 8-week wash-out from injectable testosterone. If his baseline testosterone lies below the normal range, then this would be clear evidence of adequate wash-out, irrespective of the wash-out duration, in my opinion.

In regard to the (b) (4) inspection, there were significant observations, and these have been described briefly in section 1 (Introduction) of this memo. There are summarized herein:

1. The "audit trial" of the "Analyst" software was not turned on for all validation and analytical runs. Therefore, audit trail records were not available for 50 of the analytical runs. This affected some samples measured for total testosterone and estradiol.
2. The lab used "Westguard rules" rather than run acceptance criteria stipulated in the FDA Guidance: Bioanalytical Method Validation. During their audit, DSI requested that the lab re-calculate the quality control (QC) results in each run using the FDA Guidance criteria for accepting or rejecting runs. Many runs which passed by Westguard rules did not pass when using the FDA Guidance criteria.
3. In several runs (including samples measured for total testosterone and estradiol), the lab failed to reject the run when <75% of calibration standards in a standard curve failed to meet the acceptance criteria.
4. The incurred sample reproducibility (ISR) of the LC/MS/MS method for total testosterone was not evaluated. DSI stated that the lab should have demonstrated that the total testosterone assay was reproducible when incurred samples were re-assayed. The firm agreed to establish a standard operating procedure to describe this ISR testing.
5. Quality control (QC) samples for the SHBG assay used two lots of commercial human serum that were past expiry date. The firm agreed to improve their practices to ensure that this would not happen again.
6. The lab did not demonstrate the accuracy of the DHT radioimmunoassay. When compared to an LC/MS/MS –based assay, results of 41 of 100 pairs differed by >20%.
7. The PSA and LH assays were not evaluated at concentrations below 0.5 ng/mL and 0.07 mIU/mL, respectively.
8. The lab did not demonstrate the freeze/thaw stability of their frozen calibration standards. Freshly prepared standard curves were not used in the stability experiments.

Therefore, based upon these observations, DSI requested 1) additional audit trial records from a number of analytical runs, and 2) repeating the freeze/thaw and long-term frozen storage stability studies of all analytes using freshly prepared standard curves. DSI recommended 1)

that DHT measurements not be accepted until additional data were submitted to assure the accuracy of the DHT RIA, 2) PSA measurements < 0.5 ng/mL be considered below the limits of quantification, and 3) LH measurements < 0.59 mIU/mL be considered below the limit of quantification.

In their final reviews dated October 6, 2010, and November 18, 2010, for the June 30, 2010 submission, Sean Kasim and Martin Yau of DSI provided comments and conclusions regarding how (b) (4) and Sponsor worked together to resolve the DSI concerns from the original audit.

Dr. Kassim conducted a follow-up inspection of the (b) (4) on August 9-17, 2010. Based on the follow-up inspection, and the Sponsor's responses to the follow-up Form 483, DSI had the following comments:

1. In a document sent to the review Division on August 9, 2010 (and noted again in DSI's final review dated November 18, 2010), DSI stated that the lab's incurred sample reproducibility (of the LC/MS/MS method for **total testosterone**) experiment design appeared sufficient. These ISR data were reviewed at the 2010 inspection and the results were considered "acceptable".

2. The process that generated data to support the long-term frozen stability for **SHBG** was clarified during the August 2010 audit, and DSI concluded that the SHBG frozen stability was established to 168 days.

3. The lab provided additional long-term stability data for estradiol, free T and DHT. The DSI reports states that both the estradiol and DHT studies had greater than 66% of the samples within 15% or 20% of expected values, respectively, for estradiol and DHT. DSI stated that the DHT and estradiol long-term stability had been demonstrated up to 960 and 1025 days. Therefore, DSI concluded that the re-assay for the **DHT** and **estradiol** samples are acceptable.

4. DSI stated that the average bias or decrease in **free T** samples was less than 15% indicating that degradation was not significant.

CDTL Comments:

1. *At the August 16, 2010, DRUP "filing" meeting for the June 30, 2010, CR submission, Dr. Kassim stated to the review team that the "back-up samples are OK" for use in the re-analysis for serum total testosterone.*
2. *At the October 4, 2010, DRUP "mid-cycle" meeting for the June 30, 2010, CR submission, Dr. Kassim stated to the review team that the Sponsor had responded acceptably to concerns about long-term stability for DHT and estradiol. Thus, the back-up samples could be used for the re-analysis of serum DHT and estradiol from invalid runs.*
3. *At the November 18, 2010, DRUP "wrap-up" meeting for the June 30, 2010, CR submission, Dr. Kassim stated to the review team that while there was some degradation in*

free T, it did not preclude use of the back-up samples for free T data in the re-analysis, and that data (from re-analysis of samples from invalid runs) could also be accepted.

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)
In their final review dated August 19, 2009, of the April 17, 2009, submission, CSS provided some initial language for the label under Section 9, "Drug Abuse and Dependence".

In their final review dated October 20, 2010, of the June 30, 2010, submission, CSS recommended that DRUP accept the Sponsor proposed language for Section 9 with the addition of one sentence. That sentence was added and the Sponsor accepted the change.

Division of Medication Errors and Prevention (DMEPA)
DMEPA was asked to consult on 1) the trade name, and 2) the container/carton labeling, the Full Prescribing Information (FPI), and the Patient Information, with regard to potential medication errors.

In regard to the tradename*:*
In their final review dated July 29, 2009, of the April 17, 2009, submission, DMEPA found the proposed proprietary name, FORTESTA, acceptable.

In their final review dated November 2, 2010, of the June 30, 2010, submission, DMEPA conducted a "re-assessment" of the proprietary name. The Proprietary Name Risk Assessment findings indicated that the proposed name FORTESTA is not vulnerable to name confusion that could lead to medication errors nor is the name considered promotional. Thus, the Division of Medication Error Prevention and Analysis (DMEPA) had no objection to the proprietary name, Fortesta, for the product.

In regard to the container/carton, FPI and Patient Information labeling:
In their final review dated December 17, 2010, of the June 30, 2010, submission, DMEPA reviewed the container, carton and package insert labeling and found that the Sponsor had implemented all DMEPA's previous recommendations. DMEPA further noted that the Sponsor's revisions did not introduce any additional areas of vulnerability that could lead to medication errors. Therefore, DMEPA had the following conclusion:

> "*The revised labels and labeling submitted by the Applicant adequately addresses our concerns from a medication error perspective. We do not have any additional comments at this time.*"

Division of Drug Advertising, Marketing and Communication (DDMAC)
A consultation regarding labeling for Fortesta was requested and completed by DDMAC.

In their final review dated October 1, 2009, of the April 17, 2009, submission, Janice Maniwang of DDMAC provided comments on various sections of the label. At that time, 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.

In their final review dated December 3, 2010, of the June 30, 2010, submission, Janice Maniwang of DDMAC again provided comments on various sections of the label. Each of the DDMAC comments were considered individually and discussed within the Clinical review team. Almost all of the DDMAC comments were incorporated into labeling.

Division of Drug Risk Assessment (DRISK)
DRISK was asked to comment on 1) the Risk Evaluation and Mitigation Strategy (REMS), and 2) the Medication Guide.

In regard to the REMS:
In their final review dated September 1, 2009, of the April 17, 2009, submission, DRISK completed a review of the Sponsor's REMS. DRISK noted that the necessary components of the REMS were the Medication Guide and the Timetable for Assessments.

In their final review dated November 22, 2010, of the June 30, 2010, submission, DRISK noted that the REMS was re-submitted with this CR. DRISK ensured that the REMS included elements outlined in the REMS Notification Letter and that it met statutory requirements under FDAAA. The DRISK final conclusion was a concurrence with the proposed REMS.

In regard to the Medication Guide:
DRISK was provided with a "substantially complete" PI on November 26, 2010, to be used as the basis for their edits to the Sponsor-proposed Medication Guide. The Medication Guide had been included in the June 30, 2010, CR submission. DRISK also used previous Medication Guides for other topical testosterone gel products to make edits to the Sponsor's proposal for consistency throughout the class. The final DRISK review was provided to the Division on December 6, 2010. All the DRISK edits were conveyed to Sponsor, who accepted all the Agency's proposed changes.

Labeling

Full Prescribing Information
During review of the June 30, 2010 CR submissions, labeling discussions were held with the entire review team on November 15 and 18, 2010. Another review team meeting was held on November 23, 2010 to discuss just the Dosage & Administration section. These meeting were productive in generated Full Prescribing Information (FPI) acceptable to all disciplines as well

as to the Study Endpoint and Labeling Development Team (SEALD) in the Office of New Drugs Immediate Office (OND/IO).

The Division's edited FPI was conveyed to Sponsor on November 26, 2010. Following the Sponsor's response on November 30, 2010, a second set of Division edits were conveyed to Sponsor on December 7, 2010. The Sponsor accepted virtually all of the Division's edits, and returned the document on December 9, 2010.

With minor edits (all accepted by Sponsor), the FPI returned on December 9, 2010 was found acceptable by the review team and by SEALD. In their final review dated December 16, 2010, SEALD concluded:

> "*This memo confirms that all critical prescribing information (PI) deficiencies found on the SEALD Labeling Review filed December 15, 2010, for this application have been addressed. SEALD agrees that the PI is ready for approval at this time.*"

Medication Guide
DRISK was provided with a "substantially complete" PI on November 26, 2010, to be used as the basis for their edits to the Sponsor-proposed Medication Guide. On December 6, 2010, the Division received an edited version of the Medication Guide from the Division of Risk Management (DRISK), and this document was conveyed to Sponsor on December 7, 2010. The Sponsor accepted all the DRISK edits to the Medication Guide and returned the document on December 9, 2010.

12. Recommendations/Risk Benefit Assessment

12.1 Recommended Regulatory Action

I recommend that NDA 21-463 for FORTESTA be approved.

12.2 Risk Benefit Assessment

In regard to efficacy, the dose regimen for FORTESTA of 40 mg of testosterone once daily starting dose, with 10-70 mg daily day dose adjustment, was shown to provide adequate replacement of testosterone in hypogonadal men (as measured by testosterone C_{avg}), while not providing excessive testosterone (as measured by testosterone C_{max}). The results of the Sponsor's re-assay and re-analyses are an accurate assessment of efficacy of FORTESTA, and are concordant with the original assay and original analysis. My impression is that efficacy was demonstrated on Day 90 in Study FOR1C, when a starting dose of 40 mg of testosterone was used, coupled with assessment of the serum total testosterone concentration at 2 hours after dosing on Days 14 (± 3 days), 35 (± 3 days), and 60 (± 3 days) of the study, and adjustment of the FORTESTA dose in 10 mg and 20 mg gradations as pre-defined in the study.

The percentage of successful C_{avg} responders increased modestly from Day 35 (73%) to Day 90 (76%), and the number of C_{max} outliers (>2500 ng/dL), decreased from n=2 to n=0. As noted by the Clinical Pharmacology team, this data suggests that a single dose adjustment

might not be sufficient for FORTESTA. While a third dose adjustment was incorporated in Study FOR1C, it does not appear that a third titration step significantly increases the overall efficacy or safety of FORTESTA. The reader is referred to Section 7.7 of this memo for additional details.

The proposed product label will:

1. Instruct prescribers to check the serum testosterone concentrations at approximately 14 and 35 days after starting therapy (using the serum T concentration at 2 hours after dosing – "C_2").
2. Adjust the dose by a specific amount based upon the Days 14 and 35 serum testosterone concentrations (at C_2).
3. Instruct prescribers to re-check the serum total testosterone concentrations after 14 and 35 days following any dose adjustment.
4. Instruct prescribers on the dose adjustments that are needed based upon the follow-up serum total T concentration measurements.
5. Instruct prescribers to check serum testosterone concentrations periodically thereafter

This dosage and administration paradigm was discussed with the Clinical Pharmacology review team (Drs. Hyunjin Kim and Myong-Jin Kim) and the Clinical reviewer (Dr. Gudong Fang), who all found it to be acceptable.

In my opinion, therefore, the results from Study FOR1C and the monitoring stipulated in labeling provide adequate support for the efficacy of FORTESTA as testosterone replacement therapy in hypogonadal men. The product is effective for the proposed indication.

In regard to safety, the results from study FOR01C and other phase 3 trials revealed the expected adverse reactions associated with a topical testosterone gel (e.g., application site reaction, slight increase in serum PSA, increase in hematocrit, change in lipid profile, etc). The product labeling will note the adverse reactions and the potential adverse reactions with advice for monitoring. The Sponsor has conducted a "transfer study" study to show that clothing effectively blocks transfer of testosterone from a user to another person. The Sponsor has conducted a "showering" study to demonstrate that the user may swim or shower at 2 hours after dose application. While the Sponsor has not conducted a "wash-off" study to demonstrate that FORTESTA may be removed from the skin by soap and water, the Sponsor has committed to conduct such a study as a postmarketing requirement (PMR).

Therefore, based upon the demonstrated efficacy of FORTESTA from study FOR01C and overall safety as shown from study FOR1C and the integrated safety database, along with acceptable Medication Guide Labeling, and a PMR to conduct a wash-off study, FORTESTA will be 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 as a postmarketing requirement (PMR) to demonstrate that FORTESTA may be washed off the skin with soap and water. The Sponsor accepted this PMR and provided a draft protocol and acceptable written commitment dates.

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

/s/

MARK S HIRSCH
12/24/2010

GEORGE S BENSON
12/29/2010